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UPDATE

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iloprost trometamol

› Current understanding of pulmonary arterial hypertension

› Current diagnostic and therapeutic standards

› Current view of future disease management

Pulmonary hypertension therapy – The past and the future

Future treatments in development include activators or stimulators of sGC and tyrosine kinase inhibitors such as sorafenib.

It is well-known that continuous treatment with intravenous epoprostenol (prostacyclin) improves survival of patients with primary pulmonary hypertension (PPH), compared with conventional therapy (Barst RJ et al., NEJM 1996; Sitbon O et al., JACC 2002). Intravenous prostacyclin was the first specific treatment approved for PPH. Nowadays, intravenous prostacyclin is not used as first-line treatment for PPH any more, because other specific therapies that can be administered per inhalation or orally are available. These therapies are more convenient for the patient and show fewer systemic side effects, Werner Seeger, Giessen/Germany, pointed out.

Aerosolized iloprost, a stable prostacyclin analogue, has been shown to reduce pulmonary artery pressure and to improve gas exchange in the adult respiratory distress syndrome as early as 1993 (Walmrath et al., Lancet 1993; 148: 961). In 2002, the study AIR was published, a multicenter international landmark trial that showed that inhalation of iloprost (Ventavis®) can improve event-free survival (significantly more dropouts and deaths in the placebo group, p=0.024) and prolonged the 6-min walking distance by 36.4 m (p=0.004) compared with placebo (Olschewski H et al., New Engl J Med 2002; 347: 322–9).

In order to further improve this specific therapy, a controlled-release formula of iloprost has been tested recently that allows alveolar prostanoid release for more than 24 hours after one single inhalation (Kleemann E et al., Pharm Res 2007; 24: 277–87).

Other specific therapies used in PPH today are endothelin receptor antagonists such as bosentan or phosphodiesterase-5-inhibitors such as sildenafil. As these therapies target different molecular pathways and therefore act synergistically with prostacyclin (Fig. 1), combination therapy with two or even three of these specific compounds seems to be more effective and is used in today' s routine clinical practice.

Furthermore, new specific treatments are being developed that are supposed to further improve survival. Above all, these are substances that stimulate or activate the soluble guanylate cyclase (sGC) such as BAY 63-2521, and substances that target the tyrosine kinase signalling pathway such as imatinib or sorafenib. The latter may be the first to truly reverse remodeling in pulmonary arteries of PAH patients.

Fig. 1

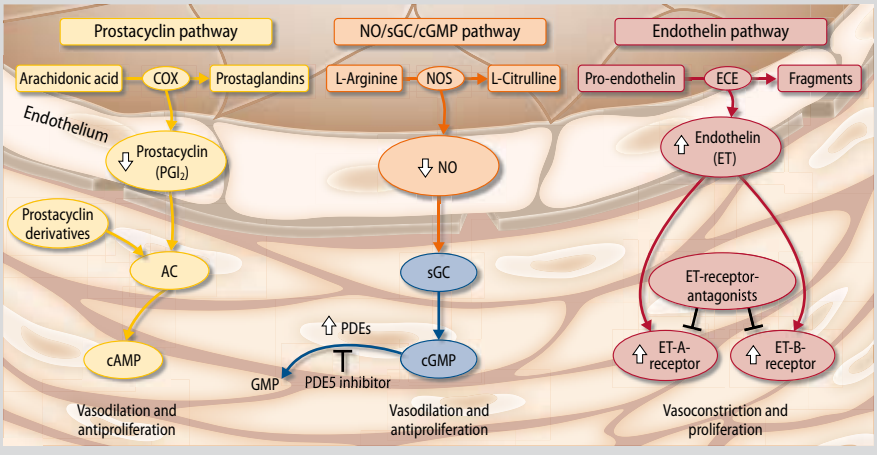


Fig. 1 › Different pathways represent logical pharmacological targets (sGC = soluble guanylatcyclase, cGMP = cyclic guanosine monophosphate, COX = cyclooxygenase, NOS = NO-synthase, ECE = endothelin-converting enzyme, AC = adenylat cyclase, PDEs = phosphodiesterases, GMP = guanosin monophosphate, cAMP = cyclic adenosin monophosphate)

Current understanding of the disease

Within the past 10 years, the understanding of the pathophysiology of pulmonary arterial hypertension (PAH) has changed rapidly. It has been shown that endothelial dysfunction and smooth muscle proliferation play a key role in the pathogenesis of PAH. The burden of the disease is high. It still leads to death within less than 3 years if it remains undiagnosed or untreated. Therefore, early diagnosis and optimal monitoring are of great importance for the prognosis of the patients.

In 2003, the current diagnostic classification of pulmonary hypertension was established (Simonneau G et al., J Am Coll Cardiol 2004; 43, 12 suppl S: 5S–12S; Table 1). However, as Zhi-Cheng Jing, Beijing/China, emphasized, most data available are from Western populations. According to a Chinese registry from 1999–2004, the 5-year survival of chinese patients with idiopathic or familial PAH is 20.8% versus 27% in the USA, according to the NIH registry (Jing ZC et al., Chest 2007; 132: 373–9). A new Chinese registry was started in September 2006: 38.2% of the patients registered were diagnosed with PAH associated with congenital heart disease (CHD), compared with 11.2% in a French registry. These CHD-PAH patients did not respond at all in the acute vasoreactivity test. In patients with severe PAH but only small atrial septum defect (ASD), the shunt does not explain the severity of the pulmonary vascular disease, as Jing pointed out. Therefore, the diagnosis and classification are confusing. CHD-PAH should be classified in group 1 under 1.6 as a subgroup of its own, Jing suggested. Patients with small ASD and severe PAH may be reclassified as patients with idiopathic PAH plus ASD. Moreover, Jing suggested that patients with idiopathic PAH should be classified in two different subgroups, because responders show a variant pulmonary arteriopathy, whereas non-responders have a more complex arteriopathy with severe remodeling which must be understood as a different vascular disease.

Patients with small atrial septum defect (ASD) and severe PAH may be reclassified as patients with idiopathic PAH plus ASD.

Pathology and pathophysiology of PAH

PAH can be divided into a precapillary disease, a postcapillary disease (PVOD), and a capillary disease (PCH; Pietra GG et al., J Am Coll Cardiol 2004; 43, 12 suppl S: 25S–32S). In the precapillary disease, muscular arteries with exaggerated proliferation of smooth muscle cells are predominant. Furthermore, a concentric laminar intimal fibrosis, also termed onion-bulb like lesion, is typical. Concentric non-

Table 1

1. Pulmonary arterial hypertension
1.1 Idiopathic PAH
1.2 Familial PAH
1.3 Associated with: › Collagen vascular disease › Congenital systemic-to-pulmonary-shuts › Portal hypertension › HIV infection › Drugs and toxins › others
1.4 Associated with significant venous or capillary involvement: Pulmonal Veo-Occlusive Disease, Pulmonary Capillary Haemangiomatosis
1.5 Persistent pulmonal hypertension of the newborn
2. PH with left heart disease
2.1. Left-sided atrial or ventricular heart disease
2.2. Left-sided valvular heart disease

