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## 261. Treatment of human pulmonary hypertension

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**P2280****Experience with inhaled iloprost in paediatric pulmonary arterial hypertension**

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**Background:** Inhaled iloprost has been approved for the treatment of Pulmonary Arterial Hypertension (PAH) in adults, but there are few studies about its effects in children.

**Objectives:** To review long-term effects and outcomes of inhaled iloprost treatment in children with PAH.

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**Methods:** Retrospective review of clinical and haemodynamic evolution in children with PAH after inhaled iloprost therapy.

**Results:** Between 2000-2010 25 patients with PAH were treated with inhaled iloprost (17 female; range 3 months to 12-years-old): 11 idiopathic, 1 pulmonary veno-occlusive disease, 4 associated with congenital heart disease, 7 lung disease, 1 schistosomiasis and 1 congenital metabolic disease. Clinical and haemodynamic parameters at baseline were: WHO class II in 3, III in 16, IV in 6, and median of mean pulmonary arterial pressure 56 mmHg (range 29-90 mmHg). Iloprost was started as initial therapy in 14 patients: 8 as monotherapy and 6 as combined treatment, and in 11 cases was added during the follow-up. Mean dose was 50 µg/day. Median follow-up was 3.6 years (range 1 month to 10 years). There were no serious side effects but facial flushing was often observed in those using a mask. During the follow-up iloprost was discontinued in 1 patient due to abdominal pain, 1 patient was lost, 12 patients improved their functional class, 3 remained stable, 3 received a lung transplant, 1 a heart-lung transplant and 4 died.

**Conclusions:** Inhaled iloprost is well tolerated in children, both as monotherapy and as a combined treatment, with minimal side effects. Although uncontrolled, data suggest long-term clinical benefit from continued therapy in 60% of patients.

## P2281

### Sildenafil (SIL) reduces serum creatinine (SCr) in patients with pulmonary arterial hypertension (PAH): Relationship to clinical outcomes

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**Purpose:** Elevated SCr associates with poor outcome in PAH. We retrospectively analyzed the effect of SIL on SCr in PAH patients (pts) from SUPER-1 and -2 studies. SCr relationships with 6-min walk distance (6MWD), functional class (FC), time to clinical worsening (TTCW), and survival were examined.

**Methods:** PAH pts received placebo (PBO) or SIL 20, 40, or 80 mg TID in SUPER-1 and open-label SIL titrated to 80 mg TID (as tolerated) in SUPER-2. SCr, 6MWD, FC, and TTCW were assessed at baseline (BL) and wk 12 in SUPER-1; survival was tracked for 3 y in SUPER-2. Analysis of covariance (treatment as a factor; BL value as covariate) assessed SCr change from BL to wk 12 (posthoc). Relationships between SCr and  $\geq 10\%$  6MWD increase and  $\geq 1$ -class FC improvement (using logistic regression) and TTCW and survival (Cox regression) were assessed.

**Results:** BL characteristics were similar among groups (N=277); PAH was mostly idiopathic (63%) and FC II (39%) or III (58%). SCr increased at wk 12 vs BL with PBO (0.032 mg/dL) and decreased with SIL (-0.001, -0.035, and -0.048 mg/dL for 20, 40, and 80 mg TID, respectively); the difference vs PBO with 80 mg TID was significant ( $P=0.032$ ). SCr reduction was associated with improved 6MWD (OR 4.74; 95% CI, 1.07-21.05;  $P=0.04$ ) and FC (OR 6.64; 95% CI, 1.37-32.16;  $P=0.019$ ). Pts with higher SCr had higher risk of worsening (HR 44.38; 95% CI, 6.67-295.32;  $P<0.0001$ ) and a trend toward higher risk of mortality (HR 2.62; 95% CI, 0.22-30.55;  $P=0.44$ ).

**Conclusion:** In posthoc analysis, sildenafil dose-dependently decreased SCr in PAH pts; reduced SCr was associated with improved 6MWD and FC and reduced risk of clinical worsening.

