Agency for Health Technology Assessment in Poland
Department of Health Technology Assessment

CLINICAL EFFECTIVENESS ANALYSIS OF BOSENTAN, EPOPROSTENOL, ILOPROST, SILDENAFIL AND TREPROSTINIL IN TREATMENT OF PULMONARY ARTERIAL HYPERTENSION.

A SYSTEMATIC REVIEW OF RANDOMISED CONTROLLED TRIALS.

(version 2.1)

Warsaw, 2009

Agencja Oceny Technologii Medycznych
Al. Lotników 22, 02-668 Warszawa tel. +48 22 56 67 200 fax +48 22 56 67 202
e-mail: sekretariat@aotm.gov.pl
www.aotm.gov.pl

Authors

Authors: Lidia Becla, Bogusława Osińska, Kinga Malottki - AHTAPol

Following Clinical Experts and Drugs Manufacturers Representatives took part in Decision Problem setting:

- *Prof. dr hab. n. med. Adam Torbicki* – Institute of Tuberculosis and Lung Diseases, Warsaw
- *Prof. dr hab. Lech Poloński* - Silesian Centre for Heart Diseases , Zabrze
- *Dr hab. med. Mariusz Gąsior* – Silesian Centre for Heart Diseases , Zabrze
- *Dr n. med. Tadeusz Zębik* – Silesian Centre for Heart Diseases , Zabrze
- *Adam Hadasik* – National Health Found
- *Andrzej Śliwczyński* – National Health Found
- *Magdalena Chodorowska, Jacek Wcisło, Marzena Kulis* – Pfizer Polska sp. z o.o.
- *Magdalena Olszewska, Roman Hożejowski, Andrzej Dziukała* – Schering Polska sp. z o.o.
- *Patric Durand, Karl Bögl* – Actelion Pharma Schweiz AG
- *Michał Opuchlik* – AOP Orphan Pharmaceuticals SA

External reviewers:

- *Dr David Moore* - Department of Public Health & Epidemiology, University of Birmingham, Edgbaston, Birmingham, UK
- *Dr Yen-Fu Chen* - Department of Public Health & Epidemiology, University of Birmingham, Edgbaston, Birmingham, UK

Completion date: August 2007

Peer review date: 17th December 2008

Summary

Pulmonary arterial hypertension (PAH) is a group of disorders characterized by increasing pulmonary vascular resistance resulting in development of right ventricular failure and premature death. Pulmonary hypertension is defined as increase of mean pulmonary artery pressure above 25 mmHg at rest or 30 mmHg during exercise. Current clinical classification of pulmonary hypertension was developed on the Third World Symposium on Pulmonary Hypertension in Venice (2003) and discerns the following types of PAH: 1) idiopathic, 2) familial, 3) associated with connective tissue diseases, congenital systemic-to-pulmonary shunts, portal hypertension, HIV infection, drugs and toxins or other disorders, 4) associated with significant venous or capillary involvement (pulmonary veno-occlusive disease, pulmonary capillary hemangiomatosis), 5) persistent pulmonary hypertension of the newborn. Due to low prevalence PAH was considered a so-called orphan disease by the European Commission. Based on epidemiological data from other countries, estimated prevalence in Poland is 600 cases in the whole country and incidence – 116 new cases annually.

Aim of the report: The aim of this report is to compare efficacy and safety of bosentan, epoprostenol, iloprost, sildenafil and treprostinil with those of conventional treatment in patients with pulmonary arterial hypertension.

Methods: Analysis of efficacy and safety was performed according to "Guidelines on Health Technology Assessment (HTA)" published in March 2007 and guidelines of the Cochrane Collaboration – "*Cochrane Handbook for Systematic Reviews of Interventions*" (version 4.2.6). At first, primary clinical studies taken into account in three credible systematic reviews were included in the study. In order to identify clinical trials published later than dates of the last search specified in the retrieved secondary reports, the following medical databases were searched: Medline (via PubMed), EmBase and *The Cochrane Central Register of Controlled Trials*. The final search was performed on 29.01.2007. Two independently working investigators searched for publications, analyzed abstracts and complete texts of the studies according to the review inclusion criteria as well as assess their credibility (using *Jadad* scale) and extract data. Within the target population two subgroups of patients were considered for analysis: individuals with primary pulmonary hypertension and those with pulmonary arterial hypertension associated with other diseases. Calculations and metaanalyses were performed using *StatsDirect* (version 2.6.2) statistical software.

Results: Nineteen randomized clinical trials, in which a total number of 1795 patients with PAH participated, were included in the systematic review. In most of the clinical trials the patients continued conventional treatment with anticoagulants, vasodilators, diuretics and/or digitalis glycosides. The analysis demonstrated that two of the five investigated drugs (i.e. epoprostenol and sildenafil) are significantly more efficacious than conventional treatment or placebo with regard to death rate. For the comparison of epoprostenol vs. conventional treatment in patients with primary PAH, in an observation period of 8-12 weeks, the odds ratio is 0.09 (95% CI: 0.02 to 0.56), NNT = 5 (4 to 13), while for the comparison of sildenafil vs. placebo in children and fetuses, in an observation period of 4-42 hours, OR = 0.10 (95% CI: 0.01 to 0.89), NNT = 4 (95% CI: 3 to 13).

Analysis based on the results of 1 to 3 randomized clinical studies for each comparison demonstrated that bosentan as well as epoprostenol, iloprost and sildenafil significantly increase exercise capacity (assessed according to the NYHA/WHO classification) as compared to placebo in the population of all patients with PAH – both primary and associated with other diseases (bosentan vs. placebo: OR = 2.25 (95% CI: 1.21 to 4.18), NNT = 7 (95% CI: 4 to 21); epoprostenol vs. placebo: OR = 37.99 (95% CI: 8.43 to 171.22), NNT = 7 (95% CI: 2 to 4); iloprost vs. placebo: OR = 2.25 (95% CI: 1.02 to 5.13), NNT = 9 (95% CI: 5 to 79), sildenafil vs. placebo: OR = 6.94 (95% CI: 2.78 to 17.31), NNT = 4 (95% CI: 3 to 6). Among patients with primary PAH exercise capacity assessed according to the NYHA/WHO classification increased significantly more often in the epoprostenol group and the iloprost group as compared to the placebo group (epoprostenol vs. placebo: OR = 26.44 (95% CI: 4.49 to 155.81), NNT = 3 (2 to 4); iloprost vs. placebo: 4.92 (95% CI: 1.19 to 28.66)). In patients with PAH associated with other diseases statistically significant differences with regard to this outcome were observed only for the comparison of epoprostenol vs. placebo, in favor of epoprostenol (OR = 65.40 (95% CI: 5.69 to 2742.21), NNT = 3 (95% CI: 2 to 4)).

In four intervention groups (bosentan, iloprost, sildenafil, treprostinil) significantly higher improvement in exercise capacity measured using the 6-minute walk test was found as compared to

control groups in the population of all patients with PAH. Weighted mean difference in increase of walk distance was 43.33 m (95% CI: 27.55 to 59.12) for the comparison of bosentan vs. placebo (4 studies); 36.4 m (p = 0.004) – iloprost vs. placebo (1 study); 55.82 m (95% CI: 38.03 to 73.61) – sildenafil vs. placebo (3 studies) and 16.00 m (95% CI: 4.40 to 27.60) treprostinil vs. placebo (1 study). In patients with primary PAH statistically significant differences between the groups were observed for the comparison of epoprostenol vs. conventional treatment: WMD = 46.94 m (95% CI: 17.30 to 76.59). In the two remaining comparisons (iloprost vs. placebo and treprostinil vs. placebo) differences between the assessed groups did not reach statistical significance. In patients with PAH associated with other diseases no significant differences between the assessed groups with regard to this outcome were demonstrated.

In safety analysis no statistically significant differences between the bosentan and placebo groups as well as sildenafil and placebo groups with regard to incidence of any of the assessed adverse events were found. In assessment of jaw pain significant differences were observed between epoprostenol, iloprost and treprostinil on one side and appropriate control groups on the other, in disfavor of the investigated drugs: epoprostenol vs. placebo: OR = 327.00 (95% CI: 27.58 to 11155.05), NNH = 2 (95% CI: 2 to 2); iloprost vs. placebo: OR = 4.40 (95% CI: 1.13 to 24.94), NNH = 12 (6 to 54); treprostinil vs. placebo: OR = 3.14 (95% CI: 1.49 to 7.09), NNH = 12 (8 to 28). Treatment with epoprostenol is related to statistically significantly higher risk of occurrence of nausea (OR = 3.56 (95% CI: 1.36 to 9.83), NNH = 5 (95% CI: 3 to 13)) and diarrhea (OR = 17.33 (95% CI: 4.62 to 94.37), NNH = 3 (95% CI: 2 to 4) as compared to the conventional treatment group. Risk of serious syncope or flushing is higher for patients treated with iloprost as compared to placebo; OR = 7.77 (95% CI: 1.32 to 45.66), NNH = 23 (95% CI: 10 to 83) for serious syncope and OR = 3.73 (95% CI: 1.57 to 9.53), NNH = 6 (95% CI: 4 to 14) for flushing. Use of treprostinil is related to significantly higher incidence of edema as compared to the placebo group (OR = 3.80 (95% CI: 1.44 to 11.69), NNH = 16 (95% CI: 9 to 42)), pain at the injection site (OR = 17.65 (95% CI: 11.14 to 27.96), NNH = 2 (95% CI: 2 to 2), reaction at the injection site (OR = 14.87 (95% CI: 9.21 to 24.11), NNH = 2 (95% CI: 2 to 2), hematoma or induration of the injection site (OR = 56.00 (95% CI: 3.31 to 2670.59), NNH = 2 (95% CI: 2 to 3) and sudden vasodilation (OR = 2.46 (95% CI: 1.13 to 5.67), NNH = 17 (95% CI: 9 to 77). It should be noted that analysis of efficacy and safety of specific interventions was based on a limited number of randomized clinical studies, with relatively short observation periods.

Conclusions: Bosentan, epoprostenol, iloprost and sildenafil significantly increase exercise capacity (according to the NYHA classification and the 6-minute walk test) comparing to placebo in the PAH population. In safety analysis no statistically significant differences were observed between bosentan and placebo as well as sildenafil and placebo groups. Comparing to placebo, in epoprostenol group significantly more often jaw pain, nausea and diarrhea occurred, in iloprost group there was higher incidence of serious syncope or flushing and jaw pain and in the treprostinil group – sudden vasodilation, edema, jaw pain and reaction, pain, hematoma or induration at the injection site. The use of these five drugs in addition to CT is more effective than CT alone.

Contents

Keywords

Pulmonary arterial hypertension

Primary pulmonary arterial hypertension

Pulmonary arterial hypertension associated with other diseases

Bosentan

Epoprostenol

Iloprost

Sildenafil

Treprostinil

1. CHARACTERISTICS OF THE DECISION PROBLEM

1.1. Description of the health problem – pulmonary arterial hypertension

Pulmonary arterial hypertension (PAH) is a group of diseases characterized by progressive increase of pulmonary vascular resistance resulting in development of right ventricular failure and premature death. Pulmonary hypertension is defined as increase of mean pulmonary artery pressure above 25 mmHg at rest or 30 mmHg during exercise.[7]

Due to low prevalence PAH was considered a rare disease (i.e. a disease of prevalence not higher than five patients per 10,000 of general population) by the European Commission. Similar regulations are in force in Australia[2] and the USA[3].

1.1.1. Clinical classification of PAH

Current clinical classification of pulmonary hypertension was developed on the Third World Symposium on Pulmonary Hypertension in Venice (2003). In this classification the following types of pulmonary arterial hypertension are discerned:

1. idiopathic PAH
2. familial PAH
3. PAH associated with:
    - connective tissue diseases
    - congenital systemic-to-pulmonary shunts
    - portal hypertension
    - HIV infection
    - drugs and toxins
    - other disorders (thyroid disorders, rare metabolic or genetic diseases such as: glycogen storage disease, Gaucher's disease, hereditary hemorrhagic teleangiectasia – Rendu-Osler-Weber disease, hemoglobinopathies, myeloproliferative disorders, splenectomy)
4. associated with significant venous or capillary involvement
    - pulmonary veno-occlusive disease
    - pulmonary capillary hemangiomatosis
5. persistent pulmonary hypertension of the newborn.[7]

1.1.2. Morphology and pathogenesis of PAH

PAH is a group comprised of various types of the disease, of different etiology but characterized by similar signs and symptoms as well as – in most cases – similar response to applied treatment. At the basis of the pathology of PAH lie morphological lesions in vessel walls resulting in increased pulmonary vascular resistance and subsequent right ventricular failure. Histopathological lesions present in the types of PAH mentioned above are of similar character but different intensity and distribution in the pulmonary vascular bed. The main histopathological lesions include:

- pulmonary arteriopathy (hypertrophy of specific layers of the vessel wall, inflammatory lesions in the arteries)
- lesions related to hypertrophy of the wall of veins and venules
- pulmonary venous thrombosis
- pulmonary microvasculopathy (proliferation of capillary vessels in the lungs).