3. PH associated with lung diseases/hypoxemia
3.1 Chronic obstructive pulmonary disease
3.2 Interstitial lung diseases
3.3 Sleep-disordered breathing
3.4 Alveolar hypoventilation disorders
3.5 Chronic exposure to high altitudes
3.6. Developmental abnormities
4. PH due to chronic thrombotic and/or embolic disease
4.1. Thromboembolic obstruction of prox. pulmonal arteries
4.2. Thromboembolic obstruction of distal pulmonal arteries
4.3.No thrombotic pulmonary embolism
5. Miscellaneous
Sarcoidosis, histiozytosis X, lymphangiomatosis
Compression of pulmonary vessels

Table 1 › Clinical classification of pulmonary Hypertension, Venice, 2003 (from Simonneau G et al., J Am Coll Cardiol 2004; 430, 12 suppl S: 5S–12S)

laminar intimal thickenings and eccentric intimal thickenings are seen, too, as well as plexiform, dilated lesions or thrombotic lesions, and perivascular inflammatory infiltrates. In PVOD, preseptal venules with occluding intimal proliferation or loose intimal fibrosis, and alveolar septa with signs of congestion are typical.

Abnormal smooth musle and endothelial cell proliferation and remodeling are main features of PAH, together with vasoconstriction and thrombosis of the small pulmonary arteries.

Thus, abnormal smooth muscle and endothelial cell proliferation and remodeling are main features of PAH, together with vasoconstriction and thrombosis of the small pulmonary arteries, summarized Marc Humbert, Paris/France. Several molecular pathways are involved (Humbert M et al., New Engl J Med 2004; 351: 1425–36). The signalling pathways of endothelin, nitric oxide (NO) and prostacyclin are well-known today, and have led to the development of the specific drugs used in today's clinical routine. Additional molecular mechanisms have been discovered recently and are leading the way to new therapeutic compounds.

Recent data suggest a cross-talk between endothelial and smooth muscle cells. The hypothesis, that endothelial cell derived chemokines may contribute to pulmonary artery smooth muscle cell proliferation in human idiopathic PAH was published recently (Sanchez O et al., Am J Respir Crit Care Med 2007; 176: 1041–47). In familial PAH, mutations of the tumor growth factor beta (TGF-β) and type II receptor BMPR2 are detected in 80% of patients (Machado RD et al., Hum Mutat 2006; 27: 121–32). Environmental factors may also play a role as shown in an adenovirus inhalation model (Song Y et al., Circulation 2005; 112: 553–62).

Figure 2 summarizes the factors that are known to influence the manifestation and progression of PAH.

The role of remodeling in PAH

Remodeling is defined as structural changes of the vascular wall characterized by intimal, medial, and adventitial thickening in response to hypoxia, inflammation, hemodynamic changes or vascular disease, explained Ralph Schermuly, Giessen/Germany. Remodeling takes place through de novo muscularization and distal migration of smooth muscle cells. Several theories explain the de novo appearance of smooth muscle cells in nonmuscular small arteries. Adventitial and interstitial fibroblasts are recruited to the vessel wall (Stenmark KR et al., Circ Res 2006; 99: 675–91). Extravasation and alignment of circulating precursors contribute to vascular remodeling (Hayashida K et al., Chest 2005; 127: 1793–8). Endothelial-to-mesenchymal transition takes place (Arciniegas et al., Am J Physiol Lung Cell Mol Physiol 2007; 293: L1–8). At present, several new treatments are being developed that target remodeling in PAH (Fig. 3). In future, an individualized therapy seems possible that is tailored according to functional parameters, biomarkers, circulating cells, imaging techniques and genomics.

Fig. 2

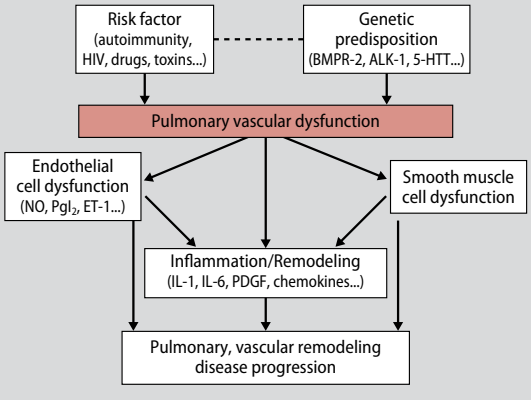


Fig. 2 › Factors that are known to influence the manifestation and progression of PAH (PGI_2 = prostacyclin, PDGF = platelet derived growth factor)

Fig. 3

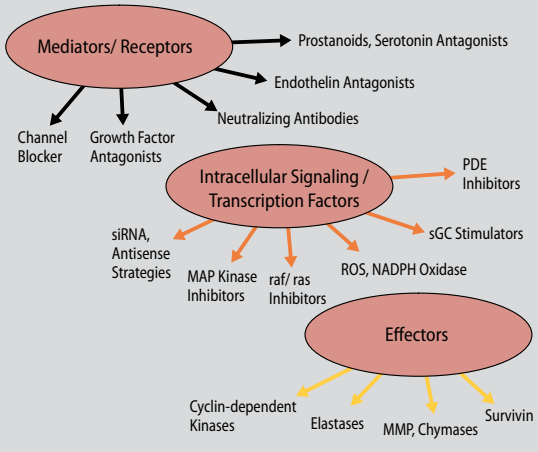


Fig. 3 › How to target remodeling (presented by Schermuly)

Current diagnostic standards

The earlier the diagnosis, the better the outcome. As pulmonary arterial hypertension (PAH) is a rare disease, patients are often diagnosed very late. This needs to be changed. Even mildly symptomatic patients (dyspnea, fatigue) should be investigated early if risk factors for PAH are present – for example patients with scleroderma, relatives of patients with familial PAH, and probably also patients with chronic hemolytic disorders.

In the diagnosis of PAH, echocardiography is an important screening method, said Nazzareno Galiè, Bologna/Italy. Although echo doppler results correlate with the mean pulmonary arterial pressure (mPAP) measured during cardiac catheterization, there are too many false-positive or false-negative echo findings that make it difficult to rely on this method as Galiè explained (Mukerjee D et al., Rheumatology 2004; 43: 461–6).

Therefore, the definite diagnosis can be made only by means of right heart catheterization. If a pulmonary artery systolic pressure (PASP) between 36mmHg and 50mmHg is found in the echocardiogram and the patient is symptomatic or has a connective tissue disease (CTD), a right heart catheterization should be undertaken. According to the European guidelines, PAH is diagnosed when the mPAP is above 25mmHg at rest or above 30mmHg during exercise (Galiè N et al., Eur Heart J 2004; 25: 2243–78).

Echocardiography in therapeutic management

Echocardiography also plays a role in evaluating the severity of the disease and the prognosis of the patient. Important prognostic parameters in patients with idiopathic PAH are pericardial effusion, the right atrial size, the left ventricular eccentricity index, the Doppler right ventricular (= Tei) index, the tricuspid regurgitant area, and the tricuspid anular plane systolic excursion (TAPSE).

Selected echocardiographic and Doppler parameters such as the pericardial effusion score and the Tei index can also be used to monitor the treatment effect. In controlled studies, epoprostenol and bosentan were found to improve echocardiographic and Doppler changes typical for PAH.