## P2282

### Epoprostenol with expanded stability has the same pharmacokinetic and hemodynamic profiles as epoprostenol in healthy subjects

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Pharmacokinetics (PK) and hemodynamics of two formulations of epoprostenol sodium for injection, epoprostenol with expanded stability (EPO-ES, Veleti<sup>®</sup>) and epoprostenol (EPO, Flolan<sup>®</sup>), were compared in an open-label, crossover, ascending-dose study in healthy males. Subjects received sequential, 2-hour (h) infusions of EPO-ES or EPO at 2, 4, 6 and 8 ng/kg/min. Due to the short half-life (t<sub>1/2</sub>) of epoprostenol sodium, plasma PK were assessed via the concentration versus time profiles of two primary metabolites, 6-keto-prostaglandin F<sub>1α</sub> (kPF) and 6,15-diketo-13,14-dihydro-prostaglandin F<sub>1α</sub> (ddPF). Plasma concentration-versus-time profiles of EPO-ES and EPO with regard to kPF and ddPF were superimposable. Levels of kPF and ddPF 2h after the end of each infusion were comparable. Geometric means of the total area under the curve (AUC<sub>0-∞</sub>) for kPF, were 2021 and 1972 pg·h/mL (90% CI of geometric mean ratio (GMR): 97, 107), and 665 and 654 pg·h/mL (90% CI of GMR: 94, 111) for ddPF following administration of EPO-ES and EPO, respectively. Similar changes in hemodynamic variables were observed during EPO-ES and EPO infusion. Average maximum increases from baseline were approximately 30% in both cardiac output and cardiac index with either formulation, and 19% and 27% in heart rate for EPO-ES and EPO, respectively. Both formulations had comparable treatment-emergent adverse event (TEAE) profiles. Headache was the most common TEAE reported. Overall, EPO-ES and EPO have the same PK, hemodynamic, safety, and tolerability profiles.

## P2283

### Switch from sitaxentan to another ERA in PAH: Single center short term safety observations

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**Background & aims:** In December 2010 the Endothelin Receptor Antagonist (ERA) Sitaxentan (SIT) has been withdrawn from the market. Therefore patients with pulmonary arterial hypertension (PAH) had to be switched to other PAH-therapies. There are differences in the side effect-profile of the ERAs Ambrisentan (AMB), Bosentan (BOS) and SIT including drug interactions. We describe the short term safety in PAH-patients at our center who were switched from SIT to another ERA.

**Methods:** All patients switched from SIT to AMB or BOS for more than 4 weeks were included. We collected liver function tests (LFT), INR, WHO functional class (FC) and new side effects.

**Results:** Patients on SIT (n=16) were seen 13 days (4-32) after the withdrawal notification. Mean duration of SIT therapy was 478 days (93-2332). Patients were switched to AMB (n=10) or BOS (n=6) on the basis of personal experience and expected side effects. Mean follow-up was 41 days.

LFTs under SIT were all within the normal range and remained normal in all but one patient who had ALAT increase from 13 to 242 U/l on BOS, normalizing after BOS cessation. The WHO FC did not change in any patient. Three patients complained about new or worsening peripheral edema, 2 on AMB and 1 on BOS. In 4 out of 12 patients receiving oral anticoagulation who were in therapeutic range under SIT, the INR dropped below 2 after switch to AMB (1) or BOS (3). One patient died suddenly 10 days after switch to BOS.

**Conclusion:** PAH-patients who are switched from SIT to another ERA can experience in part serious safety problems and should be closely monitored.

## P2284

### Double combination therapy in patients with pulmonary arterial hypertension associated with congenital heart defects

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**Purpose:** Patients with pulmonary arterial hypertension associated with congenital heart defects (PAH-CHD) are currently treated with targeted therapy. According to recent guidelines PAH-CHD patients with inadequate clinical response should also be treated with combination therapy (CT). We assessed the effects of double CT in a group of PAH-CHD patients.

**Methods:** In the last 6 years, 43 adult patients with PAH-CHD (age 43±14 ys, 65% females) already treated with monotherapy were included. Twenty-nine were treated with bosentan (125 mg bid) and 14 were treated with sildenafil (20 or 25 mg tid). Twelve patients had a ventricular septal defect, 5 patients had an atrial septal defect, 5 had a patent ductus arteriosus, 8 had combined defects, and 13 had corrected defects. At baseline and after CT (with sildenafil or bosentan according with the first-line treatment) 6-minute walk test (6MWT) and right-heart catheterization were performed.

**Results:** One patient did not perform 6MWT and another one did not undergo RHC after combination therapy. The table shows the haemodynamic and functional changes after a mean treatment period of 4.8±2.1 months of CT.

	mPAP (mmHg)	mBP (mmHg)	Qpi (L/min/m <sup>2</sup> )	PVR (WU)	SaO <sub>2</sub> (%)	6MWT (m)
B	81±24	86±17	2.5±0.9	24±19	89±8	422±101
CT	75±21	85±14	2.8±1.1	19±17	90±7	457±92
p	0.002	0.6	0.013	0.003	0.2	0.003

mPAP, mean pulmonary arterial pressure; mBP, mean blood pressure; Qpi, pulmonary cardiac index; PVR, pulmonary vascular resistance; SaO<sub>2</sub>, systemic artery oxygen saturation.