Pathogenetic processes involved in PAH are currently not well understood. Increase of pulmonary vascular resistance is a result of disturbed balance between prothrombotic, mitogenic, proinflammatory and vasoconstrictory factors on one side and anticoagulative, antimitotic and vasodilatory mechanisms on the other. This in turn results in vasoconstriction, proliferation, formation of thrombi and triggering of inflammatory response in the pulmonary vascular bed, leading to increase of pulmonary vascular resistance with subsequent pulmonary hypertension, pressure overload of the right ventricle, right ventricular failure and death.[7]

1.1.3. Epidemiology

Idiopathic pulmonary arterial hypertension (PAH) occurs in 1-2 persons per million individuals in general population annually. Annual incidence of PAH (according to NICE data) is 2 to 4 cases per 1 million of population. It is assessed that in Poland ca. 60 persons annually fall ill with PAH.

Prevalence may be estimated at 15 cases in 1 million of adult population, of which 5.9 cases are those of idiopathic PAH. If data collected in France would be extrapolated to Polish population, prevalence of PAH should be assessed at 600 cases in the whole country and incidence at 116 new cases annually.

Mean age of patients (both men and women) with primary PAH is 36.4 years; the highest incidence is observed in the third decade of life in women and the fourth decade in men. The risk of falling ill is ca. 1.7 times higher for women than for men. [8],[11],[16]

1.1.4. Symptoms, signs and prognosis

A classical symptom of PAH is effort dyspnea due to inability to increase cardiac output because of right ventricle overload during effort. Other symptoms of pulmonary hypertension include fatigue, weakness, chest pain, syncope and abdominal distension. With time, progress of the disease and increase of right ventricular failure new signs appear: jugular venous distension, hepatic enlargement, peripheral edema, ascites, central cyanosis, sometimes

peripheral or mixed cyanosis as well. Mortality in untreated PAH is high; mean survival time from the moment of diagnosis does not exceed 3 years.[7],[11],[16]

1.1.5. Diagnostics

Pulmonary hypertension should be suspected in case of symptoms and signs observed in patients with diseases that may be associated with PAH: connective tissue diseases, portal hypertension, congenital heart diseases with left-to-right shunt or HIV infection, as well as in patients with abnormal findings in ECG, chest X-ray or echocardiography performed for other reasons.

Diagnostics is based on tests making it possible to detect pulmonary hypertension, identify its clinical category and type as well as to assess the patient's exercise capacity and hemodynamic parameters. The most important diagnostic tests include:

- electrocardiography (ECG) – allows for assessment of signs of right ventricular hypertrophy and overload as well as right atrial enlargement;
- chest X-ray imaging (RTG) – abnormal findings are observed in ca. 90% of patients with idiopathic PAH;
- Doppler transthoracal echocardiography (TTE) – makes it possible to detect PAH and assess severity of the disease as well as its causes and consequences; the following parameters are evaluated: pulmonary artery systolic pressure, size and function of the heart ventricles, assessment of the heart valves; TTE allows also for diagnosis of congenital and acquired heart diseases with possible left-to-right shunt;
- transesophageal echocardiography (TEE) – seldom required; performed in order to confirm presence of small atrial septal defects;
- pulmonary function tests and arterial blood gasometry;
- ventilation-perfusion scintigraphy;
- computed tomography (CT) of the chest (especially high resolution CT);
- spiral lung CT with contrast, pulmonary angiography, nuclear magnetic resonance (NMR) imaging;
- laboratory blood tests and immunological testing;
- ultrasonography (USG) of the abdomen;
- assessment of exercise capacity – usually six minute walk test (6MWT) is performed; results of this test reversely correlate with the NYHA functional classification; usually at the same time severity of effort dyspnea is assessed using the Borg Dyspnea Score;
- hemodynamic tests, e.g. catheterization of the right heart (to confirm the diagnosis, especially in patients with cardiac function classified as NYHA II-III), pulmonary artery pressure (systolic, diastolic, mean), pulmonary capillary wedge pressure, pulmonary vascular resistance, arterial blood and mixed venous blood oxygen saturation.

Some parameters, assessed initially and after treatment, have prognostic value. These include:

- NYHA classification of functional ability;

- exercise capacity (e.g. 6-MWT);
- echocardiographic parameters (e.g. dimensions of the right atrium);
- hemodynamic parameters (e.g. right atrial pressure, mean pulmonary artery pressure, cardiac output, mixed venous blood oxygen saturation, decrease of vascular resistance);
- some other laboratory blood tests, e.g. uricemia, concentration of the type-B natriuretic peptide, plasma concentration of neurohormones.[7]

1.1.6. Treatment

Treatment of PAH depends on such factors as: progression of the disease, its etiology and response to applied treatment. Financial capacity of the payer is an important factor limiting possibilities of introduction of an appropriate treatment option, especially in relation to new, expensive drugs.

The following therapeutic options are used in treatment of PAH:

1. non-pharmacological management, aimed at limitation of the effect of unfavorable factors, e.g. stay at high altitudes (in hypoxemic conditions), prevention of infections, pregnancy, psychological support;
2. pharmacological treatment:
   - so-called conventional treatment, including oral anticoagulants, diuretics, oxygen therapy, digitalis glycosides, dobutamine, calcium channel blockers; this option is actually symptomatic treatment of right ventricular failure and pulmonary vasodilation; calcium antagonists may be used in patients, for whom reactivity of pulmonary vessels was confirmed – a condition fulfilled by less than 13% of patients with idiopathic PAH;
   - in the 1990s new medications were introduced: synthetic prostacyclin and its analogues (epoprostenol, treprostinil, beraprost, iloprost), endothelin-1 receptor antagonists (bosentan, sitaxsentan, ambrisentan) and type 5 phosphodiesterase inhibitors (sildenafil). In case of sitaxsentan and ambrisentan the class of recommendation is currently not established (due to limited number of randomized studies).
   - ➢ Bosentan is registered as an “orphan medicine” in Europe (central registration), USA and Australia for treatment of patients with PAH in NYHA class III (Tracleer)[2],[3],[4],[9];
   - ➢ Epoprostenol (brand name: Flolan); the drug was registered in Poland for treatment of idiopatic PAH in NYHA class III and IV[6]; registration in Poland expired at the end of 2006; the drug is registered in USA and Australia as an “orphan drug” for treatment of PAH in NYHA class III and IV[2];[3];;
   - ➢ Iloprost is registered in Europe (a central procedure) for treatment of PAH in NYHA class III as well as in Australia and the USA in NYHA class III and IV as an “orphan medicinal product”; marketing in Poland is authorized by a central procedure (Ventavis) for a drug administered in inhalations.[2],[3],[4],[9]

- Sildenafil was registered in Europe as an “orphan medicine” (central registration) for adult patients with PAH in NYHA class III (Revatio);[4],[9]
- Treprostinil is registered in Europe (a central procedure) for treatment of PAH in NYHA class III ; the drug is also registered in Australia and USA as an “orphan medicine” for treatment of PAH in NYHA class III and IV (Remodulin).[2],[3],[4]

According to product characteristics of drugs analyzed in this report all of them are indicated for the treatment of the NYHA class III and only epoprostenol can be used in IV NYHA class. However, European Society of Cardiology Guidelines recommend also bosentan and treprostinil for treatment patients in IV NYHA class.

A report prepared by prof. Adam Torbicki, MD, PhD states that the number of Polish patients with indications for guided treatment of PAH may be estimated at 318 persons. Approximately 57 new cases of PAH with indications for treatment should be expected annually.

It should be noted that currently there are few credible reports available concerning treatment of children. Strategy of diagnostics and treatment is generally similar to that applied for adult patients with primary PAH, with the exception of the newborn with persistent pulmonary hypertension, in whom additional use of nitric oxide (NO) is attempted. Nevertheless, this therapeutic option has not been included in the guidelines for treatment of PAH due to lack of appropriate clinical studies.

3. surgical treatment (atrial septostomy as palliative treatment, pulmonary or cardiopulmonary transplantation). [7]

1.2. DESCRIPTION OF THE INTERVENTIONS

1.2.1. BOSENTAN

Bosentan is a double endothelin receptor antagonist (ERA) with affinity to both type A and type B receptors (ETA and ETB). Bosentan decreases both pulmonary and systemic vascular resistance leading to increase of cardiac output without increase of the heart rate.

Bosentan was registered for treatment of patients with PAH in NYHA class III and IV in the USA and Canada. In Europe the European Medicines Agency (EMEA) authorized use of bosentan in patients in NYHA class III with a reservation that safety and efficacy of the drug in patients under 12 years of age was not appropriately documented.[3],[9],[10]

Moreover, this drug was registered as an "*orphan medicine*" in Europe (central registration) and Australia for treatment of patients above 12 years of age with PAH in NYHA class III.

As a medicinal product it was authorized for marketing under a brand name of Tracleer, 62.5 and 125 mg tablets.

1.2.1.1. Therapeutic indications (according to the EMEA registration)[9]

Treatment of pulmonary arterial hypertension (PAH) in order to improve exercise capacity and symptoms in patients with grade III functional status (NYHA).

Efficacy has been shown in:

- primary (idiopathic and familial) pulmonary hypertension;
- PAH secondary to scleroderma without significant interstitial pulmonary disease;
- PAH associated with congenital systemic-to-pulmonary shunts and Eisenmenger's physiology.

1.2.1.2. Dosage

Tracleer treatment should be initiated at a dose of 62.5 mg twice daily for 4 weeks and then increased to the maintenance dose of 125 mg twice daily.

Some patients not responding well to 125 mg twice daily of Tracleer may slightly improve their exercise capacity when the dose is increased to 250 mg twice daily.

1.2.1.3. Contraindications

- Hypersensitivity to bosentan or to any of the excipients;
- Child-Pugh Class B or C, i.e. moderate to severe hepatic impairment;

- baseline values of liver aminotransferases, i.e. aspartate aminotransferases (AST) and/or alanine aminotransferases (ALT), greater than 3 times the upper limit of normal;
- concomitant use of cyclosporine A;
- pregnancy;
- women of childbearing potential who are not using reliable methods of contraception.

Efficacy of Tracleer has not been established in patients with severe pulmonary arterial hypertension.

The benefit/risk balance of bosentan has not been established in patients with NYHA class I or II functional status of pulmonary arterial hypertension.

Tracleer should only be initiated if systemic systolic blood pressure is higher than 85 mmHg.

1.2.1.4. Interaction with other medicinal products and other forms of interaction

Bosentan may interact with other drugs, such as: hormonal contraceptives, cyclosporine A, tacrolimus, sirolimus, glibenclamide, warfarin, simvastatin, ketoconazole, digoxin (interaction marked as unlikely to be of clinical relevance), epoprostenol, rifampicin, sildenafil (care is recommended in case of concomitant administration of those drugs).

1.2.1.5. Adverse events

Based on the results of clinical trials and an exposure of patients to the medication in the post-marketing period, the following adverse events were reported:

Respiratory, thoracic and mediastinal disorders	upper respiratory tract infection nasopharyngitis pneumonia
Cardiac disorders	edema of the lower limbs palpitations edema
Gastrointestinal disorders	dyspepsia dry mouth nausea vomiting, abdominal pain, diarrhea
Nervous system disorders	headache
Vascular disorders	flushing hypotension
Skin & subcutaneous tissue disorders	pruritus hypersensitivity reactions including dermatitis, pruritus and rash
General disorders	fatigue
Hepatobiliary disorders	abnormal hepatic function aminotransferase elevations associated with hepatitis and/or jaundice Rare: liver cirrhosis, liver failure
Immune system	anaphylaxis and/or angioedema

1.2.1.6. Class of recommendation and level of evidence

In "Guidelines on diagnostics and treatment of PAH" issued by the European Society of Cardiology the class of recommendation and level of evidence for efficacy of bosentan were evaluated as follows:

- in NYHA class III patients with idiopathic PAH and PAH associated with scleroderma without significant lung fibrosis: class of recommendation – **I**; level of evidence – **A;**
- in NYHA class IV patients with idiopathic PAH and PAH associated with scleroderma without significant lung fibrosis: class of recommendation – **II**; level of evidence – **B**[7].

1.2.2. EPOPROSTENOL

Epoprostenol is a synthetic salt of prostacyclin. Due to its short half-life in the circulation the drug is administered as continuous intravenous infusion by means of infusion pumps and permanent tunneled catheters (Hickman).

Epoprostenol was authorized for marketing in Poland (brand name: Flolan)[6]; registered in Australia[16] as an *"orphan medicine"* for treatment of PAH in NYHA class III and IV; authorized for marketing in the USA[10] for treatment of idiopathic pulmonary arterial hypertension and pulmonary arterial hypertension associated with connective tissue diseases in NYHA class III and IV.

1.2.2.1. Therapeutic indications

Flolan – a medication containing epoprostenol – was registered in Poland in 2006.