Right heart catheterization and pharmacological testing

Resting right heart catheterization is mandatory in patients with PAH

- to confirm the diagnosis of PAH
- to rule out other forms of pulmonary hypertension
- to test acute pulmonary vasoreactivity
- to evaluate the prognosis
- to guide therapy (treatment decision and follow-up on therapy).

Exercise right heart catheterization (RHC) has to be properly evaluated and is not yet a standard, said Gerald Simonneau, Paris/France. According to a multicenter 5-year retrospective evaluation in almost 6.000 patients and a 6-month prospective evaluation in almost 1.500 patients, serious adverse events related to RHC in patients with pulmonary hypertension are rare. The overall serious adverse event rate was 1.1%, and only four deaths were related to the catheter procedures (=0.055%; Hoeper MM et al., J Am Coll Cardiol 2006; 48: 2546–52).

The goal of acute vasoreactivity testing is to select PAH patients who might respond favorably to long-term oral vasodilator therapy (mainly calcium channel blockers). Furthermore, the test identifies patients with a better long-term prognosis. Substances used for the test are NO, adenosine, or prostacyclin. Acute response is defined as a fall in mPAP and pulmonary vascular resistance (PVR) by more than 20%, or as a fall in mPAP by more than 10mmHg, reaching a mPAP under 40mmHg and a normal cardiac output (CO) (Sitbon O et al., Circulation 2005; 111: 3105–11). Responders may be treated by high dose calcium channel blockers very successfully.

Role of biochemical markers

Biochemical markers in PAH are the BMPR2 genotype to test susceptibility for PAH (Machado RD et al., Hum Mutat

Pericardial effusion and the Tei index can also be used to monitor the treatment efficacy.

Although echo doppler results correlate with the mean pulmonary arterial pressure, there are too many false-positive or false-negative echo findings that make it difficult to rely on this method.

BNP has the most clinical utility of the currently available biochemical markers.

2006; 27: 121–32) and the brain natriuretic peptide (BNP) that is useful for staging of PAH and has some prognostic value (Nagaya N et al., Circulation 2000; 102: 865–70). A third marker is troponin, which also has some prognostic value (Torbicki A et al., Circulation 2003; 108: 844–8). Diagnostic biochemical markers or markers that are useful for screening do not exist.

According to Martin Wilkins, London/Great Britain, BNP has the most clinical utility of the currently available biochemical markers. Combinations of biomarkers are likely to be more informative than single measurements. For the development and qualification of new biomarkers, access to large and well-phenotyped populations is mandatory.

Current therapeutic standards

Although hardly mentioned in the 2004 guidelines, combination and even triple therapies have been the everyday reality for years in specialized, experienced centers, because there is a clear-cut clinical need. The recommendations of the guidelines and the clinical experience with combination therapy are summarized in this chapter.

The new German Guidelines of diagnosis and therapy of chronic pulmonary hypertension were published in 2006 and 2007 (Olschewski H et al., Pneumologie 2006; 60: 749–71; Olschewski H et al., Clin Res Cardiol 2007; 96: 301–30) and therefore include new data that were not available when the European Guidelines were published in 2004 (Galiè N et al., Eur Heart J 2004; 25: 2243–78). Furthermore, the German Guidelines address not only PAH but also the other groups of chronic pulmonary hypertension. Evidence grades and grades of recommendation in the German Guidelines and the ESC Guidelines follow the same definition (Table 2).

In patients with chronic hypoxic pulmonary hypertension the optimization of the underlying lung disease is crucial.

Regarding pulmonary hypertension in left heart disease, the German Guidelines recommend therapy of the underlying disease (revascularisation, valve operation, medical treatment with ACE inhibitors, beta blockers, etc.). Intravenous prostacyclin is contraindicated in left heart failure, emphasized Horst Olschewski, Graz/Austria. In patients with chronic hypoxic pulmonary hypertension the optimization of the underlying lung disease is crucial. If this is not sufficient, these patients may be treated like PAH patients (evidence grade: C; grade of recommendation: IIb). Patients with chronic obstructive pulmonary disease (COPD) often improve with long-term oxygen therapy (evidence grade A). Patients with chronic thromboembolic pulmonary hypertension (CTEPH) should receive anticoagulation therapy and should be evaluated for pulmonary endarterectomy. In non-operable patients, medical therapy as in PAH is recommend-ed (C, IIa).

The endothelin receptor antagonist (ERA) bosentan has received an A I recommendation for patients in NYHA class III. In contrast to the European Guidelines, the new ERAs sitaxsentan and ambrisentan have received an A I recommendation, taking the latest phase-III trials into account. The PDE-5-inhibitor sildenafil has received an A I recommendation in both guidelines. Tadalafil will be evaluated when the latest study results are published.

Regarding the prostanoids, epoprostenol has received an A I in both guidelines. Inhaled iloprost (Ventavis®) has been upgraded to A I in the German Guidelines and in the updated American Guidelines (ACCP) owing to the positive results of the STEP and the AIR 2 trials. Intravenous iloprost (Ilomedin®) has a C IIa recommendation in both the German and the European Guidelines. Treprostinil s.c. has a B IIa recommendation and oral Beraprost a B IIb recommendation.

Combination therapy was graded C IIb before the results of new trials and the first goal-oriented therapy results were published (Hoeper M et al., Eur Respir J 2005; 26: 858–63). In the next update of either guideline, combination therapy will receive a B IIa or an A I recommendation, said Olschewski.

Pharmacological aspects of combination therapy

Patients with PAH may need multiple drugs, and not only specific PAH drugs such as inhaled iloprost, sildenafil, or bosentan. It is important to know what may happen when certain drugs are combined to avoid serious toxic side effects for the patient, said Karin Fattinger, Bern/Switzerland.

Sildenafil is a cGMP-specific phosphodiesterase inhibitor with a bioavailability of 38–41%. It is metabolized mainly by the cytochrome P450 (CYP) enzymes 3A4 and 2C9. Numerous drugs inhibit the CYP3A4-mediated metabolism of other drugs. For example, if sildenafil and erythromycin are given at the same time, the plasma concentration of sildenafil is augmented by 300% (Muirhead GJ et al., Br J Clin Pharmacol 2002; 53, suppl 1: 37S–43S). This means that the physician needs to reduce the daily sildenafil dose to one third as long as the patient is being treated with erythromycin. If ritonavir is given, the sildenafil plasma concentration is augmented by 1100% (Muirhead GJ et al., Br J Clin Pharmacol 2000; 50: 99–107). A list of well-known CYP3A4-inhibitors – several antibiotics and antimycotics – can be found in Table 3.