**Conclusions:** CT improves exercise capacity and hemodynamics in patients with PAH-CHD already on monotherapy. Sequential CT appears to be an appropriate approach also in patients with PAH-CHD.

## P2285

### ACE2 activation improves pulmonary endothelial function and attenuates monocrotaline-induced pulmonary hypertension

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Angiotensin converting enzyme 2 (ACE2), a member of the vasoprotective axis of the renin angiotensin system, protects the lungs against acute lung injury and pulmonary hypertension. The present study was undertaken to test the hypothesis that activation of endogenous ACE2 by diminazene aceturate (DIZE), a putative ACE2 activator would prevent and reverse monocrotaline (MCT)-induced pulmonary hypertension. In the prevention protocol, DIZE was administered at the same time as MCT, while for the reversal protocol DIZE was injected after 3 weeks of MCT

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administration. A single subcutaneous injection of MCT (50mg/kg) resulted in elevated right ventricular systolic pressure (RVSP) associated with the development of right ventricular hypertrophy (RVH). DIZE administration (15mg/kg per day s.c.) significantly prevented increases in RVSP (Control: 31±3 mmHg; MCT: 57±7 mmHg; MCT+DIZE: 41±4 mmHg; n=5-8; p<0.05) and attenuated RVH (Control: 0.23±0.004 mmHg; MCT: 0.43±0.03 mmHg; MCT+DIZE: 0.26±0.01 mmHg; n=5-8; p<0.05). In subsequent studies, we observed a 63% decrease in acetylcholine-induced vasorelaxation of the pulmonary arteries from MCT challenged rats. DIZE treatment resulted in 50% improvement in acetylcholine-induced vasorelaxation, signifying better pulmonary endothelial function. Furthermore, DIZE treatment reversed MCT-induced increases in RVSP (Control: 33±2 mmHg; MCT: 78±6 mmHg; MCT+DIZE: 56±5 mmHg; n=7-11; p<0.05) and RVH (Control: 0.24±0.002 mmHg; MCT: 0.54±0.02 mmHg; MCT+DIZE: 0.44±0.03 mmHg; n=7-11; p<0.05). These data suggest that DIZE's primary protective effects are mediated by ACE2 activation, though other off-target effects may also contribute.

#### P2286

##### Effect of treatment on exercise endurance tolerance and ventilatory efficiency in patients with pulmonary arterial hypertension (PAH)

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Incremental CardioPulmonaryExercise Test (CPET) or 6-Minute Walking Test, (6'MWT) are utilized for the evaluation of Pulmonary Arterial Hypertension (PAH) patients (pts), although the parameters obtained (e.g. peak oxygen uptake -V'O<sub>2</sub>Peak - and walking distance, respectively) have a different predictive value, depending on outcomes of interest (e.g. prognosis, response to therapy). We evaluated the effect of treatment on principal indexes obtained during CPET, constant work rate test on cycle ergometer (CWR) (e.g. endurance time, TLim), and 6'MWT. **Methods:** Nine naïve PAH pts (age 41±15 SD years; mean PAP 51±13 SD mmHg) underwent, before (PRE) and after (POST) treatment, CPET, CWR (80% max work load at PRE-CPET) and 6'MWT. V'O<sub>2</sub>, CO<sub>2</sub> output (V'CO<sub>2</sub>), ventilation (V'E), heart rate (HR) and other derived parameters (V'E/V'CO<sub>2</sub>) were measured breath-by-breath (Quark b2, COSMED, Rome, Italy); PRE- and POST- values at peak and at isotime were compared (paired t-test). **Results:** During CWR, POST-TLim resulted significantly longer than PRE-TLim (POST-TLim 11'24"± 6'07" vs PRE-TLim 5'38"±3'03", p<0.02) and POST-V'E/V'CO<sub>2</sub> at peak and at isotime was significantly lower compared to PRE-value at peak (p<0.01 and p<0.02 respectively). During CPET, POST-V'O<sub>2</sub>Peak was not significantly higher than PRE-V'O<sub>2</sub>Peak (p=0.06). POST 6'MWT distance resulted significantly higher than PRE-one (p<0.03). **Conclusions:** The better POST-treatment exercise tolerance in PAH pts seems to be linked to a ventilatory efficiency improvement, and the parameters obtained at CWR and 6'MWT, compared to CPET, appear to be more sensible to the effect of medical treatment.