According to the summary of product characteristics, epoprostenol is indicated in:

- treatment of primary pulmonary arterial hypertension in NYHA class III and IV;
- hemodialyzed patients, when use of heparin is contraindicated or associated with risk of bleeding

Available information concerning use of Flolan in children and patients above 65 years of age with primary pulmonary hypertension is limited.

Flolan is available in 2 pharmaceutical forms: vials containing 0.5 and 1.5 mg of epoprostenol sodium in a form of powder that needs to be dissolved in order to prepare intravenous infusions.

1.2.2.2. Dosage

According to the summary of product characteristics the recommended dose in primary PAH is established individually during short-term administration, beginning from 2 ng/kg/min and increasing the dose until the maximum hemodynamic benefit is achieved or an undesired effect limiting further administration is encountered. During treatment using long-term

intravenous infusion the dose is adjusted according to effects achieved and adverse events encountered. In most cases target dose is 20-40 ng/kg/min (values and strategies of dose increase vary between centers).

Short-time administration of epoprostenol in order to adjust the dose is performed in hospital settings. The drug is administered in continuous infusion by means of a portable infusion pump and a permanent intravenous catheter; the patient must therefore be appropriately prepared and motivated for such treatment.

1.2.2.3. Contraindications

- Known hypersensitivity to the drug;
- congestive heart failure due to severe left ventricular failure;
- pulmonary edema occurring during dose adjustment period;
- no information concerning use of epoprostenol during pregnancy and lactation is available.

1.2.2.4. Interaction with other medicinal products and other forms of interaction

- Activity of anticoagulants may be enhanced;
- epoprostenol may enhance activity of other vasodilators;
- epoprostenol may decrease thrombolytic efficacy of tissue plasminogen activator;
- concomitant use of epoprostenol and drugs affecting platelet aggregation (e.g. non-steroid anti-inflammatory drugs) may result in increased risk of bleeding.

1.2.2.5. Adverse events

- flushing (“hot flush”)
- headache
- gastrointestinal disorders (nausea, vomiting, intestinal cramps)
- jaw pain
- dry mouth
- fatigue
- reddening above the injection site
- chest pain or pressure
- decreased platelet count
- tachycardia or bradycardia

- anxiety, nervousness, excitement
- adverse events related to administration of the drug: local infection, pain at the site of administration, catheter occlusion, sepsis[6]

1.2.2.6. Class of recommendation and level of evidence

In "Guidelines on diagnostics and treatment of PAH" issued by the European Society of Cardiology the class of recommendation and level of evidence for efficacy of epoprostenol were evaluated as follows:

- in patients with idiopathic PAH and PAH associated with connective tissue diseases: class of recommendation – **I**, level of evidence – **A;**
- in patients with other types of PAH: class of recommendation – **IIa**; level of evidence – **C**. [7]

1.2.3. ILOPROST

Iloprost is a synthetic analogue of prostacyclin. The following pharmacological activities were observed in vitro:

- inhibition of platelet aggregation, adhesion and release reaction;
- dilation of arterioles and venules;
- increase of density of capillary vessels and decrease of enhanced vascular permeability induced by such mediators as serotonin or histamine in the smallest vessels;
- stimulation of endogenous potential fibrinolytic activity.

Iloprost is registered in Europe (central registration)[9] for treatment of PAH in NYHA class III and in Australia[2] and the USA (FDA)[3] in NYHA class III and IV.

Iloprost has been qualified as an orphan drug („*orphan medicinal iloprost*").

In Europe iloprost has been authorized for marketing by EMEA under a brand name of Ventavis as inhalation solution (1 or 2 ml ampoules containing the drug at a concentration of 10 μg/ml).

Iloprost is also manufactured as solution for continuous intravenous infusion, but this pharmaceutical form is not authorized for marketing in Europe.

1.2.3.1. Therapeutic indications

According to the EMEA registration[9], iloprost is indicated to improve exercise capacity and symptoms in patients with PAH in NYHA class III.

1.2.3.2. Dosage

Ventavis is intended for inhalation use by nebulization.

The recommended single dose is 2.5 micrograms or 5.0 micrograms (as delivered at the mouthpiece of the nebulizer), according to the individual need and tolerability. The dose per inhalation session should be administered 6 to 9 times per day according to the individual need and tolerability.

1.2.3.3. Contraindications

- Hypersensitivity to iloprost or to any of the excipients;
- conditions where the effects of iloprost on platelets might increase the risk of hemorrhage (e.g. active peptic ulcers, trauma, intracranial hemorrhage);
- severe coronary heart disease or unstable angina; myocardial infarction within the last six months; decompensated cardiac failure if not under close medical supervision; severe arrhythmias; cerebrovascular events (e.g. transient ischemic attack, stroke) within the last 3 months;
- pulmonary hypertension due to venous occlusive disease;
- congenital or acquired valvular defects with clinically relevant myocardial function disorders not associated with pulmonary hypertension;
- pregnancy, lactation.

1.2.3.4. Interaction with other medicinal products and other forms of interaction

Iloprost may increase the effect of vasodilators and antihypertensive agents.

Iloprost can inhibit platelet function and its use with anticoagulants (such as heparin or coumarin-type anticoagulants) or other inhibitors of platelet aggregation (such as acetylsalicylic acid, non-steroidal anti-inflammatory medicinal products, ticlopidine, clopidogrel and glycoprotein IIb/IIIa antagonists: abciximab, eptifibatide and tirofiban) may increase the risk of bleeding.

1.2.3.5. Adverse events

In clinical trials the following adverse events were reported:

Cardiovascular disorders	Very common: vasodilation, hypotension Common: dizziness related to hypotension, syncope
Respiratory, thoracic and mediastinal disorders	Very common: severe cough – during administration of the drug by inhalation
Nervous system disorders	Common: headache
Musculoskeletal and connective tissue disorders	Common: jaw pain/trismus
bleeding events (mostly hematoma)	Common as expected in this patient population with a high proportion of patients taking anticoagulant co-medication

1.2.3.6. Class of recommendation and level of evidence

In "Guidelines on diagnostics and treatment of PAH" issued by the European Society of Cardiology the class of recommendation and level of evidence for efficacy of iloprost in inhalation were evaluated as follows:

- in patients with idiopathic PAH: class of recommendation – **IIa**; level of evidence – **B**[7].

1.2.4. SILDENAFIL

Sildenafil is a potent, selective inhibitor of type 5 phosphodiesterase (PDE5) specific for cyclic guanosine monophosphate (cGMP) – the enzyme responsible for degradation of cGMP. This enzyme is present in the cavernous bodies of the penis as well as in pulmonary circulation. Sildenafil increases concentration of cGMP in smooth muscle cells of the pulmonary vessel wall causing their relaxation. In patients with pulmonary hypertension this may lead to dilation of the pulmonary vessels with slight vasodilation in the systemic circulation.

Sildenafil was registered in Europe as an "orphan medicine" for adult patients with PAH in NYHA class III (brand name: Revatio).[4]

1.2.4.1. Therapeutic indications

According to the EMEA registration[9], sildenafil is indicated for treatment of patients with PAH class III according to the WHO functional classification in order to improve exercise capacity. Efficacy of the drug was demonstrated in primary PAH and secondary PAH associated with connective tissue diseases.

In Europe sildenafil has been authorized for marketing by EMEA under a brand name of Revatio, in the form of oral tablets containing 20 mg of sildenafil.

Efficacy and safety of the drug in children and adolescents has not been investigated in large, controlled clinical studies. Use of sildenafil in this group of patients is therefore not recommended.

1.2.4.2. Dosage

According to the summary of product characteristics, the recommended dose in patients above 18 years of age is 20 mg three times daily.

1.2.4.3. Contraindications

- Hypersensitivity to the active substance or to any of the excipients;
- co-administration of the drug with nitric oxide donors (such as amyl nitrite) or nitrates in any form is contraindicated;
- combination with CYP3A4 inhibitors (e.g. ketoconazole, itraconazole, ritonavir);
- Revatio is contraindicated in patients with loss of vision in one eye because of non-arteritic anterior ischemic optic neuropathy (NAION);

- safety of sildenafil has not been studied in the following subgroups of patients: severe hepatic impairment, recent history of stroke or myocardial infarction, severe hypotension (blood pressure < 90/50 mmHg); use of sildenafil in these patients is therefore contraindicated.

1.2.4.4. Interaction with other medicinal products and other forms of interaction

Due to metabolism of sildenafil interactions with other drugs are possible, e.g.:

- α- and ß-adrenolytics
- drugs containing ketoconazole or itraconazole
- ritonavir and saquinavir (used in treatment of HIV infection)
- bosentan
- carbamazepine, phenytoin, phenobarbital, St. John's wort and rifampicine
- erythromycin, clarithromycin, telithromycin and nefazodone
- nitrates or nitric oxide donors (such as amyl nitrite).

1.2.4.5. Adverse events

Based on the results of clinical trials before and after the registration, the following common adverse events were reported:

Infections and infestations	cellulitis, influenza, sinusitis
Blood and the lymphatic system disorders	anemia
Metabolism and nutrition disorders	fluid retention
Psychiatric disorders	insomnia, anxiety
Nervous system disorders	headache, migraine, tremor, paresthesia, burning sensation, hypoesthesia
Eye disorders	retinal hemorrhage, visual disturbance, blurred vision, photophobia, chromatopsia, cyanopsia, eye irritation, blood shot eyes/red eyes, visual acuity reduced, diplopia
Ear and labyrinth disorders	vertigo
Vascular disorders	flushing
Respiratory, thoracic and mediastinal disorders	bronchitis, epistaxis, rhinitis, cough, nasal congestion
Gastrointestinal disorders	diarrhea, dyspepsia, gastritis, gastroenteritis, gastroesophageal reflux disease, hemorrhoids, abdominal distension, dry mouth
Skin and subcutaneous tissue disorders	alopecia, erythema, night sweats
Musculoskeletal, connective tissue and bone disorders	limb pain, myalgia, back pain
General disorders	fever

1.2.4.6. Class of recommendation and level of evidence

In "Guidelines on diagnostics and treatment of PAH" issued by the European Society of Cardiology the class of recommendation and level of evidence for efficacy of sildenafil were evaluated as follows:

- class of recommendation – **I**; level of evidence – **A**..[7]

1.2.5. TREPROSTINIL

Treprostinil is a tricyclic benzidene analogue of epoprostenol, dilating pulmonary and systemic arterial vessels and inhibiting platelet aggregation. In animal studies it was demonstrated that vasodilatory effect leads to decrease in cardiac ventricular afterload and increase of cardiac index and cardiac ejection volume. Chemical stability of treprostinil allows for administration at ambient temperature in a physiological solution. The drug may be administered by intravenous or subcutaneous route. For subcutaneous administration micro-infusion pumps and small subcutaneous catheters are used.

Treprostinil is registered in Australia as an "orphan medicine" for treatment of PAH in NYHA class III and IV (Remodulin)[2]; the FDA registered treprostinil for treatment of patients with PAH in NYHA class II, III and IV[3],[10]; marketing in Poland is authorized by a central procedure (registered in 2006).

1.2.5.1. Therapeutic indications

Treprostinil is indicated for treatment of patients with pulmonary arterial hypertension in NYHA class II (FDA) or III and IV, in whom conventional therapy is inefficient.

Available information concerning use of treprostinil patients below 16 or above 65 years of age is limited.

1.2.5.2. Dosage

Treprostinil is administered in continuous infusion (preferably by the subcutaneous route; intravenous administration is used in case of local reactions or pain at the injection site).

Initial recommended dose is 1.25 ng/kg/min and in case of intolerance – 0.625 ng/kg/min. In order to establish the target dose it should be increased by not more than 1.25 ng/kg/min weekly during the first 4 weeks, and then not more than 2.5 ng/kg/min, according to clinical response. Experience with doses exceeding 40 ng/kg/min is limited. Sudden discontinuation of treatment is not recommended.

Remodulin is available in 4 pharmaceutical forms: 20 ml vials containing 1, 2.5, 5 and 10 mg/ml of treprostinil.

1.2.5.3. Contraindications

- Hypersensitivity to the drug;
- care should be observed in patients with hepatic or renal impairment;
- no data concerning safety of use of treprostinil during pregnancy or lactation are available.

1.2.5.4. Interaction with other medicinal products and other forms of interaction

- Hypotension may be enhanced with concomitant use of drugs affecting the cardiovascular system, such as: diuretics, antihypertensive agents or vasodilators;
- due to inhibition of platelet aggregation the risk of bleeding with use of anticoagulants is increased;
- neither in vitro nor in vivo studies demonstrated any interactions with warfarin.

1.2.5.5. Adverse events

- Pain at the injection site (the most common adverse effect), reaction, bleeding or lividity at the injection site – these problems sometimes make it impossible to continue treatment;
- headache;
- diarrhea;
- nausea;
- skin rash;
- jaw pain;
- vasodilation, hypotension;
- vertigo;
- edema;
- pruritus. [6]

1.2.5.6. Class of recommendation and level of evidence

In “Guidelines on diagnostics and treatment of PAH” issued by the European Society of Cardiology the class of recommendation and level of evidence for efficacy of treprostinil were evaluated as follows:

- in patients with PAH class of recommendation – **IIa**; level of evidence – **B**. [7]

2. METHODS

2.1. Aim of the report

The aim of this report is to compare efficacy and safety of bosentan, epoprostenol, iloprost, sildenafil and treprostinil with those of conventional treatment in patients with pulmonary arterial hypertension. The analysis was commissioned by the Minister of Health.