The oral endothelin-A/B-receptor antagonist bosentan is highly protein bound and is metabolized by CYP3A4 und CYP2C9, too. As bosentan induces its own metabolism, the clearance increases twofold in the first week of treatment. If bosentan is combined with cyclosporine, the bosentan plasma concentration is augmented by 1700% (Treiber A et al., J Pharmacol Exp Ther 2004; 308: 1121–9). However, this is not due to CYP3A4 inhibition. It has been shown that bosentan is a substrate of hepatic organic anion uptake transporters (OATP). Cyclosporine inhibits OATP and thus inhibits the uptake of bosentan into the hepatocytes and its metabolism (Treiber A et al., Drug Metab Dispos 2007; 35: 1400). Furthermore, bosentan and its metabolites activate the pregnan-X-receptor (PXR; van Giersbergen PL et al., Eur J Pharmacol 2002; 450: 115–21), which leads to an up-regulation of CYP3A4 and 2B6 and other drug-metabolizing proteins. If bosentan is combined with sildenafil, the sildenafil plasma concentration is reduced by 53–69% (Paul GA et al., Br J Clin Pharmacol 2005; 60: 107–12; Fig. 4). At the same time, the bosentan plasma concentration is augmented by almost 50% (Table 4). Iloprost is metabolized mainly by β-oxidation. This means its metabolism is CYP-independent. Therefore, clinically relevant drug interactions have not been observed.

Iloprost is metabolized mainly by beta-oxidation and independent of CYP. Therefore, clinically relevant drug interactions have not been observed.

Disease management with combination therapy

Combination therapy is hardly mentioned in the 2004 guidelines for the treatment of PAH. However, in spite of

Table 2

Evidence grade	
A	Data derived from multiple randomized clinical trials or meta-analysis
B	Data derived from a randomized clinical trial or from multiple trials with heterogenous results
C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries
Grade of recommendation	
I	Evidence and/or general agreement that a given diagnostic procedure/treatment is beneficial, useful and effective
IIa	Weight of evidence/opinion is in favour of usefulness/efficacy
IIb	Usefulness/efficacy is less well established by evidence/opinion
III	Evidence or general agreement that the treatment is not useful/effective and in some cases may be harmful

Table 3

CYP3A4 inhibitors, which could influence plasma concentrations of sildenafil		
HIV antivirals		
› delaviridine	› nelfinavir	› saquinavir
› indinavir	› ritonavir	
Antibiotics		
› clarithromycin	› erythromycin	› telithromycin
Antimycotics		
› fluconazole	› ketoconazole	
› itraconazole	› voriconazole	
others		
› amiodarone	› diltiazem	› grapefruit juice
› aprepitant	› verapamil	

Table 2 › European Society of Cardiology Task Force: Definitions for evidence grade and grade of recommendation

Table 3 › CYP3A4-inhibitors (adapted from http://medicine.iupui.edu/flockhart)

The metabolization of iloprost is CYP-independent. Therefore, clinically relevant drug interactions have not been observed.

an effective monotherapy such as intravenous epoprostenol, that has received an evidence A rating, about 30% of the patients die within 2 years (Sitbon et al., Prog CV Dis 2002; 45: 115–28). The event-free survival of patients receiving an effective monotherapy is even lower, Jürgen Behr, Munich/Germany, pointed out: 29–44% after 2 years (Opitz et al., Eur Heart J 2005; 26: 1895–1902; Provencher et al., Eur Heart J 2006; 27: 589–95). Event-free, in this setting, includes that the patients are not switched to another monotherapy or to a combination therapy.

On the other hand, new data show that a goal-oriented treatment plan that starts with one effective monotherapy and adds other specific therapies as soon as the predefined treatment goals are not met, provides an overall survival of about 80% after 3 years. This is a clinically relevant improvement compared with the survival rates of historical controls.

After 3 years, 43% of the patients received a combination of two specific substances, 16% received a triple therapy (inhaled iloprost, bosentan and sildenafil) and 4% of the patients received even four substances, the fourth being intravenous iloprost (Hoeper et al., Eur Respir J 2005; 26: 858–63). This means, Behr said, that in specialized centers, combination and triple therapy has become everyday reality." There is a clinical need for combination therapy", Behr emphasized.

Studies with different combination therapies

The evidence that combination therapy is superior comes, at first, from pharmacology. It is well-known, that the chronically impaired production of vasodilatory mediators, such as nitric oxide (NO) and prostacyclin, along with the prolonged overexpression of vasoconstrictors such as endothelin-1, not only affects the vascular tone but also promotes proliferation of smooth muscle cells in the pulmonary arteries and vascular remodeling (Humbert M et al., New Engl J Med 2004; 351: 1425–36). Thus, these substances and their pathways represent logical pharmacological targets. For each of these three pathways an established specific therapy is available. Iloprost, sildenafil, and bosentan act synergistically, which explains why combination or triple therapy must be more effective than monotherapy.

Inhaled iloprost plus oral sildenafil has been studied to date in three smaller trials (Wilkens H et al., Circulation 2001; 104: 1218–22; Ghofrani HA et al., Ann Intern Med 2002; 136: 515–22; Ghofrani HA et al., J Am Coll Cardiol 2003; 42: 158–64). A long-term observational study published in 2003 examined the effects of giving additional sildenafil to 14 patients whose condition had deteriorated during the course of long-term treatment with inhaled iloprost. Idiopathic pulmonary arterial hypertension

Fig. 4

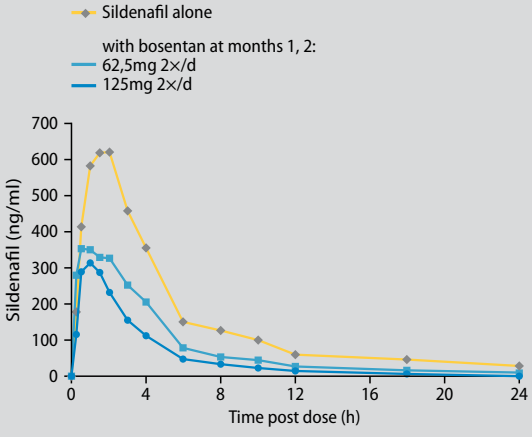


Fig. 4 › Interaction of sildenafil and bosentan (from Paul GA et al., Br J Clin Pharmacol Clin Pharmacol 2005; 60: 107–12)

Table 4

Drug	AUC of drug	AUC of bosentan
Sildenafil	– 53–69%	+ 49.8%
Simvastatin	– 34% (–46%)	no change
Cyclosporin A	– 50%*	+ 300–400% at steady-state
Glyburid	– 40%	– 29%
Warfarin	– 29% (S) to -38% (R)	NA
oral contraceptives	– 31% and –14%	

**only trough concentrations data available; data from: Paul GA et al., Br J Clin Pharmacol 2005; Dingsemanse J et al., Clin Pharmacokinet 2003; Product information Bosentan, van Giersbergen PL et al., Clin Pharmacol Ther 2002; Weber C et al., J Clin Pharamacol 1999; van Giersbergen PL et al., Int J Clin Pharmacol Ther 2006*

Table 4 › Bosentan combined with other several drugs: effect on plasma concentrations

(IPAH) was present in nine of these patients, while the other five had pulmonary hypertension associated with connective tissue disease (CTD). The combination led to an improvement in the 6-min walking distance of 90m. The effect was retained throughout the 12-month observation period (p=0.002). Other combinations, such as the combination of a prostanoid with bosentan, have been studied in smaller, uncontrolled trials, and resulted in an improvement of the 6-min walking distance of between 42.5 m and 58 m (Table 5b).