#### P2287

##### Improved survival in medically-treated chronic thromboembolic pulmonary hypertension

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**Background:** Although the key for the successful treatment of patients with chronic thromboembolic pulmonary hypertension (CTEPH) is pulmonary endarterectomy (PEA), the patients who are not indicated for surgical intervention and/or have comorbidities must therefore be medically treated. Recent new medical therapies (newTx), such as bosentan and sildenafil, may thus be able to improve the outcome of Japanese patients with CTEPH.

**Purpose:** To clarify the improved survival in CTEPH cases administered new Tx. **Methods:** Between 1986 and 2010, 202 patients were diagnosed to have CTEPH at Chiba University Hospital. Ninety-nine patients underwent PEA, while 103 patients were medically treated. 56.5% of the patients diagnosed from 2005-2010 were treated by new Tx., 19.4% of those from 1999-2004, and 8.7% of those from 1986-1998 (p<0.0001). We investigated the long-term survival from the diagnosis and prognostic factors in medically-treated CTEPH cases and also examined survival from the initiation of the new Tx. **Results:** The patients diagnosed from 2005-2010 showed a significantly improved survival (5-year survival: 87.8%) compared with those from 1999-2004 (72.2%) and from 1986-1998 (56.5%) (p=0.02). The 5-year survival from the initiation of bosentan (n=15) and sildenafil (n=24) was 90.0%, 84.2%, respectively. A multivariate analysis revealed a lower pulmonary vascular resistance (p<0.0001), no comorbidities (p=0.0009), a peripheral type (p=0.02), and recent patients (p=0.02) to be significantly better prognostic factors.

**Conclusion:** The survival in medically treated CTEPH cases was found to have improved due to the administration of new medical therapies.

#### P2288

##### Biphasic cuirass ventilation decreased the indices of pulmonary circulation in patients with secondary pulmonary hypertension

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**Introduction:** Biphasic cuirass ventilation (BCV) is a non-invasive extrathoracic positive/negative pressure mechanical ventilation. We reported BCV decreased pulmonary artery pressure (PAP) in patients with secondary pulmonary hypertension (PH) due to chronic respiratory failure (CRF). In this study, we investigated the effect of BCV on pulmonary circulation to seek the mechanism of decreasing PAP.

**Methods:** Fifteen steady-state PH caused by CRF patients were included. None were given vasodilator and nor diagnosed dehydration. PH was defined as mean PAP (mPAP) >20mmHg determined by right heart catheterization (RHC). Control mode was applied in combination with negative/positive pressure between -15 and -25cmH<sub>2</sub>O/3 and 10cmH<sub>2</sub>O. BCV was performed 1 hour/day for 2 week not to exhaust the patients. Data from RHC, the serum levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP) and noradrenalin were obtained before and after the trial of BCV. Patients were interviewed the comfort around BCV. Data were analyzed by the Wilcoxon test p<0.05 was considered statistically significant.

**Results:** mPAP, pulmonary artery occlusion pressure and cardiac index decreased significantly (27.3 to 23.1 mmHg, p=0.004, 13.9 to 9.4 mmHg, p=0.018, and 2.72 to 2.44 l/min/m<sup>2</sup>, P=0.035, respectively) without the increase in pulmonary vascular resistance index. NT-proBNP significantly decreased (240.6 to 110.4 pg/ml, p=0.025, respectively), but noradrenalin didn't change. Eleven patients (73%) answered comfortable during and after BCV.

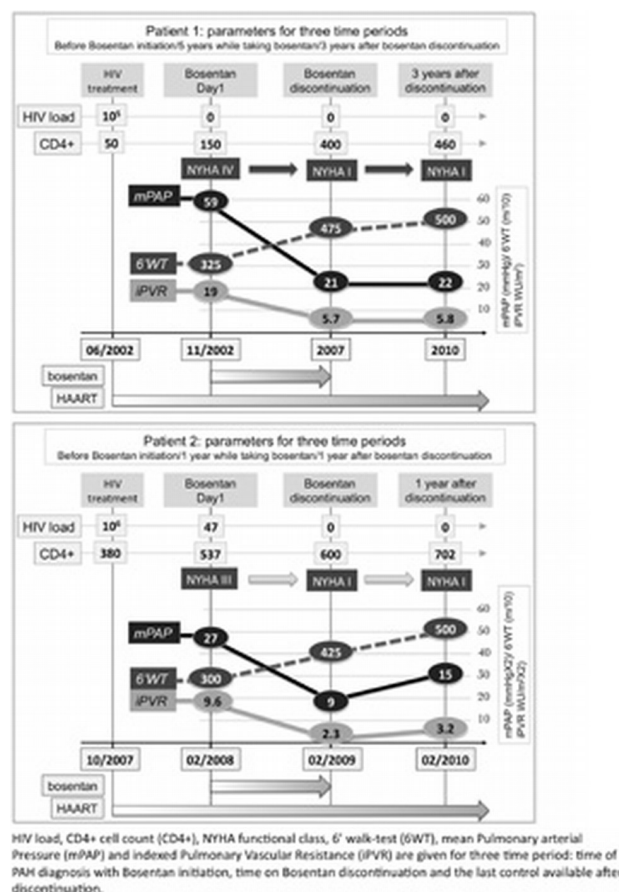
**Conclusions:** The results suggest BCV decreases cardiac load in these patients. Further studies are needed to assess the clinical and physiological effects of BCV.