2.2. Methods of efficacy and safety assessment

Analysis of efficacy and safety was performed according to "Guidelines on Health Technology Assessment (HTA)" published by the Agency for Health Technology Assessment in Poland in March 2007 and guidelines of the Cochrane Collaboration – *"Cochrane Handbook for Systematic Reviews of Interventions"* (version 4.2.6 issued in September 2006).

2.3. Search strategy for primary studies

At first primary clinical studies taken into consideration in three credible systematic reviews (*Kanthapillai 2004*, *Paramonthayan 2005*, *Liu 2006*) were included in the analysis. The search strategy for primary clinical studies published after the date of the final search stated in the reviews mentioned above is presented in the table.

Table 1.
Search strategy

ID	Field	Keywords
#1	Population	„pulmonary hypertension"
#2	Intervention I - bosentan	Bosentan
#3		Tracleer
#4		Ro 47-0203
#5		Ro-47-0203
#6		#2 OR #3 OR #4 OR #5
#7		**#6 AND #1**
#8	Intervention II - epoprostenol	Epoprostenol
#9		Epoprostanol
#10		PGI2
#11		Prostaglandin
#12		Prostacyclin
#13		PGX
#14		Flolan
#15		#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14
#16		**#15 AND #1**
#17	Intervention III - iloprost	Iloprost
#18		Ciloprost
#19		Ventavis

#20		ZK-36374
#21		ZK 36374
#22		ZK36374
#23		#17 OR #18 OR #19 OR #20 OR #21 OR #22
#24		**#23 AND #1**
#25	Intervention IV - sildenafil	Sildenafil
#26		Syldenafil
#27		Acetildenafil
#28		Desmethylsildenafil
#29		Homosildenafil
#30		Hydroxyhomosildenafil
#31		UK 92480-10
#32		UK-92,480-10
#33		Viagra
#34		Revatio
#35		#25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34
#36		**#35 AND #1**
#37	Intervention V - treprostinil	Treprostinil
#38		Remodulin
#39		UT15
#40		UT-15
#41		#37 OR #38 OR #39 OR #40
#42		**#41 AND #1**
#43	Intervention – summary descriptors	phosphodiesterase inhibitors
#44		#43 and #1
#45		vasodilator agents
#46		#45 AND #1
#47		endothelin receptor antagonists
#48		endothelin receptor antagonist
#49		#47 OR #48
#50		**#49 AND #1**
#51		#50 OR #46 OR #44 OR #42 OR #36 OR #24 OR #16 OR #7
#52	Study design	#51 Limits: English, French, German, Spanish, Polish, published in the last 2 years, Clinical Trial, Randomized Controlled Trial, Humans

The search strategy included randomized controlled clinical studies in human subjects published in the following languages: English, Polish, German, French and Spanish. Date of the final search: 29.01.2007.

Results of the literature search using this strategy are presented in the annexes.

The search was performed independently by two investigators. In case of discrepancies the problem was discussed until consensus was achieved.

2.4. Search of medical databases

Two independently working investigators searched for publications and analyzed abstracts and complete texts of the studies according to the review's inclusion criteria and a protocol developed *a priori*. All discrepancies were solved by consensus or with assistance of a third person.

In order to retrieve secondary studies (HTA reports, metaanalyses and systematic reviews) the following internet sources were searched:

- *Cochrane Library*:
  - *The Cochrane Database of Systematic Reviews*;
  - *Health Technology Assessment Database*;
- INAHTA *(International Network of Agencies for Health Technology Assessment)*;
- CRD (*Centre for Reviews and Disseminations*):
  - *Health Technology Assessment (HTA) Database*;
  - *Ongoing Reviews Database*;
- Medline via PubMed;
- EmBase.

If credible HTA reports and/or systematic reviews were found, primary studies taken into consideration by the authors of those reports were included in the analysis, provided that the reports were related to the investigated population, intervention and endpoints, and the inclusion criteria for clinical studies were similar to those applied in this analysis; in the next stage primary clinical studies published after the date of the final search stated in the retrieved reports were searched for. The following databases were searched according to these rules:

- Medline via PubMed;
- EmBase;
- Cochrane Library (*The Cochrane Central Register of Controlled Trials*);
- BioMed Central.

References of both primary and secondary studies (HTA reports, systematic reviews, metaanalyses, review articles) were searched for additional publications. Presentations and abstracts from scientific conferences (*European Society of Cardiology*) were also reviewed as well as clinical trial registers (*National Research Register*, *U. S. National Institutes of Health – clinicaltrials.gov*, *Food and Drug Administration – Center for Drug Evaluation and Research*. Clinical experts and manufacturers of investigated drugs were also consulted (in order to find additional studies as well as to obtain information from the *Periodic Safety Update Reports*).

2.5. Inclusion criteria for primary clinical trials

2.5.1. Population

The analysis included studies, in which the population consisted of patients (adults or children) treated conventionally before enrollment, with type 1 pulmonary hypertension according to Venice classification (2003):

- pulmonary arterial hypertension (idiopathic), familial or associated with:
  - connective tissue diseases,

- ❖ congenital systemic-to-pulmonary shunts,
- ❖ portal hypertension,
- ❖ HIV infection,
- ❖ drugs and toxins
- ❖ other disorders (thyroid disorders, rare metabolic or genetic diseases such as: glycogen storage disease, Gaucher's disease, hereditary hemorrhagic teleangiectasia, hemoglobinopathies, myeloproliferative disorders, splenectomy)
- ❖ significant venous or capillary involvement (pulmonary veno-occlusive disease, pulmonary capillary hemangiomatosis);
- ❖ persistent pulmonary hypertension of the newborn.

Studies performed in a population containing patients with pulmonary hypertension other than arterial, including:

- ❖ pulmonary hypertension associated with diseases of the left heart (venous pulmonary hypertension);
- ❖ pulmonary hypertension associated with respiratory diseases and/or hypoxemia;
- ❖ pulmonary hypertension in thromboembolic disease

were excluded from the analysis unless the non-PAH patients only constituted a small proportion of the study population.

Wherever corresponding data were available in clinical studies, the following two subgroups of patients were to be analyzed:

- individuals with primary pulmonary arterial hypertension,
- those with pulmonary arterial hypertension associated with other diseases.

2.5.2. Intervention

Studies included in the analysis compared:

- bosentan with conventional treatment vs. placebo with conventional treatment;
- epoprostenol with conventional treatment vs. conventional treatment ;
- iloprost with conventional treatment vs. placebo with conventional treatment ;
- sildenafil with conventional treatment vs. placebo with conventional treatment ;
- treprostinil with conventional treatment vs. placebo with conventional treatment ;
- epoprostenol, iloprost, treprostinil, bosentan or sildenafil vs. any of the above (head to head comparisons).

An additional inclusion criterion was previous conventional treatment in both assessed groups.

Studies concerning bosentan, epoprostenol, iloprost, sildenafil or treprostinil used in combination treatment (i.e. when one of the compared groups was treated with more than one of the assessed drugs) were excluded from the analysis. No limitations as to the observation period were assumed.

2.5.3. Endpoints

2.5.3.1. Primary

- Exercise capacity (six-minute walk test) as a prognostic factor related to survival time
- Change of the NYHA or WHO functional class
- Assessment of dyspnea (Borg Dyspnea Score) and fatigue
- Time to exacerbation of the symptoms of pulmonary hypertension (change of treatment or pulmonary transplantation)
- Number of hospitalizations and/or outpatient visits
- Quality of life
- Mortality
- Adverse events

2.5.3.2. Secondary

- Hemodynamic parameters (mean pulmonary artery pressure, pulmonary vascular resistance, cardiac index, cardiac output, arterial blood oxygen saturation, mixed venous blood oxygen saturation)

2.5.4. Study design

The analysis included only randomized controlled clinical studies in human subjects published (as complete texts) in the following languages: English, Polish, German, French and Spanish.

2.6. Credibility assessment

Based on titles and abstracts of the publications a preliminary list of studies fulfilling the inclusion criteria was prepared. In the following stage of selection the studies were verified based on their complete texts, taking into consideration all the inclusion criteria. The final list of studies was thus completed; the studies were then carefully examined as to their credibility and results.

Each of the stages of selection and credibility assessment was performed independently by two investigators; in case of disagreement the list of included studies and their score were established by consensus or with assistance of a third person. A diagram illustrating detailed process of selection of publications and results of the search at different stages is presented in the annex.

Credibility of the retrieved systematic reviews/metaanalyses was assessed using the QUOROM (*Quality Reporting of Meta-analyses*) questionnaire, consisting of five areas related to the abstract, introduction, methodology, results and discussion of the metaanalysis. Detailed description of the QUOROM questionnaire is presented in the annex.

Credibility of the included clinical trials was assessed using the 5-point *Jadad* scale, consisting of five questions. Four of them are related to randomization and blinding, which allow for elimination or significant limitation of the effect of potential confounders (e.g. stage of the disease, age, gender or attitude of the personnel). One of the questions is related to patients lost from the study, making it possible to assess unjustified exclusion of patients from the study by the investigators. Such information, if provided by the authors, allows for so-called intention-to-treat (ITT) analysis. Detailed description of the *Jadad* scale is presented in the annex.

2.7. Statistical analysis

Data extraction and analysis was performed by two independently working investigators, using a unified form. In case of disagreement the final opinion was established by consensus or with assistance of a third person.

For dychotomous variables (e.g. occurrence of a certain endpoint) the odds ratio (OR) was calculated with 95% confidence interval (CI). If OR was statistically significant, the remaining parameters of efficacy and safety were also calculated, i.e. for negative outcomes: the relative risk (RR) and the relative risk reduction (RRR) as well as the absolute risk reduction (ARR) and the number needed to treat (NNT), and for positive outcomes: relative benefit (RB), relative benefit increase (RBI), absolute benefit increase (ABI) and number needed to harm (NNH), all with 95% confidence intervals.

Peto method or Haldane method were used to avoid errors caused by zero event. The Peto method was used provided there was no a large imbalance between the sizes of the treatment vs. control groups. Haldane correction was considered in case of significant imbalance between groups.

For continuous variables compared between groups or change of these variables in relation to baseline values (e.g. mean change in intensity of pruritus) weighted mean difference (WMD) or standardized mean difference (SMD) was calculated with 95% confidence interval. The analysis only included data for which standard deviation (SD) or standard error (SE) were reported, or for which calculation of these parameters was possible.

Metaanalysis of the results was performed using a fixed effect model if no statistically significant heterogeneity of the results was found. For those endpoints, for which statistical significance in the heterogeneity test was achieved, a random effect model was used. The cut-off of statistical significant was p=0,10. The calculations were made using *StatsDirect* (version 2.6.2) statistic software.

Sensitivity analysis was performed by including and excluding differing data into the metaanalysis in case of uncertain parameters, i.e. when differences between included studies (concerning the patients' inclusion criteria, the patients' baseline characteristics, dosage of the drugs, duration of the observation period or definition of the endpoints) were found.

If such operations had no significant effect on the result of metaanalysis, it was assumed that the results are true; however, if the results changed and led to opposite conclusions, the final results were interpreted more carefully.

3. RESULTS

3.1. Bosentan vs. placebo

3.1.1. Results of search for the studies

Four multicenter randomized clinical studies fulfilling the inclusion criteria were identified during performed search. In the retrieved studies bosentan (BOS) used in combination with conventional treatment (CT) was compared to placebo (PL) with CT. All the studies were double-blind; in one of them *(Barst 2006)* the BOS arm was not blinded for assessment.

Evaluation of all the studies, publications related to particular clinical trials and duration of observation periods are presented in the table below.

Table 2.
Characteristics of the clinical trials included in the analysis; BOS vs. PL

Study	Publications	Observation period	*Jadad* score
Channick 2001	*Badesch 2002* *Channick 2001* *Denton 2006* *McLaughlin 2005* *Sitbon 2003*	12 weeks	4
Rubin 2002	*Denton 2006* *Galie 2003* *McLaughlin 2005* *Rubin 2002*	16 weeks	3
Barst 2006	*Barst 2006*	18 weeks	3
BREATHE-5	*Galie 2006* *Gatzoulis 2006*	16 weeks	5

For two studies the *Jadad* score was three points, for one – four points and for one – five points. Duration of the observation period differed between the studies – from 12 to 18 weeks. In Channick 2001 trial, follow-up after 12 weeks varied between individuals and overall study period was between 12 and 28 week.