Regarding randomized controlled trials, five such trials have been performed with prostanoids (Table 5a). The combination of intravenous prostacyclin with bosentan did not show a significant effect which may be due to the small number of patients enrolled (BREATHE-2: Humbert M et al., Eur Respir J 2004; 24: 353–9). The COMBI study was terminated early as the end point could not be achieved (only 40 patients enrolled; Hoeper et al., Eur Respir J 2006; 28: 691–4).

The combination of intravenous prostacyclin with sildenafil was studied in a large trial with 265 patients and showed significant results in all clinical endpoints (PACES: Simonneau G et al., ATS 2007). The 6-min walking distance improved by 26m. The combination of inhaled iloprost with bosentan was investigated in the STEP trial and led to an improvement in the 6-min walking distance of 26 m (McLaughlin et al., Am J Resp Crit Care Med 2006; 174: 1257–63). This means that a gain of 26 m is a realistic expectation when a second drug is added, said Behr.

In the STEP study 67 PAH patients were assigned to receive either inhaled iloprost or placebo in addition to their bosentan therapy, which continued at the same dosage as before. The main aim of the trial was to evaluate the safety of the combination, thus the statistical power as well as the number of patients enrolled in the trial were set with this end point in mind. As results show, serious side effects were not more frequent under bosentan plus iloprost than under bosentan plus placebo.

The secondary end points provided clear evidence of the efficacy of the combined therapy, although the study was not powered for efficacy. Besides the improvement of 26 m in the 6-min walking test, an improvement in the NYHA functional class was seen in 34% of the patients who received iloprost but in only 6% of the placebo patients (p=0.002). Furthermore, with inhaled iloprost significant reductions in the median pulmonary artery pressure (p<0.001) and in the pulmonary vascular resistance (p<0.001) were observed. Most importantly, clinical deterioration, a very robust endpoint, was not seen in any of the iloprost patients during the 12 weeks of the trial, but was seen in 15% of the patients who had been receiving only bosentan monotherapy (p=0.02), Behr pointed out (Fig. 5).

Table 5a

Therapy	Study design	Results
PGI_2 i.v. plus Bosentan	n=33; RCT	n.s.: 6MWT, HD, WHO-FC
Bosentan plus Iloprost p.i.	n=65; RCT	6MWD: +26m TTCW improved
Bosentan plus Iloprost p.i.	n=40; RCT/OL	6MWD n.s.
PGI_2 i.v. plus Sildenafil	n=265; RCT	6MWT:+26 m, p=0.0046 HD, TTCW: improved
Bosentan plus Treprostinil p.i.	n=235; RCT	6MWT +20 m, (+14 m) secondary end points n.s.

top down: Humbert M et al., ERJ 2004; McLaughlin et al., AJRCCM 2006; Hoeper M et al., ERJ 2006; Simonneau G et al., ATS 2007; Press release

Table 5b

Therapy	Study design	Results
Prostanoid plus Bosentan	n=20; OL, uncontr.	6MWD: + 58m, VO_2max ↑
Iloprost p.i. plus Sildenafil	n=14; OL, uncontr.	6MWD: +90m
Prostanoid plus Bosentan	n=11; OL, uncontr.	6MWD: +42.5m
Treprostinil s.c. plus Sildenafil	n=9; OL, uncontr.	time on treadmill increased
Bosentan plus Treprostinil	n=25; OL, uncontr.	6MWD: +49m (trough) FC improved: 9/11 pts.

top down: Hoeper m et al., ERJ 2003; Ghofrani A et al., JACC 2003; Seyfarth et al., Chest 2005; Gomberg-Maitland et al., AJC 2005; Channik et al., JACC 2006

Tabels 5a/5b › Overview of study results with combination therapies (RCT = randomized controlled trial; OL = open label; n.s. = not significant; 6MWT = 6-min walking test; HD = hemodynamics; FC = functional class; TTCW = time to clinical worsening)

Conclusion

Monotherapies are often of transient benefit in PAH. Arguments pro combination therapy are

- the evidence of pharmacological synergism
- the synergistic effects shown in acute hemodynamic studies
- and the clinical improvement shown in several observational and some randomized studies.

Arguments contra combination therapy are the fact that small randomized controlled trials showed controversial results and that not all patients may benefit.

Since inhaled iloprost is pulmonary selective and pharmacologic drug interactions are unlikely, it is an ideal combination partner for both endothelin receptor antagonists such as bosentan and PDE-5 inhibitors such as sildenafil. Synergistic effects of iloprost-aerosol and sildenafil as well as iloprost-aerosol and bosentan have been shown in clinical trials.

It is not recommendable to withdraw a drug and switch to another, once the patient deteriorates. Whether to follow a sequential approach – i.e. to start simultaneously with one specific drug and add another in case of insufficient response or deterioration – or a first-line combination approach – i.e. to start with two specific substances – is still an ongoing discussion. However, new data coming from the open-label extension of the STEP study as well as from the PACES study support first-line combination therapy. The STEP open-label extension study shows that patients who received monotherapy plus placebo during the randomized phase had a significantly worse clinical course during the extension period than patients who had already received combination therapy during the randomized phase (Frost A et al., ATS 2007, poster 716; Fig. 6). The PACES study presents very similar data. This may implicate, Behr speculates, that the postponement of combination therapy may have negative consequences for outcome and prognosis of PAH patients.

Fig. 5

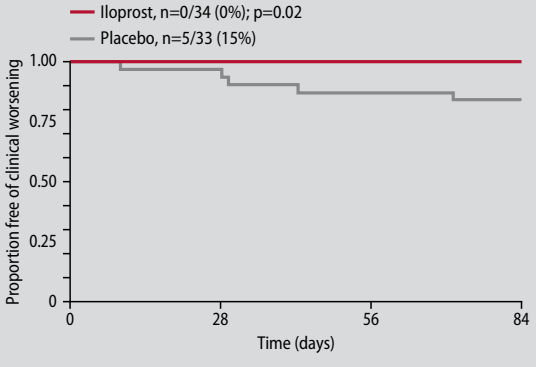


Fig. 5 › Bosentan plus Iloprost-Aerosol or Placebo – the STEP study (from McLaughlin et al., Am J Resp Crit Care Med 2006; 174: 1257–63)

Fig. 6

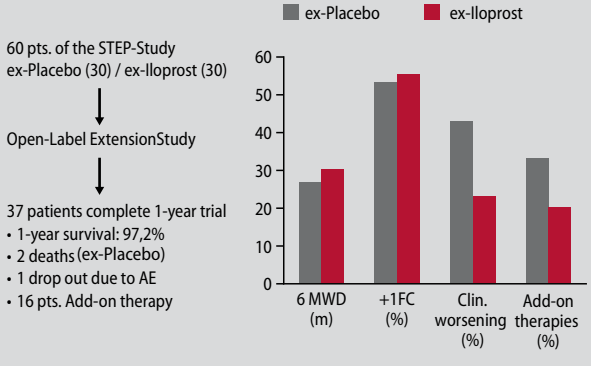


Fig. 6 › STEP study – open-label extension (from Frost A, ATS 2007, poster 716; 6 MWD = 6-min walking distance; FC = functional class)

Current view of future disease management

Current therapeutic strategies in PAH are unspecific (diuretics, oxygen, calcium channel blockers, anticoagulants) or specific. The specific treatments aim predominantly at vasodilation. New molecular mechanisms have been discovered recently that play an important role in PAH pathophysiology and may enable the development of new specific compounds that act predominantly antiproliferatively and could reverse remodeling.