#### P2289

##### Cure pulmonary arterial hypertension associated with HIV (PAH-HIV)? ... Toward an answer

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PAH-HIV is a severe condition associated with HIV infection. Guidelines propose





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to associate a specific PAH treatment with a highly active anti-retroviral therapy (HAART).

Recent studies report some excellent response to Bosentan treatment, with hemodynamic normalization and long term benefit of this treatment. But, there is no data upon specific treatment discontinuation

We report here two patients with persistent remission after Bosentan cessation. Patients were women, IV drugs users, one of African origin 36-years old, the other Caucasian of 46-years old. Diagnosis of PH was performed respectively one year and twenty years after diagnosis of HIV infection. Both patients received HAART and Bosentan.

Because of persistent normalization of hemodynamic and functional parameters, bosentan was withdrawn respectively 5 and 1 years after beginning. Both patients remain asymptomatic with normal hemodynamic results respectively at 42 and 12 months after bosentan discontinuation.

Data are illustrated on figure for both patients.

**Conclusion:** We propose herein to go one step further in PAH treatment with these two cases of cured PAH-HIV, despite more than three years of Bosentan discontinuation. But we recommended not stopping treatment without complete clinical, hemodynamic and immunological persistent normalization during at least one year.

## P2290

### Effects of BAY 41-8543 and sildenafil on right heart structure and function in pulmonary artery banded mice

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**Background:** Right ventricular (RV) pressure overload causes RV remodeling. Impaired NO/cGMP signaling is involved in the pathogenesis of LV hypertrophy. We assessed the effects of the soluble guanylate cyclase (sGC) stimulator BAY 41-8543, the PDE5 inhibitor sildenafil, and combination treatment on RV function and RVH in an animal model of chronic pressure-overload.

**Methods:** RVH was induced by pulmonary artery banding (PAB) in mice. Treatment started 7 days after surgery for 14 days, after which RV morphology and function were studied using Magnetic Resonance Imaging. Fibrosis was assessed by histology.

**Results:** PAB led to RV dysfunction (decreased RV stroke volume (40.5 vs. 23.0ml [Sham vs. PAB]) and decreased RV ejection fraction (70.0 vs. 43.0%). Treatment with sildenafil did not change RV function, whilst BAY 41-8543 and combination treatment led to significant improvements (RV stroke volume: 23.0 vs. 27.3 vs. 32.1 vs. 31.8; RV ejection fraction: 43.3 vs. 54.1 vs. 55.7 vs. 63.8 [all values as%; placebo vs. sildenafil vs. BAY 41-8543 vs. combination treatment]). PAB mice showed an increased RV/(LV+S) ratio (0.25 vs. 0.39). Drug treatment had no effects on RV/(LV+S) ratio. PAB mice displayed an increased collagen content; sildenafil had no effects on collagen content, whereas BAY 41-8543 and combination treatment both decreased collagen content (7.6 vs. 1.2 vs. 8.8 vs. 3.3 vs. 3.3 [all values as%; placebo vs. sham vs. sildenafil vs. BAY 41-8543 vs. combination treatment]).