3.1.2. Description of the population

The population of patients enrolled in particular clinical studies consisted of patients with idiopathic pulmonary arterial hypertension (*Channick 2001, Rubin 2002, Barst 2006*) as well as PAH associated with scleroderma (*Channick 2001, Rubin 2002*), congenital heart disease (*Barst 2006*), systemic lupus erythematosus (*Rubin 2002*) and Eisenmenger's syndrome *(BREATHE-5)*. In the study of *Barst 2006* heart disease was defined as operated atrial or ventricular septal defect or patent Botall's duct operated at least a year before enrollment or unoperated secondary atrial septal defect (with oxygen saturation $\geq$ 88%).

In two studies (*Channick 2001* and *BREATHE-5*) efficacy of BOS was assessed in patients with PAH in WHO/NYHA class III. The study of *Rubin 2002* included patients in class III and IV, while the study of *Barst 2006* – patients in WHO/NYHA functional class II, III and IV. Taking into account the patient populations from four trials as a whole, more than 80% patients were in functional class III.

In all the studies six minute walk distance longer than 150 meters was an inclusion criterion. In three studies the distance had to be shorter than 450 meters, while in the study of *Channick 2001* the upper limit was 500 m.

Among the inclusion criteria for patients previous treatment with vasodilators, anticoagulants, diuretics, cardiac glycosides or oxygen (*Channick 2001*, *Rubin 2002*), mean pulmonary artery pressure over 25 mmHg (*Channick 2001*, *Rubin 2002*), pulmonary capillary wedge pressure below 15 mmHg and pulmonary vascular resistance index over 240 dyn*s*cm^{-5} or 3 Wood units (*Channick 2001, Rubin 2002, Barst 2006*) were also taken into account. In addition, in the study of *Barst 2006* arterial blood oxygen saturation ranged from 70 to 90%.

In the study of *Barst 2006* patients aged below 18 years were enrolled only if their body mass was not lower than 50 kg. The BREATHE-5 study included only patients aged above 12 years.

Baseline characteristics of the population of patients enrolled in particular studies are presented in the table below.

Table 3.
Baseline characteristics of the patients enrolled in particular studies; BOS vs. PL

Study	Interven-tion	Number of patients	Mean age (SD) [years]	Percen-tage of men	Percentage of patients with idiopathic PAH	Percentage of patients with PAH associated with other diseases	Percentage of patients in WHO/NYHA functional class II	Percentage of patients in WHO/NYHA functional class III	Percentage of patients in WHO/NYHA functional class IV	Percentage of patients treated with oral vasodilators	Mean 6-minute walk distance (SD) [m]	Mean time from diagnosis (SD) [months]
Channick 2001	BOS 125 mg twice daily	21	52.2 (12.2)	19%	81%	19%	0%	100%	0%	43%	360.0 (86.0)	21.1 (17.6)
	PL	11	47.4 (14.0)	0%	91%	9%	0%	100%	0%	54%	355.0 (82.0)	36.4 (34.4)
Rubin 2002	BOS 125 mg twice daily	74	50.4 (15.9)	23%	77%	23%	0%	89%	11%	-	326.0 (73.0)	30.0 (33.0)
	BOS 250 mg	70	47.0 (15.6)	19%	64%	36%	0%	92%	8%	-	333.0 (75.0)	30.0 (38.0)
	PL	69	47.2 (16.2)	22%	70%	30%	0%	94%	6%	-	344.0 (76.0)	28.0 (48.0)
Barst 2006	BOS 125 mg twice daily	47	49.0 (16.0)	22%	57%	43%	37%	62%	2%	-	337.0 (78.0)	-
	PL	62	53.0 (15.0)	24%	60%	40%	37%	57%	6%	-	321.0 (85.0)	-
BREATHE - 5	BOS 125 mg twice daily	37	37.2 (12.0)	38%	0%	100%	0%	100%	0%	-	331.9 (82.8)	23.7 (13.6)*
	PL	17	44.2 (8.5)	41%	0%	100%	0%	100%	0%	-	336.4 (67.5)	20.5 (13.0)*
TOTAL	BOS	249	47.62	23%	59%	41%	7%	87%	6%	-	333.79	27.92**
	PL	159	49.15	23%	60%	40%	12%	81%	7%	-	334.98	27.64**

* diagnosis of Eisenmenger's syndrome
** calculated from available values

The analysis included 408 patients. There were more patients in all groups treated with BOS (249) than in the groups receiving PL (159). The largest study was *Rubin 2002*, in which 213 patients took part, of whom 144 in two groups received BOS (125 and 250 mg twice daily). The remaining trials enrolled 33 to 109 patients.

Mean age of patients in all clinical trials included in the analysis was 47.62 years for patients treated with BOS, while for those receiving PL it was slightly higher – 49.15 years. On average, the oldest patients were those participating in the *Barst 2006* study (average age 49 years in the BOS group and 53 years in the PL group) and the youngest – in the BREATHE-5 trial (average age 37.2 years in the BOS group and 44.2 years in the PL group).

Male patients comprised 23% of the whole investigated population. In particular study arms this percentage ranged from 0% (*Channick 2001*) to 41% (BREATHE-5).

Patients with idiopathic PAH constituted ca. 60% of the whole analyzed population (exactly 59% in the BOS group and 60% in the PL group). In remaining patients PAH associated with other diseases was diagnosed. Percentage of patients with idiopathic PAH differed between the studies. In the *Channick 2001* trial such patients comprised over 80% of the enrolled. In contrast, in the *BREATHE-5* study only patients with PAH associated with Eisenmenger's syndrome took part. In the remaining studies percentage of patients with idiopathic PAH ranged from 57% to 77%.

Another important feature of the investigated population was the patients' WHO/NYHA functional class. Most patients were classified in WHO/NYHA class III (87% of patients treated with BOS and 81% of patients receiving PL). In the *Channick 2001* and *BREATHE-5* trials all patients were classified in WHO/NYHA class III. In the *Rubin 2002* study this percentage was 90%, while in the *Barst 2006* ca. 60% of the investigated population. Seven per cent of patients in the BOS groups and 12% in the PL groups were classified in functional class II. Such patients participated only in the *Barst 2006* study and comprised 37% of both groups. Patients in WHO/NYHA class IV took part in the *Rubin 2002* and *Barst 2006* studies and comprised (on average) 6% of patients in the experimental groups and 7% in the control groups.

Mean 6-minute walk distance at the time of enrollment was 333.79 m in the BOS groups and 334.98 m in the PL groups. For BOS this value in particular studies ranged from 326 m (*Rubin 2002*, the group receiving 125 mg BOS) to 360 m (*Channick 2001*). For PL the same value ranged from 321 m (*Barst 2006*) to 355 m (*Channick 2001*).

In all the studies excepting *Barst 2006* mean time from diagnosis of pulmonary arterial hypertension[1] till enrollment was reported. Mean value for trials, in which this value was specified, was 27.92 months for groups receiving BOS and 27.64 months for groups receiving PL. In the groups receiving BOS the shortest mean time from diagnosis was reported in the *Channick 2001* study (21.1 months) and the longest in the *Rubin 2002* study (30 months in both groups receiving BOS). In the PL groups the shortest mean time from diagnosis was reported in the *BREATHE-5* study (20.5 months) and the longest in the *Channick 2001* study (36.4 months).

An important parameter assessed at baseline in the patients enrolled in particular clinical trials was the percentage of patients receiving oral vasodilators. This information was reported only in the *Channick 2001* study, in which such patients comprised 43% of the experimental group and 54% of the control group.

[1] In the *BREATHE-5* study the time from diagnosis of Eisenmenger's syndrome was specified

3.1.3. Description of the interventions

In clinical trials included in the analysis the patients were randomly assigned to the BOS or PL group.

Characteristics of the interventions in the studies included in the analysis are presented below.

Table 4.
Description of the interventions; BOS vs. PL

Study	BOS		PL	Additional treatment
Channick 2001	Bosentan at a dose of 62.5 mg twice daily for the first four weeks, then at a dose of 125 mg twice daily until any treatment-related adverse events occurred		Placebo	Anticoagulants (warfarin), vasodilators (diltiazem, amlodipine)
Rubin 2002	Bosentan at a dose of 62.5 mg twice daily for the first four weeks, then at a dose of 125 mg twice daily for 12 weeks	BOS at a dose of 62.5 mg twice daily for the first four weeks, then at a dose of 250 mg twice daily for 12 weeks	Placebo	Anticoagulants, diuretics, calcium blockers, oxygen (as complementary treatment during visits)
Barst 2006	Bosentan at a dose of 62.5 mg twice daily for the first four weeks, then at a dose of 125 mg twice daily		Placebo	Anticoagulants, diuretics, calcium blockers, digoxin, oxygen (complementary)
BREATHE-5	Bosentan at a dose of 62.5 mg twice daily for the first four weeks, then at a dose of 125 mg twice daily		Placebo	Anticoagulants, diuretics, calcium blockers

In all studies BOS administered orally at a dose of 125 mg twice daily was compared with PL. Before administration of the proper dose, the treatment began with a period of four weeks, during which the patients were administered BOS at a dose of 62.5 mg twice daily.

Additionally in the study of *Rubin 2002* a group of patients receiving BOS at a dose of 250 mg orally (also twice daily) was assessed. Since in all remaining studies BOS was administered at a dose of 125 mg, only the group receiving BOS at the adequate dose and the PL group were taken into account in the metaanalysis. For some endpoints (e.g. the WHO/NYHA functional class) it was not possible to extract the results for the group of BOS 125 mg only. The results were therefore discussed as combined for both doses. The results for the dose of 250 mg in the *Rubin 2002* study were described wherever possible.

Apart from therapy administered within the study the patients (both the experimental and the control group) received so-called conventional treatment (CT). This treatment included drugs such as: anticoagulants, vasodilators, diuretics, glycosides and oxygen.

3.1.4. Analysis of efficacy

3.1.4.1. Mortality

Data concerning mortality were reported in all studies included in the analysis. The observation period was 12 to 18 weeks.

Summarized data concerning mortality reported in the clinical trials are presented in the table below.

Table 5.
Numbers and percentages of patients who died; BOS vs. PL

Study	BOS			PL			Statistical significance of differences between the groups; BOS vs. PL
	N	n	Percen-tage	N	n	Percen-tage	
Channick 2001	21	0	0%*	11	0	0%*	n.a.
Rubin 2002	74	1	1%*	69	2	3%*	n.s.
Barst 2006	60	0	0%*	62	0	0%*	n.a.
BREATHE-5	37	0	0%*	17	0	0%*	n.a.

* calculated from data reported in the study

In the study of *Rubin 2002* three cases of death were observed: 1 in the group of patients treated with BOS 125 mg and 2 in the PL group. The risk of death resulting from therapy with BOS at a dose of 125 mg was 47% of the risk of death in the control group. The odds ratio calculated using the *Peto* method is 0.47 (95% CI: 0.05 to 4.63). The result is not statistically significant.
In Barst 2006 two patients in placebo group died after discontinuation.
In the studies of *Channick 2001* and *BREATHE-5* no deaths were observed.

3.1.4.2. Increase of exercise capacity by two WHO/NYHA functional classes

Data concerning increase of exercise capacity by two WHO/NYHA functional classes were reported in the studies of *Channick 2001*, *Rubin 2002* and *BREATHE-5*.

Table 6.
Numbers and percentages of patients, whose exercise capacity increased by two WHO/NYHA functional classes; BOS vs. PL

Study	BOS			PL			Statistical significance of differences between the groups; BOS vs. PL
	N	n	Percen-tage	N	n	Percen-tage	
Channick 2001	21	0	0%	11	0	0%	n.a.
Rubin 2002	68	2*	3%	65	0*	0%	n.s.
BREATHE-5	37	0	0%	17	0	0%	n.a.

* calculation based on available data

This endpoint was observed only in the study of *Rubin 2002*. In other clinical trials no improvement in exercise capacity by two WHO/NYHA functional classes was observed in any of the compared groups.

The odds ratio calculated from the results of the *Rubin 2002* study using the *Peto* method is 7.18 (95% CI: 0.44 to 116.03); the odds of improvement in exercise capacity by at least two WHO functional classes was therefore more than seven times higher in the bosentan group than in the placebo group. The result is not statistically significant.

In the *Rubin 2002* study, in the group treated with BOS at a dose of 250 mg increase of exercise capacity by two WHO functional classes was observed in 1% of patients. The odds ratio calculated using the *Peto* method is 7.76 (95% CI: 0.15 to 391.27); the odds of occurrence of this endpoint was therefore nearly eight times higher in the BOS 250 mg group than in the placebo group. The result is not statistically significant.

3.1.4.3. Increase of exercise capacity by one WHO/NYHA functional class

Information concerning improvement in exercise capacity by one WHO/NYHA functional class was presented in all the studies. However, the data were not always complete and the results of all the four clinical trials could not therefore be included in the metaanalysis. The observation period with regard to this endpoint was 12-18 weeks.

In the context of the studies included in the analysis, increase of exercise capacity in the WHO/NYHA classification was defined as reclassification of a patient from functional class III to class II. The observation period differed between the included studies and ranged from 12 weeks (Channick 2001) through 16 weeks in *Rubin 2002* and *BREATHE-5)* to 18 weeks in the *Barst 2006* trial .