Prognostic evaluation is a key factor to drive treatment decision-making and assessment of efficacy. However, a gold-standard parameter has not yet been identified, and a combination of parameters assessing symptoms, exercise capacity and pathophysiology is likely to be required, said Nazzareno Galiè, Bologna/Italy. Observational and interventional strategies need to be implemented to validate this approach.

New therapeutic approaches

The following factors play a major role in PAH: vasoconstriction, smooth muscle and endothelial cell proliferation, and thrombosis in situ. At present, one of the most challenging tasks is to develop a drug that is able to reverse the remodeling of the small pulmonary arteries. New specific agents that target the soluble guanylate cyclase (sGC) may provide this mechanism of action and also optimize vasodilation. The sGC is necessary for the production of cyclic guanosine monophosphate (cGMP; Fig. 7). A rise in cGMP results in vasodilation, anti-aggregation, anti-remodeling of vascular smooth muscle cells, and reduction of right ventricular hypertrophy, said Stefan Schaefer, Wuppertal/Germany. NO needs to bind to the iron group of sGC to stimulate the rise in cGMP. The new sGC stimulators BAY 63-2521 and BAY 41-2272 raise cGMP levels via different pathways than NO. They activate the sGC in a NO- and Fe II heme-independent manner and, if NO is present, act synergistically with NO (Stasch J-P et al., Br J Pharmacol 2002; 136: 773–83; Ghofrani A et al., Nature Rev 2006; 5: 689–702).

BAY 63-2521 and BAY 41-2272 stand for a new pharmacological principle, explained Schaefer. The target, sGC, is downregulated in PAH and is localized in the smooth muscle cells of pulmonary arteries. In the monocrotaline rat model sGC stimulation with BAY 41-2272 resulted in a significant reduction of right ventricular pressure and hypertrophy (Dumitrascu et al., Circulation 2006; 113: 286–95). In lambs with acute pulmonary hypertension inhalation of the sGC stimulator BAY 41-8543 produced selective pulmonary vasodilation (Evgenov OV et al., Am J Respir Crit Care Med 2007; 176: 1138–45). As these results are very promising, clinical trials with PAH patients have been initiated.

Another new therapeutic target is the phosphodiesterase 1 (PDE1). In the rat model PDE1 inhibition reverses pulmonary vascular remodeling (Schermuly et al., Circulation 2007; 115: 2331–9). The neutrophil elastase is a further new target which has been shown to be beneficial in animal models (Zaidi SH et al., Circulation 2002; 105: 516–21).

Anti-remodeling effects of imatinib and sorafenib

In 1998 the hypothesis was published that primary pulmonary hypertension is a (pseudo)malignant disease, because cancer-like features such as monoclonal endothelial cell proliferation in primary, but not in secondary, PAH could be demonstrated (Lee S-D et al., Am Soc Clin Invest 1998; 101: 927–34). Tyrosine kinases (TKs) are up-regulated in many cancers and stimulate an intracellular pathway that leads to increased proliferation, anti-apoptosis, migration and invasion. In PAH, the platelet-derived growth factor receptor (PDGFR) is upregulated (Schermuly RT et al., J Clin Invest 2005; 115: 2811–21), and the PDGFR antagonist imatinib, which acts via TK inhibition, was investigated in a PAH patient. Addition of imatinib to triple therapy improved the 6-min walking distance by almost 140 m (Ghofrani et al., New Engl J Med 2005; 353: 1412–3). Thus, imatinib, which acts purely in an anti-proliferative manner, appears to be the first substance to truly reverse remodeling in pulmonary arteries.

Sorafenib (Nexavar®), a multikinase inhibitor that is approved for the treatment of renal cell and hepatocellular

carcinoma, is being investigated in PAH, too. In the monocrotaline model, sorafenib reduced right ventricular pressure and hypertrophy to an even greater extent than imatinib. The muscularization of the pulmonary artery was also reduced. Furthermore, only sorafenib, but not imatinib, was able to prevent right ventricular remodeling due to pulmonary banding and reversed myocyte hypertrophy.

As Schaefer summarized, sGC stimulators, PDE1 inhibitors, and kinase inhibitors will be the future therapies of PAH that add optimized vasodilation and reverse remodeling to the current armamentarium (Fig. 8).

First clinical results with the sGC stimulator BAY 63-2521 in patients with PAH

BAY 63-2521 is an oral stimulator of the sGC. It acts independently of NO and targets the reduced form of sGC. It also enhances the sensitivity of sGC to low levels of bioavailable NO. BAY 63-2521 has shown its efficacy in experimental models of pulmonary hypertension and has shown a favorable safety profile in healthy volunteers (phase I; Dumitrascu R et al., Circulation 2006; 113: 286–95; Evgenov OV et al., Nat Rev Drug Discov 2006; 5: 755–68).

In a phase-II study safety, tolerability and pharmacokinetics of BAY 63-2521 were assessed. Secondary objectives were to investigate the impact of single ascending doses of BAY 63-2521 on pulmonary vascular resistance and mean pulmonary arterial pressure in patients with moderate-to-severe PH and to measure pulmonary and systemic hemodynamics and gas exchange parameters. Patients with PAH, chronic thromboembolic PH or interstitial lung disease associated with PH were included into the trial, explained Werner Seeger, Giessen/Germany.

No serious adverse events or clinically relevant effects on laboratory values were seen. Mild adverse events that were possibly drug-related (hot flush, dizziness, nasal congestion) were observed in three of 19 patients and all had resolved by study completion. Thus, BAY 63-2521 has a favourable safety profile, concluded Seeger. Furthermore, the new drug decreased pulmonary arterial pressure and pulmonary vascular resistance to a greater extent than did inhaled NO. At the same time, the cardiac index increased approximately by 30%. Systolic blood pressure was maintained above 110mmHg. The effects correlated closely with the plasma concentration of the drug.

In summary, BAY 63-2521 favorably influenced all major hemodynamic parameters in patients with PH in a concentration-dependent manner. The new drug showed no pulmonary selectivity and did not produce any deterioration in gas exchange, despite causing strong pulmonary vasodilation. Thus, BAY 63-2521 has a high potential as a novel therapy for PH.