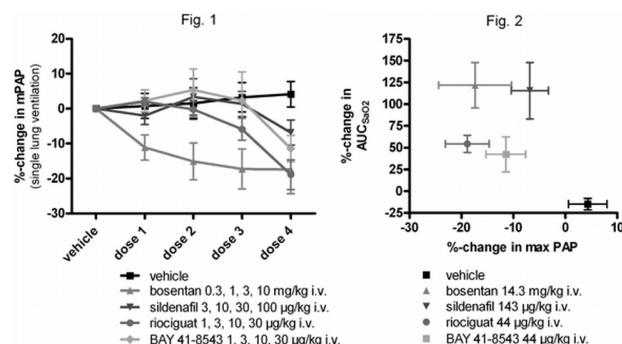
**Conclusions:** Even though none of the treatments led to significant changes in RV mass, BAY 41-8543 and combination treatment significantly improved RV function, accompanied by decreased fibrosis.

## P2291

### Comparison of different vasodilators in a model of secondary pulmonary hypertension (PH): Desaturation effects

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Approved therapies for arterial PH when applied in secondary forms can cause desaturation. Therefore we established an animal model to evaluate PH-therapeutics



under experimental conditions of heterogeneous lung injury in respect to oxygenation.

Single-lung ventilation was induced in minipigs (4-5 kg BW). Hemodynamics (e.g. mean pulmonary artery pressure (mPAP), blood pressure (BP)) and arterial hemoglobin saturation (SaO<sub>2</sub>) were monitored. We compared 5 groups (n=6 each): vehicle control, the endothelin antagonist bosentan, the PDE5 inhibitor sildenafil, and the sGC stimulators BAY 41-8543 and riociguat. Cumulative doses were applied before successive unilateral ventilation, chosen to achieve equal BP reduction. Effects on desaturation (area under the SaO<sub>2</sub> curve, AUC<sub>SaO2</sub>) and mPAP during single-lung ventilation were compared to vehicle.

Single-lung ventilation resulted in transient increases in mPAP and desaturation. The vasodilators were compared in respect to their ability to decrease mPAP and the unwanted increase in AUC<sub>SaO2</sub>. All drugs dose-dependently decreased mPAP (Fig. 1) and increased AUC<sub>SaO2</sub>. Maximal changes in both parameters are shown in Fig. 2 (mean±SEM, n=6).

The sGC stimulators and bosentan effectively reduced mPAP; the sGC stimulators caused less desaturation. Future investigations will have to confirm these findings in patients.

## P2292

### Optimization of tissue targeting properties of macitentan, a new dual endothelin receptor antagonist, improves its efficacy in a rat model of pulmonary fibrosis associated with pulmonary arterial hypertension

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**Introduction:** We investigated the efficacy of macitentan, a new tissue targeting dual endothelin (ET) receptor antagonist, in a model of pulmonary fibrosis associated with pulmonary hypertension and compared it with dual ET receptor antagonist, bosentan.

**Methods and results:** Oral administration of macitentan for 19 days dose-dependently decreased lung hydroxyproline content with a statistically significant effect observed at 30 and 100 mg/kg/day vs. non-treated bleomycin rats (n = 8-12). Overall, macitentan (100 mg/kg/d) consistently inhibited the development of pulmonary fibrosis by 18-27% in three independent studies and decreased right ventricle hypertrophy by 25-28% in two of these three studies. In contrast, bosentan (300 mg/kg/d) inhibited the development of pulmonary fibrosis in only one of the three experiments, by 23%, and had no effect on the development of right ventricle hypertrophy. Administration of radiolabeled 14C-macitentan or 14C-bosentan to bleomycin-treated rats showed greater drug distribution in the lung compared to the distribution in healthy animals. Notably, distribution of macitentan into the parenchyma of bleomycin-treated rats was greater than that of bosentan.

**Conclusion:** Repeated experiments demonstrated that macitentan is more efficacious than bosentan in preventing the development of lung fibrosis and right ventricle hypertrophy. Greater ability of macitentan to distribute into the tissue could explain its improved efficacy profile, as it would achieve a more complete blockade of ET receptors.

## P2293

### First and second line treatment pattern among pulmonary hypertension patients enrolled in a managed care health plan

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**Purpose:** To describe first and second line treatment pattern among PH patients enrolled in managed care health plan.

**Methods:** Data were derived from the MarketScan claims database. PH patients were identified anytime during 4/1/2006 to 3/31/2009 using the ICD-9 claim of 416.X. First line therapy was defined as the first PH-related pharmacy claim within ±12 months of the diagnosis claim. Second line treatment was defined as separate PH-related pharmacy claim post the first line PH-related pharmacy claim. PH-related treatment included prescriptions for high-dose calcium channel blockers (CCBs), endothelin receptor antagonists (ERAs), phosphodiesterase type 5 inhibitors (PDE5s), or prostacyclin analogues (PAs). CCB users had no diagnosis claim of essential hypertension anytime during the study period.