Data for the BOS (125 mg) and the PL groups (extracted from the studies) are presented below.

Table 7.
Numbers and percentages of patients, whose exercise capacity increased by one WHO/NYHA functional class; BOS vs. PL

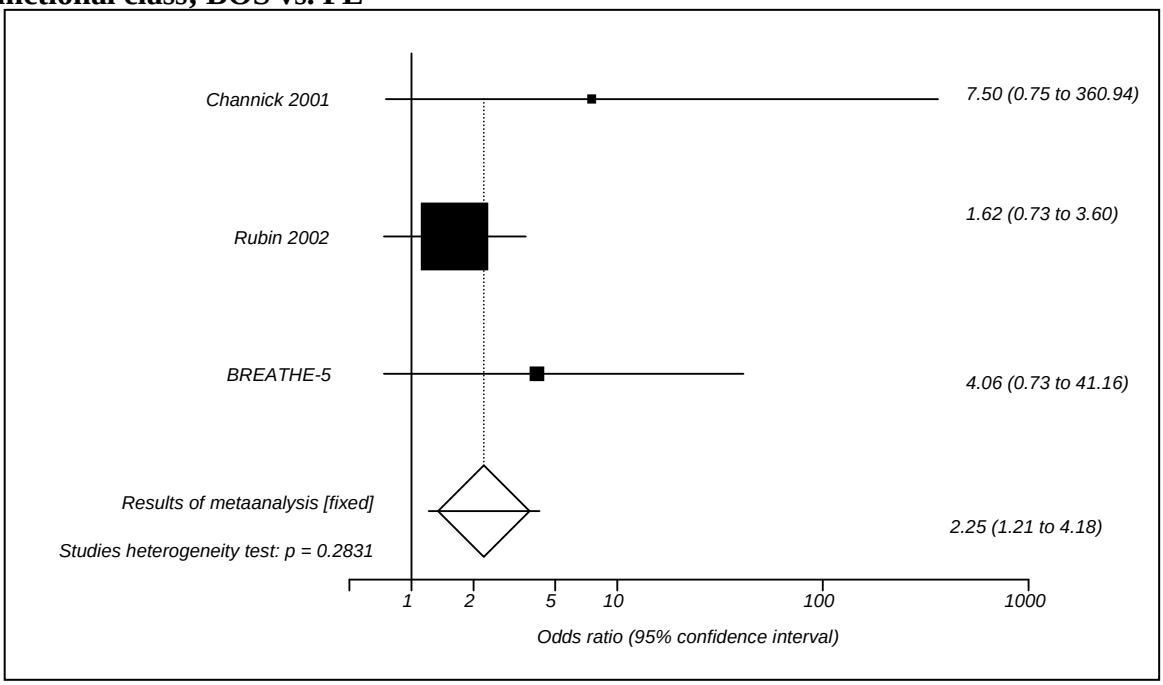
Study	BOS			PL			Statistical significance of differences between the groups; BOS vs. PL
	N	N	Percen-tage	N	N	Percen-tage	
Channick 2001	21	9	43%	11	1	9%	n.d.
Rubin 2002**	68	26*	38%	65	18*	28%	n.s.
Barst 2006	60	n.d.	n.d.	62	6*	10%	n.s.
BREATHE-5	37	13	35%	17	2	13%	n.s.*

* calculated from data reported in the study
** BOS at a dose of 125 mg

From the available data it may be concluded that the percentage of patients with improvement in exercise capacity according to the WHO/NYHA classification was higher in the bosentan group than in the placebo group. In the *Barst 2006* study complete data were not reported; the results of this clinical trial were therefore not included in the metaanalysis.

A metaanalysis for all patients, in whom this endpoint occurred within an observation period of 12-18 weeks, is presented below.

Figure 1.
Metaanalysis for all patients with increase of exercise capacity by one WHO/NYHA functional class; BOS vs. PL



The odds ratio is 2.25 (95% CI: 1.21 to 4.18, p = 0.0156). It means that the odds of increase of exercise capacity by one WHO/NYHA functional class in the group of patients treated with BOS was 2.25 times higher than the same odds in the placebo group. The result is statistically significant.

Additional EBM parameters for increase of exercise capacity according to the WHO/NYHA classification are presented below.

Table 8.
Additional EBM parameters for increase of exercise capacity according to the WHO/NYHA classification; BOS vs. PL

RB (95% CI)	RBI (95% CI)	ABI (95% CI)	NNT (95% CI)
1.77 (1.12 to 2.80)	0.77 (0.12 to 1.80)	0.166 (0.048 to 0.285)	7 (4 to 21)

The probability of improvement in exercise capacity by one WHO/NYHA functional class in the BOS group is 177% of the same probability in the control group (95% CI: 1.12 to 2.80, p = 0.0144) – the result is statistically significant. The relative benefit increase between the experimental group and the control group is 77% (95% CI: 0.12 to 1.80). The absolute benefit increase is 0.166 (95% CI: 0.048 to 0.285; p = 0.0059). In order to observe one additional case of increase of exercise capacity according to the WHO/NYHA classification, BOS instead of PL must be administered to 7 patients for a period of 12-18 weeks; NNT = 7 (95% CI: 4 to 21).

In the study of *Rubin 2002* 34% of patients receiving 250 mg BOS improved their exercise capacity by one WHO functional class. The odds ratio is 1.34 (0.59 to 3.06); the odds of increase of exercise capacity by one WHO functional class in the BOS 250 mg group was therefore 134% of this odds in the placebo group. The result is not statistically significant.

3.1.4.4. Decrease of exercise capacity according to the WHO/NYHA functional classification

Decrease of exercise capacity according to the WHO/NYHA functional classification was assessed in three studies. In trials this endpoint was defined as reclassification from WHO/NYHA functional class III to IV (*Chanick 2001*, *Barst 2006*, *BRATHE-5*) or from class II to III (*Barst 2006*). Duration of the observation period in evaluated studies was 12-18 weeks.

Numbers and percentages of patients in particular studies, in whom decrease of exercise capacity according to the WHO/NYHA classification was observed, are presented below.

Table 9.
Numbers and percentages of patients, in whom decrease of exercise capacity according to the WHO/NYHA classification was observed; BOS vs. PL

Study	BOS			PL			Statistical significance of differences between the groups; BOS + CT vs. CT
	N	n	Percen-tage	N	n	Percen-tage	
Channick 2001	21	0	0%	11	2	18%	n.s.*
Barst 2006	60	5*	9%	62	8*	13%	n.s.*
BREATHE-5	37	1	3%	17	1	6%	n.s.*

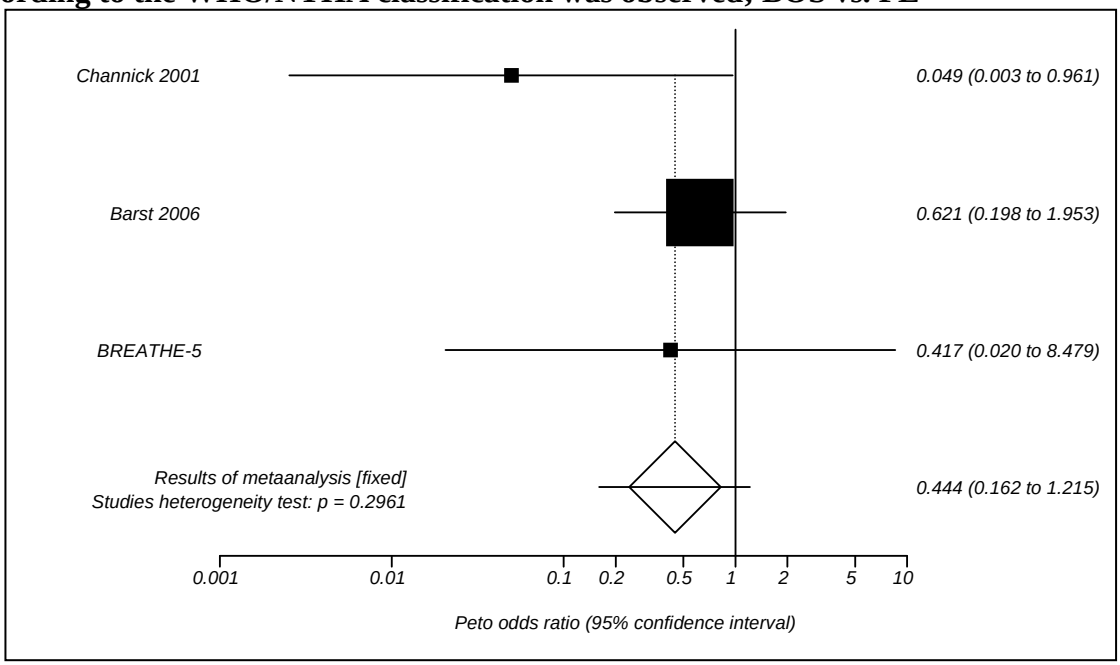
* calculated from data reported in the study

In evaluated clinical trials the percentage of patients, in whom decrease of exercise capacity according to the WHO/NYHA classification was observed, was lower in the group treated with BOS as compared to PL. However, differences between the groups were not statistically significant in any of the studies.

Due to small number of events (reclassification into a higher WHO/NYHA functional class) the odds ratio was calculated using the *Peto* method.

A metaanalysis of the results of three studies with an observation period of 12-18 weeks is presented below.

Figure 2.
Metaanalysis for the total number of patients, in whom decrease of exercise capacity according to the WHO/NYHA classification was observed; BOS vs. PL



The odds ratio calculated using the *Peto* method is not statistically significant – 0.444 (95% CI: 0.162 to 1.215, p = 0.1139). The odds of reclassification from WHO/NYHA functional class III to IV is therefore lower in the BOS group and is 44% of the odds in the PL group.

3.1.4.5. Results of the 6-minute walk test

Distance covered by the patients in 6 minutes was assessed in all the studies included in the analysis. Summary of data extracted from the studies is presented below. It should be noted that in each of the studies the patients treated with BOS achieved on average a better result than the control group. Those results were statistically significant.

Table 10.
Results of the 6-minute walk test; BOS vs. PL

Study	Intervention	N	Baseline value (SD) [m]	Final value (SD) [m]	Change from baseline (SD) [m]	Mean difference in change between the groups (95% CI)
Channick 2001	BOS	21	360 (86)	430 (64)	70 (n.d.)	76 (12 to139) p = 0.021
	PL	11	355(82)	349 (146)	-6 (n.d.)	
Rubin 2002	BOS**	144	330 (74)	n.d.	36 (n.d.)	44 (21 to 67) p < 0.001
	PL	69	344 (76)	n.d.	8 (n.d.)	
Barst 2006	BOS	60	337 (78)	n.d.	23.0 (n.d.)	29.5 (0.30 to 58.70)* p = 0.05
	PL	62	321 (85)	n.d.	-6.5 (n.d.)	
BREATHE-5	BOS	37	331.9 (82.8)	n.d.	43.4 (49.2)	53.1 (15.37 to 90.83)* p = 0.008
	PL	17	366.4 (67.5)	n.d.	-9.7 (92.0)	

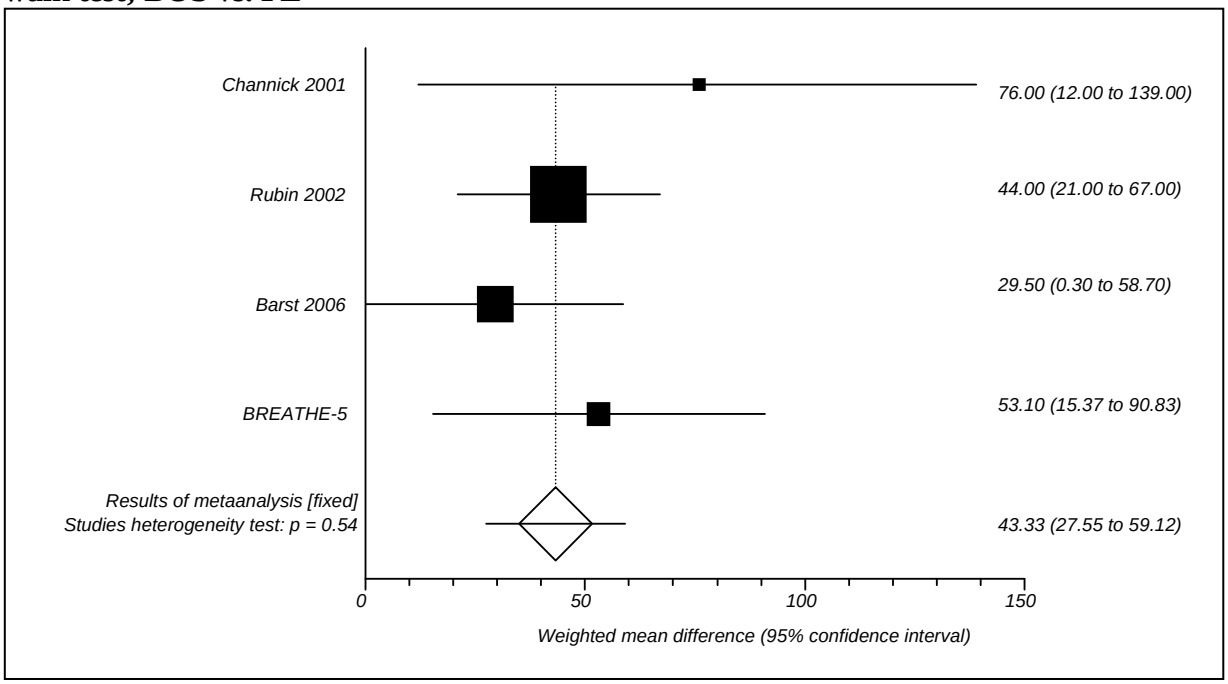
* calculation based on available data
** combined BOS groups – doses of 125 and 250 mg

From these data it may be concluded that in all evaluated clinical trials increase of exercise capacity assessed by the 6-minute walk test was statistically significantly higher in the bosentan group as compared to the placebo group.