Fig. 7 › Soluble guanylate cyclase – a new target in PAH

Fig. 8 › Future therapies of PAH

Fig. 7

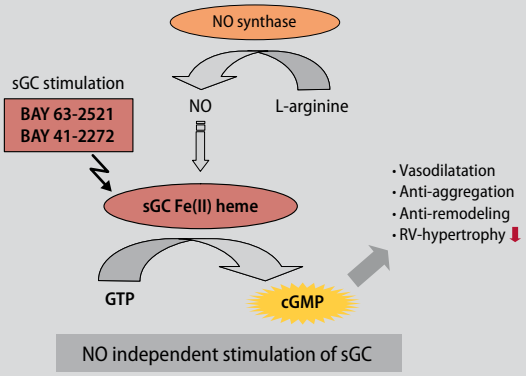
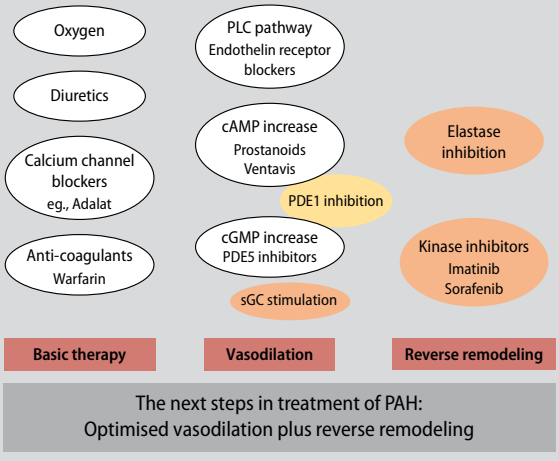


Fig. 8



Short presentation session 1
Use of iloprost in different therapeutic indications

Use in pregnancy, cardiac surgery, prevention of lung cancer, and other indications were the topics of the six short presentations that were chosen for session 1.

Iloprost in pregnant patients

The pre-existence or gestational occurrence of pulmonary hypertension (PH) is associated with a high risk of maternal death (30–50%). Therefore, patients with PH are counselled to avoid pregnancy or are offered early interruption, said David Kiely, Sheffield/UK. For some women, pulmonary arterial vasodilator therapy during pregnancy and the puerperium may improve the chances of maternal survival. A review of 13 pregnancies showed that eight patients were treated with iloprost. None of the women died, and nebulized iloprost was well-tolerated. However, presentation and natural history of PH in pregnancy is highly variable. Patients should be managed by a multidisciplinary team of specialists.

Iloprost in cardiac surgery

Patients with PH are at substantially increased risk of perioperative morbidity and mortality following cardiac surgery. Therefore, Michael Winterhalter, Hannover/Germany, conducted a prospective randomized trial with the objective of comparing the efficacy of inhaled iloprost and nitric oxide (iNO) in reducing pulmonary hypertension during cardiac surgery immediately after weaning from cardiopulmonary bypass (CPB). A total of 46 patients (mPAP > 26mmHg preoperatively at rest, after anesthesia induction, and at the end of cardiopulmonary bypass) scheduled to undergo cardiac surgery were enrolled (J Cardiothoracic Vascular Anesthesia, in press). Although both substances have a positive effect on pulmonary arterial pressure, pulmonary vascular resistance and cardiac output, the direct comparison showed that inhaled iloprost was more effective than inhaled NO. No major side effects related to iNO or iloprost were observed during the study.

Iloprost in anaesthesiologic management

Armin Sablotzki, Germany, presented the case of a 64-year-old woman with struma permagna, lung fibrosis for 15 years, and several co-morbidites. She was in NYHA class III/IV with an mPAP of 48 mmHg. If such a patient needs to undergo a surgical procedure, the perioperative mortality can reach up to 50%. The main cause of death is right heart failure.

No standard exists for the treatment of these patients. An interdisciplinary approach by a skilled staff is necessary. Regarding the anesthesiologic management, luxury oxygenation and inhalative vasodilation are general principles, and routinely administered. The inhalation of vasodilators is useable in both general and regional anesthesia and offers the advantage of selective pulmonary vasodilation and a low rate of side effects. Inhaled iloprost can be easily administered intraoperatively. It does not reduce the mean systemic arterial pressure or the coronary blood flow. The rate of non-responders is low. Intermittent administration according to the clinical need is easily possible.

Intravenous iloprost in PAH

The intravenous administration of prostanoids is recommended in all relevant global and regional treatment guidelines. Iloprost, epoprostenol, and, recently, treprostinil, are mentioned. Christian Opitz, Greifswald/Germany, presented the latest experience with the stable prostacyclin analogue iloprost, published in 2007 (Ewert R et al., Clin Res Cardiol 2007; 96: 211–7). Continuous intravenous iloprost was used to revert treatment failure (clinical decompensation to NYHA class IV) of chronic first-line inhaled iloprost therapy in patients with idiopathic PAH. Between 1997 and 2002 24 patients were enrolled in the study. After the switch, hemodynamics improved significantly. Thus, intravenous iloprost was able to recruit additional vasodilator potential. During the titration phase, headache and flush were the most common side effects.

Fig. 9

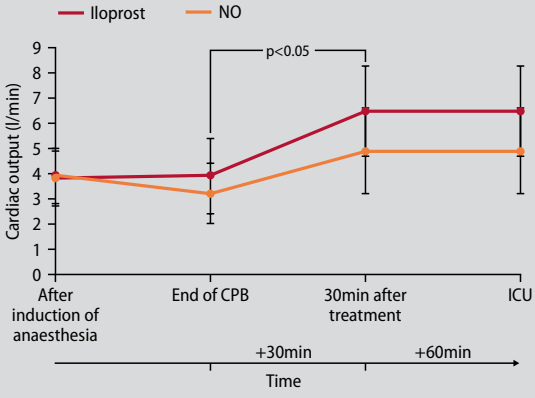


Fig. 9 › The use of inhaled iloprost compared to iNO in cardiac surgery (presented by Winterhalter)

The mean iloprost dose at the end of the titration phase was 1.6 ng/kg/min. Sixteen patients received chronic intravenous iloprost treatment. At hospital discharge, all patients were in NYHA class III. Long-term follow-up in January 2006 showed: three patients were continuing on intravenous iloprost therapy, seven had undergone transplantation, three had died, and two had been switched to a combination therapy. It was concluded that chronic therapy is well-tolerated by most patients.

Opitz summarized that i.v. iloprost can be used as an initial therapy to switch severely ill patients with treatment failure. Compared with other prostacyclins, iloprost shows comparable efficacy with an advantageous drug profile.

Iloprost for prevention of lung cancer

Chemoprevention studies may lead the way to a new paradigm in lung cancer. According to Robert Keith, University of Colorado/USA, it has been proven that prostacyclin (PGI_2) acts in an anti-metastatic way. Single administration of PGI_2 inhibits metastasis to both liver and lung (Honn, Science 1981). The survival curve depends on the PGI_2 expression (Stearman RS et al., Am J Pathology 2005; 167: 1763). New data showing that prostacyclin prevents pulmonary endothelial cell apoptosis induced by cigarette smoke have been published recently (Nana-Sinkam SP et al., Am J Respir Crit Care Med 2007; 175: 676–85).

In subjects at high risk for lung cancer, a randomized phase-II chemoprevention study is under way. The patients receive either oral iloprost or placebo. The main aim of the study is to determine whether oral iloprost can reverse premalignant histological changes in the bronchial epithelium. Recruitment was supposed to be finished by December 2007 (goal: 152 patients), and the final bronchoscopies will be done by mid of 2008.

The use of intravenous iloprost in the treatment of Buerger' s disease

Buerger' s disease is defined as a vasculitis affecting mainly small and medium-sized arteries of the limbs. Buerger' s disease is more common in Asia than in the Western world, said Kürsat Bozkurt, Istanbul/Turkey. The diagnosis is made in about 10% of patients with peripheral arterial disease, and major or minor amputations are necessary in 27% of cases (Bozkurt AK et al., Vascular 2004; 12: 192–7). The main aims of conservative treatment are the avoidance of amputation and the relief from pain. Absolute abstinence from smoking is crucial for therapeutic success at any stage of the disease, emphasized Bozkurt.