**Results:** Final study sample was 2,252, with a mean age of 61.2 years (SD±16.41), and 57% females. 46% of PH-patients had CCB as the first line treatment followed by PDE5s (38%), ERAs (13%), and PAs (3%). 16% of the sample had some second line treatment over a 12-month follow-up. Combination therapy was only observed in the CCB-cohort, where 39 patients added an ERA/PDE5/PA to their current treatment. Switching was most common among ERA (61%) and PA (50%) first line users, with majority switching to PDE5. Total average treatment days for first-line PH-prescription varied from a low of 21 (SD=81.44) days among PA-users to 266 (SD=131.39) among ERA-users, respectively.

**Conclusions:** CCBs and PDE5 were the most prescribed first line treatment among PH-patients. Future research would need to explore the choice of first line treatment on clinical and economic outcomes.

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## P2294

**Pulmonary hypertension in patients treated with Src/Abl kinase inhibitor dasatinib**

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**Background:** Cases of severe pulmonary hypertension (PH) have been reported in chronic myelogenous leukemia (CML) patients treated with Src/ABL tyrosine kinase inhibitor dasatinib.

**Methods:** The present report summarizes the clinical characteristics and outcomes of dasatinib-associated PH cases from the French PH Registry.

**Results:** Between 1st January 2008 and 30th September 2010, 11 patients with either a diagnosis of CML and/or a treatment with imatinib, dasatinib or nilotinib were identified corresponding to 2 prevalent imatinib-treated CML patients previously reported by our group and who developed PH prior to treatment with imatinib (Souza et al, Thorax 2006;61:736) and 9 incident patients who were all exposed to dasatinib at the time of PH diagnosis. The lowest estimate of incident PH occurring in patients exposed to dasatinib was 9/2,900 (0.31%), as compared with no incident case reported with imatinib or nilotinib in the same period. A relationship was suspected between dasatinib exposure and occurrence of pre-capillary PH and dasatinib was stopped in all patients immediately after PH diagnosis. Clinical, functional and haemodynamic improvements were observed within 4 months of dasatinib discontinuation, in all patients. However, complete clinical and hemodynamic recovery was not observed in most patients and only 4 patients reached normal pulmonary vascular resistance < 3 Wood units after a median follow-up of 4 months (min-max 3-15).

**Conclusion:** Dasatinib therapy may promote severe pre-capillary PH, suggesting a direct and specific effect of dasatinib.

## P2295

**Everolimus improves exercise capacity and pulmonary vascular resistance in patients with advanced pulmonary hypertension – A pilot study**

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**Background:** In recent years, pulmonary arterial hypertension (PAH) has been recognized to be a predominantly proliferative process. The inhibitor of the mammalian target of rapamycin (mTOR) everolimus inhibits cellular protein synthesis and growth in cells of the vascular wall.

**Methods:** Ten patients with PAH (n=8) or chronic thromboembolic pulmonary hypertension (CTEPH) and progressive disease despite therapy with at least two vasodilating drugs were included in a prospective open label pilot study. All patients were treated additionally with everolimus. Safety and tolerability were observed. Pulmonary vascular resistance (PVR) and 6-minute walking distance (6MWD) were considered as primary endpoints.

**Results:** In two patients study medication was stopped prematurely due to an adverse event. The remaining 8 patients exhibited a significant improvement in PVR (1049±438 vs. 689±235 dyn\*sec\*cm<sup>-5</sup>; p=0.004) and 6MWD (246±105 vs. 313±127m; p=0.04) after 6 months of therapy with everolimus.

**Conclusion:** Antiproliferative with everolimus therapy was tolerated in ten patients in this pilot study. The observed improvements in PVR and in 6MWD may stimulate further consideration of mTOR inhibition in pulmonary hypertension.

## P2296

## P2297

**Ambrisentan improves exercise capacity and symptoms in patients with portopulmonary hypertension**

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**Introduction:** Ambrisentan, a selective endothelin receptor antagonist has been approved in several countries for pulmonary arterial hypertension. No data have been published on the efficacy of ambrisentan on improvement of exercise capacity in patients with portopulmonary hypertension (PoPH).

**Patients and methods:** We retrospectively analyzed the safety and efficacy of ambrisentan in patients with PoPH in four German university hospitals.

**Results:** 14 patients with moderate to severe PoPH were included. The median follow-up was 16 months (IQR, 12-21). 6 minute walk tests after 6 and 12 months improved from 376 meters (IQR, 207-440) at baseline to 415 meters (IQR, 393-475; p=0.011) and 413 meters (IQR, 362-473), respectively. WHO- functional class after 1 year of therapy with ambrisentan also improved significantly (p=0.014). No significant changes in blood gas analysis and liver transaminases were detectable.