In the *Rubin 2002* study results of the test were better in the group of patients treated with BOS at a dose of 250 mg (54 m) as compared with the BOS 125 mg group: 35 m; however, it was not possible to prove a statistically significant difference between the BOS groups (using *Mann-Whitney* U test).

A metaanalysis of the results of the studies, in which exercise capacity was assessed using the 6-minute walk test, was carried out; the results are presented below. Since the result of the studies heterogeneity test (p = 0.54) was negative, the metaanalysis was performed using a fixed effect model.

Figure 3.
Weighted mean difference in change of exercise capacity evaluated using the 6-minute walk test; BOS vs. PL



Increase of exercise capacity measured using the 6-minute walk test is higher in the BOS group as compared to the PL group, the distance being 43.33 m longer. Weighted mean difference in changes was 43.33 m (95% CI: 27.55 to 59.12; p < 0.0001). The result is statistically significant.

3.1.4.6. Borg Dyspnea Score

In three studies – *Channick 2001*, *Rubin 2002* and *Barst 2006* – severity of dyspnea was measured using the Borg Dyspnea Score. This is a subjective measure of dyspnea, assessed by the patient from 0 to 10, higher results representing more severe dyspnea. Although this endpoint was assessed in three studies, the information was presented in a way making metaanalysis impossible.

The results for particular clinical trials are presented in the table below.

Table 11.
Borg Dyspnea Score; BOS vs. PL

Study	Intervention	N	Baseline value (SD)	Final value (SD)	Change from baseline (SD)	Mean difference in change between the groups (95% CI); BOS vs. PL
Channick 2001	BOS	21	4.38 (1.80)	n.d.	n.d.	-1.6 (- 3.1 to 0.0); n.s.***
	PL	11	4.18 (1.94)	n.d.	n.d.	
Rubin 2002	BOS 125 mg	74	3.3 (2.2)	3.2 (2.58*)	-0.1 (1.72*)	-0.4 (-0.95 to 0.15), ns**
	PL	69	3.8 (2.0)	4.2 (2.49*)	0.3 (1.66*)	

* calculated from data reported in the study
** calculated from data reported in the study; for the comparison of BOS 125 mg vs. PL
*** difference between mean values in the BOS and PL group

In the study of *Channick 2001* in patients from the BOS group after 12 weeks of observation severity of dyspnea was lower by 1.6 points as compared to the PL group. The difference of mean values between the groups was -1.6 points (95% CI: -3.1 to 0.0) and the result was on the verge of statistical significance.

In the *Rubin 2002* clinical trial mean difference in changes of severity of dyspnea between the BOS 125 mg group and PL was -0.4 points (95% CI: -0.95 to 0.15), in favor of the BOS group. The result was statistically insignificant (p = 0.42). The authors of the study reported also that reduction of severity of dyspnea was 0.9 points higher in the BOS 250 mg group as compared to the PL group and the result reached statistical significance (p = 0.012).

In the study of *Barst 2006* it was only stated that after 18 weeks of observation no statistically significant difference between the compared groups was observed.

3.1.4.7. Necessity of hospitalization

The number of necessary hospitalizations was reported in the studies of *Rubin 2002* and *Barst 2006*. The observation period was 16 to 18 weeks.

In the *Rubin 2002* trial this endpoint was defined as hospitalization or discontinuation of treatment due to worsening of PAH. Data extracted from both studies are presented in the table below.

Table 12.
Numbers and percentages of patients, in whom hospitalization was necessary; BOS vs. PL

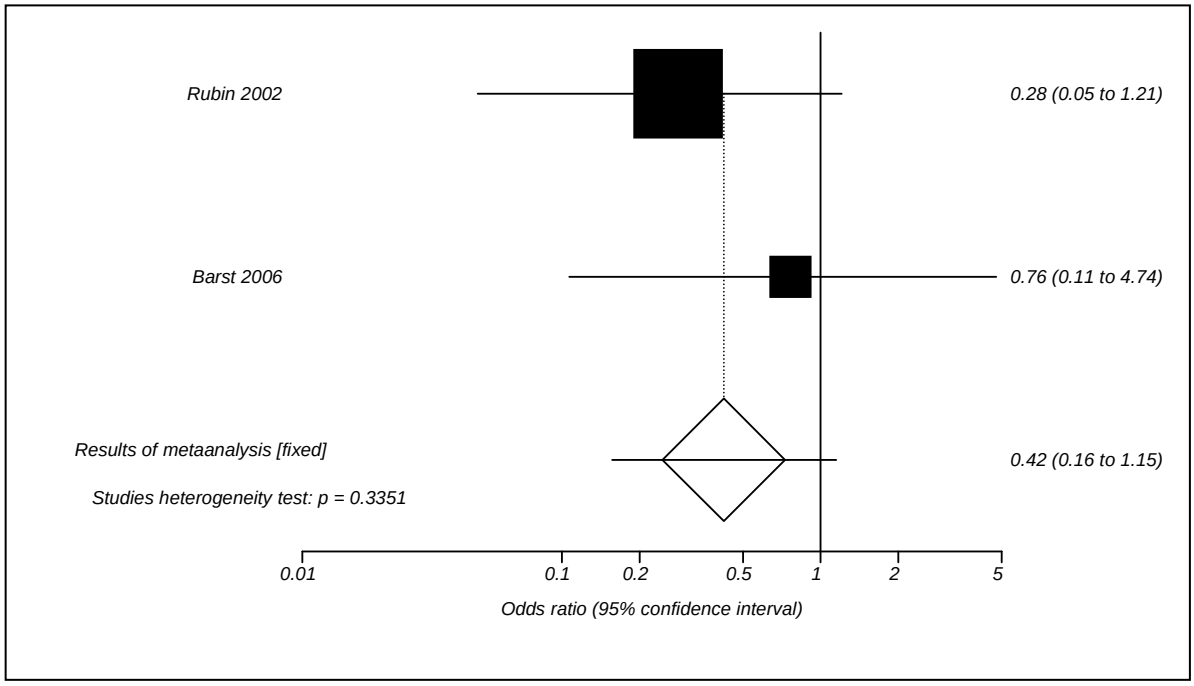
Study	BOS			PL			Statistical significance of differences between the groups; BOS vs. PL
	N	n	Percentage	N	n	Percentage	
Rubin 2002	74	3	4%*	69	9	13%*	n.s. *
Barst 2006	60	3	5%*	62	4	6%*	n.s. *

* calculated from data reported in the study

In both studies the percentage of patients requiring hospitalization due to worsening of their condition was lower in the BOS group than in the PL group.

A metaanalysis for the total number of patients, in whom hospitalization was necessary, is presented in the figure below.

Figure 4.
Metaanalysis for the total number of patients, in whom hospitalization was necessary; BOS vs. PL



From this metaanalysis it may be said that the odds of hospitalization in the group receiving BOS at a dose of 125 mg is 42% of the odds in the control group. The odds ratio is 0.42 (95% CI: 0.16 to 1.15, p = 0.1341). The result is not statistically significant.

From data available in the *Rubin 2002* study concerning the group receiving BOS 250 mg it was calculated that the odds of hospitalization in this group is 29% of the odds in the control group; OR = 0.29 (95% CI: 0.05 to 1.28). The result is not statistically significant.

3.1.4.8. Clinical worsening

Clinical worsening was assessed in three studies included in the analysis. In the study of *Channick 2001* this endpoint was defined as development of right ventricular failure or exacerbation of the symptoms of PAH. In the trials of *Rubin 2002* and *Barst 2006* clinical worsening was described as death, necessity of pulmonary transplantation, hospitalization due to PAH or necessity of additional treatment. Additionally in the *Rubin 2002* study lack of clinical improvement, exacerbation of the symptoms resulting in the patient's withdrawal from the study and atrial septostomy were taken into account, while in the *Barst 2006* study decrease in exercise capacity according to the WHO criteria and shortening of the 6-minute walk distance by at least 15% were also taken into consideration. The observation period in these studies was 12 to 18 weeks.

Data concerning clinical worsening in the included clinical trials are presented below.

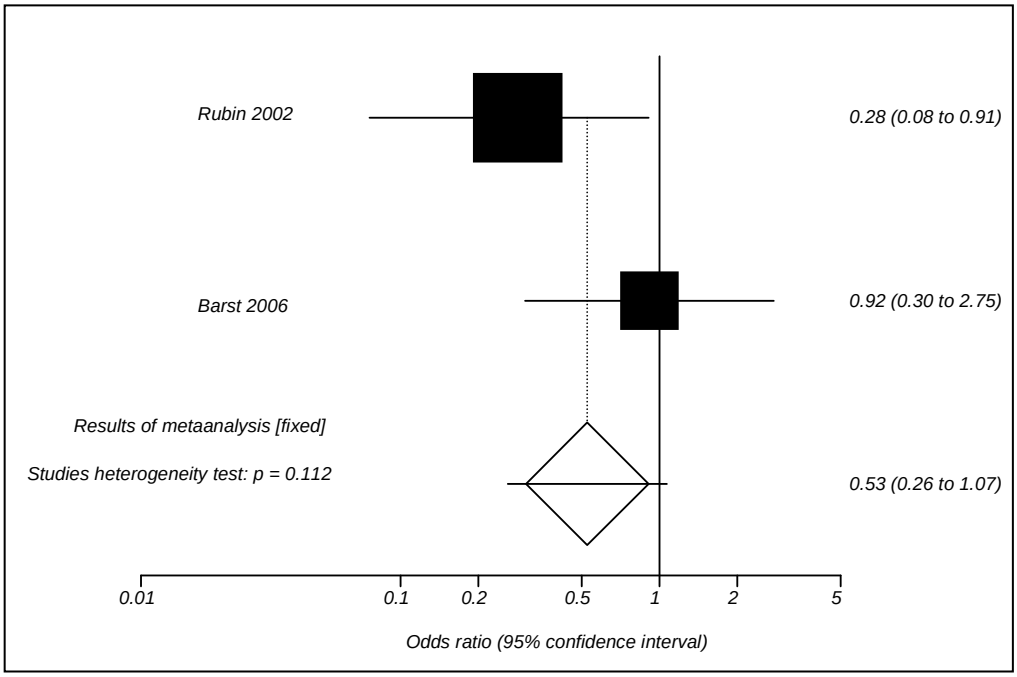
Table 13.
Numbers and percentages of patients, whose general condition worsened; BOS vs. PL

Study	BOS			PL			Statistical significance of differences between the groups; BOS vs. PL
	N	n	Percentage	N	n	Percentage	
Channick 2001	21	0	0%*	11	3	27%*	s.s. *
Rubin 2002	74	5	7%*	69	14	20%*	p = 0.02
Barst 2006	60	9	15%*	62	10	16%*	n.s. *

* calculated from data reported in the study

In all the studies clinical worsening occurred less often in the BOS groups as compared to the PL groups. However, differences between the groups were statistically significant only in the *Rubin 2002* study.

Figure 5.
Metaanalysis for the total number of patients, whose general condition worsened; BOS vs. PL



The odds ratio is 0.53 (95% CI: 0.26 to 1.07). The odds of worsening of the patient's general condition is therefore lower in the BOS group and is 53% of the odds in the PL group. The result is not statistically significant.

For the study of *Channick 2001* the odds ratio was calculated separately due to significantly different definition of the endpoint. This OR is 0.05 (95% CI: 0.00 to 0.66) and is statistically significant. NNT is 4 (95% CI: 2; 7).

In addition it should be noted that in the *Rubin 2002* study in the group of BOS 250 mg 4 cases of clinical worsening were observed. The odds ratio is 0.24 (95% CI: 0.05 to 0.82). The result is statistically significant.

For the comparison between BOS 250 mg and placebo the remaining EBM parameters were also calculated; these are presented in the table below.