Since 2003, iloprost is available and reimbursed in Turkey. In a randomized study with 200 patients from 12 major centers, the efficacy of iloprost was investigated and compared with the results obtained with lumbar sympathectomy. Iloprost was administered at 1 ng/kg/min over 6 h for 28 days. Complete healing rate, reduction of ulcer size and use of analgetics was better after 4 weeks of iloprost treatment compared with sympathectomy. After 24 weeks, the results obtained with intravenous iloprost were still significantly better than those obtained with sympathectomy (Bozkurt AK et al., Int Angiol 2006; 25: 162–8). Thus, in the Turkish Guidelines for Buerger´s disease, iloprost infusion is recommended as the superior treatment option.

Short presentation session 2
Experience with long-term treatment

The experience with long-term treatment and long-term efficacy of specific PAH drugs was addressed in the second session of short presentations.

Current data of the German Heart Center show that iloprost and/or bosentan are effective as a bridge-to-transplant therapy for patients with end-stage IPAH, said S. Hörnig, Berlin/Germany. Survival of patients on the transplantation list does not depend on vasoreactivity to iloprost. Therefore, iloprost should be given to all listed patients. However, despite the effectiveness of iloprost in end-stage idiopathic PAH, mortality on the transplantation list remains high, and transplantation appears to be more promising for survival than medical therapy. Therapy with iloprost should be started very soon after diagnosis to avoid progression to right heart failure, which is unpredictable and often develops rapidly. Iloprost treatment (alone or with bosentan) before transplantation has no impact on patients' survival after transplantation (Dandel M et al., J Heart and Lung Transpl 2007; 26: 898–906).

Patients with chronic thromboembolic PH

For patients with chronic thromboembolic pulmonary hypertension (CTEPH) pulmonary endarterectomy (PEA) is an efficient and potentially curative therapy. In most of these patients, symptomatic and hemodynamic improvements after PEA are persistent, although there are no controlled randomized trials proving this, said E. Mayer, Mainz/Germany. The operative risk is acceptable. The early results are excellent (dramatic improvement of exercise capacity), and the late results are good: improved quality of life and increased life expectancy (Mayer E et al., Ann Thorac Surg 1996; Matsuda H et al., Ann Thorac Surg 2006; 82: 1338–43). As operability is not clearly defined, the indication for surgery needs to be evaluated by an experienced interdisciplinary team.

Regarding medical treatment, short-term randomized studies and (uncontrolled) long-term studies have shown that specific medical treatment can be useful for pre- and perioperative improvement of hemodynamics, as well as for inoperable patients and patients with residual or recurrent pulmonary hypertension after PEA. However, although there have been no controlled studies, surgery remains the standard therapy for patients with CTEPH.

Patients with systemic sclerosis

PAH is a severe complication in connective tissue disease and the cause of death in 25–50% of these patients. Raynaud' s phenomenon (RP) is the first sign of vasculopathy and can be treated with intravenous iloprost (evidence level A). Intravenous iloprost is the only drug for the treatment of digital ulcers that received the evidence level A, that is, because its effectiveness was proven in two trials (Riemekasten et al., Rheumatology 2006; 45, suppl 3: iii49–iii51). According to the long-term experience from the Charité University Hospital, intravenous iloprost is also indicated for the prevention of digital ulcers and helpful in severe RP with trophic changes, as well as in RP refractory to other treatments and in patients with high disease burden, explained Gabriela Riemekasten, Berlin/Germany. In patients with systemic sclerosis receiving several iloprost courses long-term stability of lung function parameters and anti-

Fig. 10

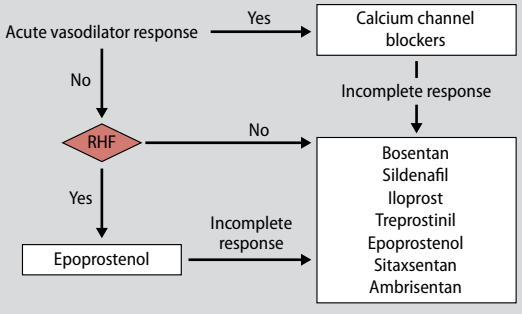


Fig. 10 › PAH paediatric treatment algorithm (adapted from Rashid A and Ivy DD, Arch Dis Child 2005: 92–9; RHF = Right Heart Failure)

Fig. 11

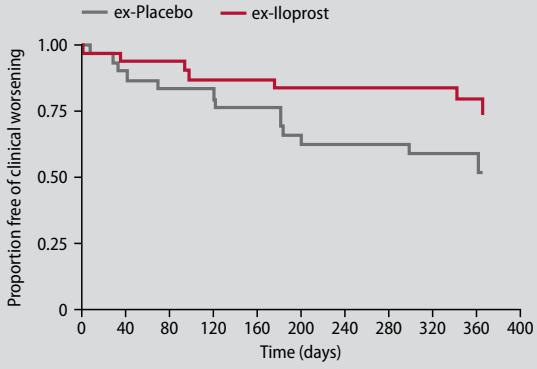


Fig. 11 › Open label extension of the STEP study: time to clinical worsening (Frost A, ATS 2007; poster 716)

fibrotic effects are observed. This supports the hypothesis that long-term use of iloprost may prevent PAH and other symptoms in patients with connective tissue disease.

Long-term experience with pediatric patients

In pediatric patients with PAH, treatment is based on adult experience and algorithm (Fig. 10). Response in the vasoreactivity test is more often seen in children than in adults, but pediatric responders must be monitored closely to ensure that they continue to be responders, emphasized Maurice Beghetti, Geneva/Switzerland. If the response is incomplete, specific treatment is mandatory. Most children with PAH need early combination and even triple therapy. "Some of our patients have a rapidly progressing disease", said Beghetti, "therefore treatment must be very aggressive, although there are no randomized data to support this."

A retrospective case review of 22 pediatric patients at five PAH centers showed that the addition of inhaled iloprost to a specific oral therapy (because of an inadequate response) or switching from intravenous PGI2 to inhaled iloprost is safe and well tolerated and efficacious in some patients. However some patients still deteriorate on inhaled iloprost and should be closely monitored (Ivy D et al., J Am Coll Cardiol, accepted). Acute inhalation of iloprost was as effective as inhaled NO in lowering mPAP and PVR.

Long-term data from the STEP trial

The STEP trial showed that the combination of inhaled iloprost and bosentan is superior to bosentan plus placebo. The composite AIR-study endpoint was achieved by 25% of the iloprost patients but by none of the patients in the placebo group (p=0.002). During the open-label extension phase, all patients received iloprost. Patients, who had already received iloprost in the double-blind phase demonstrated fewer and later clinical deteriorations than the ex-placebo patients (Fig. 11). Furthermore, a disconnect between hemodynamics and the 6-min walking distance on the one hand and survival on the other hand became obvious. These results support early onset of combination therapy and the use of hard clinical endpoints instead of surrogate parameters in future clinical trials, concluded Adaani Frost, Houston/USA.

ILOPROST for inhalation
UPDATE

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