**Conclusions:** The present study demonstrates significant improvement of exercise capacity and symptoms without relevant safety concerns during ambrisentan treatment in patients with PoPH.

## P2298

**Double combination therapy in patients with pulmonary arterial hypertension associated with connective tissue disease**

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**Background:** Pulmonary arterial hypertension associated with connective tissue disease (PAH-CTD) is a severe and progressive condition despite the availability of 3 specific classes of drugs: prostanooids (PROST), endothelin receptor antagonists (ERA) and phosphodiesterase-5 inhibitors (PDE5-I). Combination therapy (CT) has been proposed for patients with unsatisfactory response to monotherapy.

**Aim:** To examine the effect of double CT in patients with PAH-CTD who do not achieve an adequate clinical response on monotherapy.

**Methods:** Between October 1999 and December 2010, 48 PAH-CTD patients in WHO functional class III treated with monotherapy were included. At baseline and after 5±5 months on CT, all patients underwent 6-minute walk test (6MWT) and right-heart catheterization.

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**Results:** Mean age was  $58 \pm 14$  years, 85% females. Mean time from initiation of monotherapy to initiation of CT was  $18 \pm 20$  months. Forty (83%) patients received ERA+PDE5-I, 5 (10%) received PDE5-I+PROST and 3 (7%) received ERA+PROST. Four (8%) patients died before CT assessment. The table shows the haemodynamic and functional changes after CT.

(n=44pts)	RAP (mmHg)	mPAP (mmHg)	mSBP (mmHg)	CI (L/min/m <sup>2</sup> )	PVR (WU)	6MWT (m)
Monotherapy	12±6	52±11	88±11	2.2±0.5	12.1±5.5	312±111
Double CT	9±5	49±11	83±11	2.6±0.6	10.2±5.1	337±132
p	0.03	0.02	0.04	0.007	0.008	0.02

RAP, right atrial pressure; mPAP, mean pulmonary arterial pressure; mBP, mean blood pressure; CI, cardiac index; PVR, pulmonary vascular resistance.

**Conclusions:** CT in CTD-PAH patients improves exercise capacity and haemodynamics. However 8% of patient die after an average of  $3.2 \pm 1.5$  months of CT testifying the persistent severity of the condition.

#### P2299

##### **Tadalafil in idiopathic or heritable pulmonary arterial hypertension compared to pulmonary arterial hypertension associated with connective tissue disease**

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Patients (pts) with PAH associated with connective tissue disease (APAH-CTD) have a worse prognosis compared to idiopathic (I) or heritable (H)PAH. Our objective was to evaluate the clinical outcomes in these two subgroups.

In a 16 week (wk), double-blind, placebo (PBO) controlled trial with blinded 52 wk extension, pts were randomized to PBO, 20 or 40mg tadalafil (Tad) qd (APAH-CTD: n=16, 21 and 19, respectively; I/HPAH: n=54, 50 and 46, respectively); subgroup efficacy analyses included six-minute walk test (6MWT, 40mg) at Wk16 (assessed by rank permutation tests) and clinical worsening (CW, PBO and 40mg) at Wk16 and up to 68wks (20 and 40mg). Pts on 20mg without CW at 16wks remained on 20mg; all others received 40mg in the extension.

Mean changes in 6MWT from baseline to Wk16 were 32m in APAH-CTD and 38m in I/HPAH for 40mg Tad dose. PBO-corrected treatment effects on 6MWT at Wk 16 were 49m in APAH-CTD (P=0.03) and 22m in I/HPAH (P=0.04). The% of pts with CW in the Tad 40mg and PBO subgroups at Wk16 were 11 and 25% in APAH-CTD, respectively; and 4 and 15% in I/HPAH, respectively. In pts who received Tad 20 or 40mg up to 68wks, CW was 35% in APAH-CTD (n=40) and 24% in I/HPAH (n=96).

Tad 40mg improves 6MWT at Wk16 in APAH-CTD and I/HPAH; however, with PBO 6MWT decreased in APAH-CTD but not in I/HPAH pts. In addition, CW was numerically less with Tad in both subgroups at Wk16 compared to PBO. At Wk68, CW was numerically higher in APAH-CTD vs. I/HPAH. These latter data are consistent with a worse prognosis in APAH-CTD. Whether more aggressive therapy earlier in APAH-CTD pts would be efficacious requires further study.