Table 14.
Clinical worsening – additional EBM parameters; BOS 250 mg vs. PL

RR (95% CI)	RRR (95% CI)	ARR (95% CI)	NNT (95% CI)
0.28 (0.10 to 0.77)	0.72 (0.23 to 0.90)	0.15 (0.04 to 0.26)	7 (4 to 28)

The relative risk is 0.28 (95% CI: 0.10 to 0.77). The risk of clinical worsening in the BOS 250 mg group is therefore 28% of this risk in the PL group. The relative risk reduction for clinical worsening is 0.72 (95% CI: 0.23 to 0.90). The absolute risk reduction is 15 percentage points (95% CI: 0.04 to 0.26). In order to avoid one additional case of clinical worsening BOS at a dose of 250 mg must be administered instead of PL to 7 patients for at least 12 weeks (95% CI: 4 to 28).

3.1.4.9. Necessity of change of treatment

In the study of *Rubin 2002* it was necessary in some cases to introduce prostacyclin due to worsening of the patient's condition. Authors of the *Barst 2006* study reported the number of patients, in whom additional drugs (other than those evaluated in the study) were introduced, such as sitaxsentan, sildenafil, digoxin and treprostinil.

Numbers and percentages of patients, in whom change of treatment was necessary, are presented in the table below.

Table 15.
Numbers and percentages of patients, in whom change of treatment was necessary; BOS vs. PL

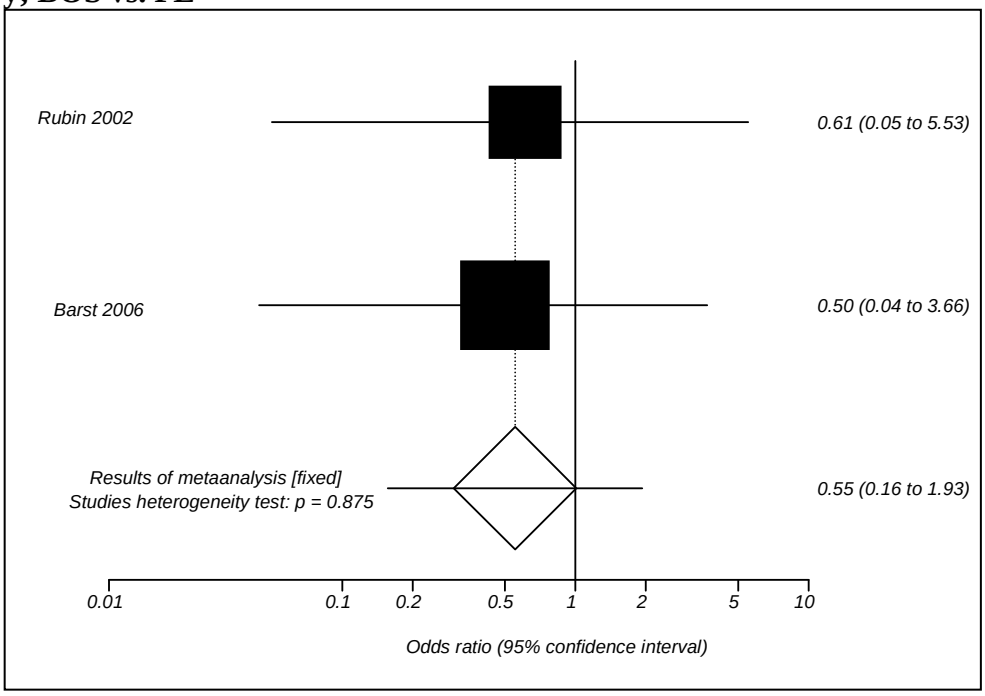
Study	BOS			PL			Statistical significance of differences between the groups; BOS vs. PL
	N	n	Percentage	N	n	Percentage	
Rubin 2002	74	2	3%*	69	3	4%*	n.s.*
Barst 2006	60	2	3%*	62	4	6%*	n.s.*

* calculated from data reported in the study

In both trials percentage of patients, in whom change of treatment was necessary, was higher in the PL group as compared to BOS. However, the difference between the groups was not statistically significant in any of the studies.

A metaanalysis of the results of the studies is presented below.

Figure 6.
Metaanalysis for the total number of patients, in whom change of treatment was necessary; BOS vs. PL



The odds that change of treatment will be necessary in the BOS group is 55% of the odds in the PL group. The odds ratio is 0.55 (95% CI: 0.16 to 1.93, p = 0.5237). The result is not statistically significant.

3.1.4.10. Pulmonary transplantation

This endpoint was assessed in the studies of *Channick 2001* and *Barst 2006*. Duration of the observation period for occurrence of pulmonary transplantation was 12-18 weeks.

No cases of pulmonary transplantation were observed in any of the studies.

3.1.4.11. Withdrawal from the study due to clinical worsening

Rate of withdrawal from the study due to clinical worsening was reported in the studies of *Channick 2001* and *Rubin 2002*. In the *Channick 2001* study clinical worsening was defined as development of right ventricular failure or exacerbation of the symptoms of PAH, while in the *Rubin 2002* trial it was defined as death, necessity of pulmonary transplantation, hospitalization due to PAH, necessity of additional treatment, lack of clinical improvement, exacerbation of the symptoms resulting in the patient's withdrawal from the study and atrial septostomy as well as syncope.

The observation period was 12 weeks in the *Channick 2001* trial and 16 weeks in the *Rubin 2002* study.

Detailed results are presented in the table below.

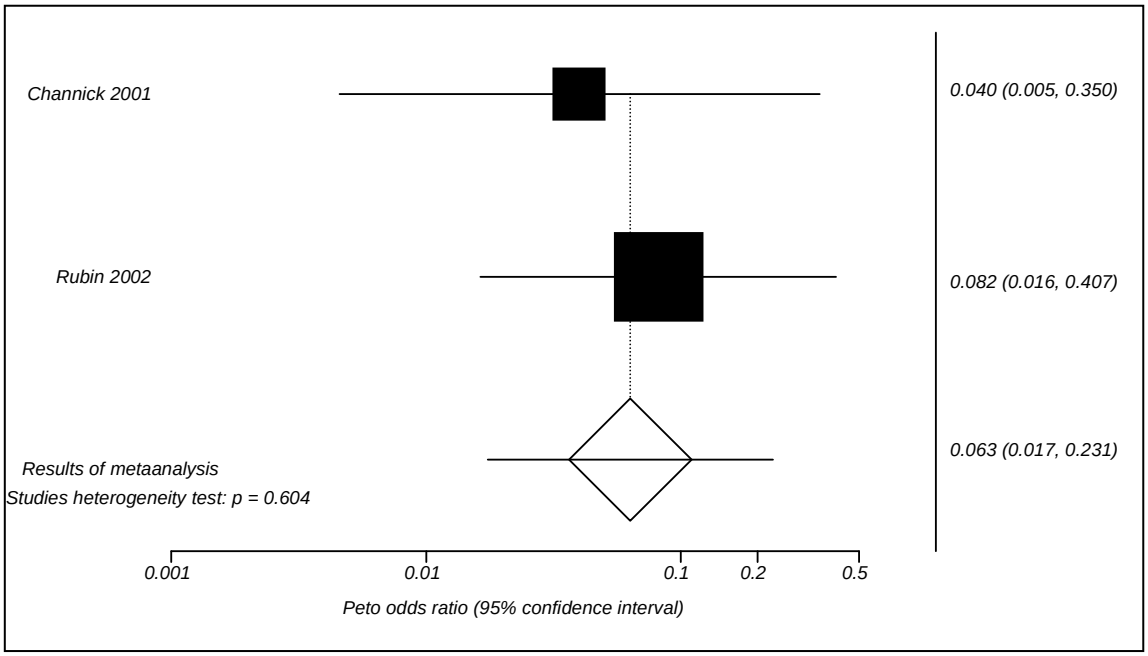
Table 16.
Numbers and percentages of patients withdrawn from the study due to clinical worsening; BOS vs. PL

Study	BOS			PL			Statistical significance of differences between the groups; BOS vs. PL
	N	n	Percen-tage	N	n	Percen-tage	
Channick 2001	21	0	0%*	11	4	36%*	s.s.
Rubin 2002	144	1	0.7%*	69	6	8.7%	s.s.*

* calculated from data reported in the study

The percentage of patients withdrawn from the study due to worsening of their general condition was in both clinical trials lower in the bosentan group than in the placebo group. Differences between the compared groups were statistically significant.

Figure 7.
Metaanalysis for the total number of patients withdrawn from the study due to clinical worsening; BOS vs. PL



The odds of the patient's withdrawal from the study due to worsening of their general condition is lower in the BOS group and is 6% of the odds in the PL group. The odds ratio is 0.06 (95% CI: 0.02 to 0.23, $p < 0.001$). The result is statistically significant.

In order to avoid one additional case of the patient's withdrawal from the study due to clinical worsening bosentan must be administered instead of placebo to 9 patients for 12-16 weeks; NNT = 9 (95% CI: 6 to 20).

3.1.4.12. Hemodynamic parameters

3.1.4.12.1. Mean pulmonary artery pressure

Results concerning mean pulmonary artery pressure were reported in the studies of *Channick 2001* and *BREATHE-5*. The observation period was 12 to 16 weeks.

Data concerning mean pulmonary artery pressure are presented in the table below.

Table 17.
Mean pulmonary artery pressure; BOS vs. PL

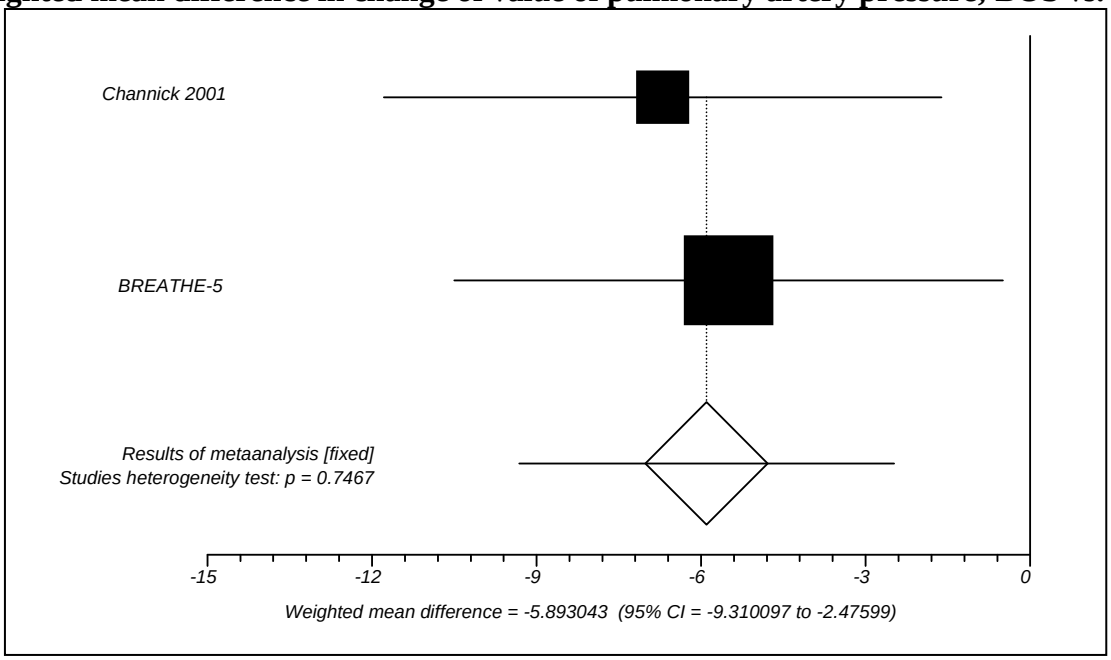
Study	Interven-tion	N	Baseline value (SD) [mmHg]	Final value (SD) [mmHg]	Change from baseline	Mean difference in change between the groups (95% CI)
Channick 2001	BOS	20	54.00 (13.00)	n.d.	-1.60	-6.70 (-11.90 to -1.5)
	PL	10	56.00 (10.00)	n.d.	5.10	
BREATHE-5	BOS	37	77.80 (15.20)	n.d.	-5.00	-5.50 (-10.50 to -0.50)*
	PL	17	72.10 (19.40)	n.d.	0.50	

* calculated from data reported in the study

In both clinical trials the difference between the experimental group and the control group was statistically significant. Mean difference in change between the groups in the study of *Channick 2001* was -6.70, while in the BREATHE-5 study it was 5.50 in favor of BOS.

Results of the metaanalysis are presented in the figure below.

Figure 8.
Weighted mean difference in change of value of pulmonary artery pressure; BOS vs. PL



Weighted mean difference in change of pulmonary artery pressure between the assessed groups is -5.89 (95% CI: -9.31 to -2.48; p = 0.0007); reduction of pulmonary artery pressure is therefore greater by 5.89 mmHg in the BOS group as compared to the PL group.

3.1.4.12.2. Pulmonary vascular resistance index

Numeric data making it possible to perform a metaanalysis for pulmonary vascular resistance index were reported in the studies of *Channick 2001* and BREATHE-5. This index was evaluated over a period of 12 to 16 weeks. Results of both clinical trials are presented below.

Table 18.
Change of pulmonary vascular resistance index; BOS vs. PL

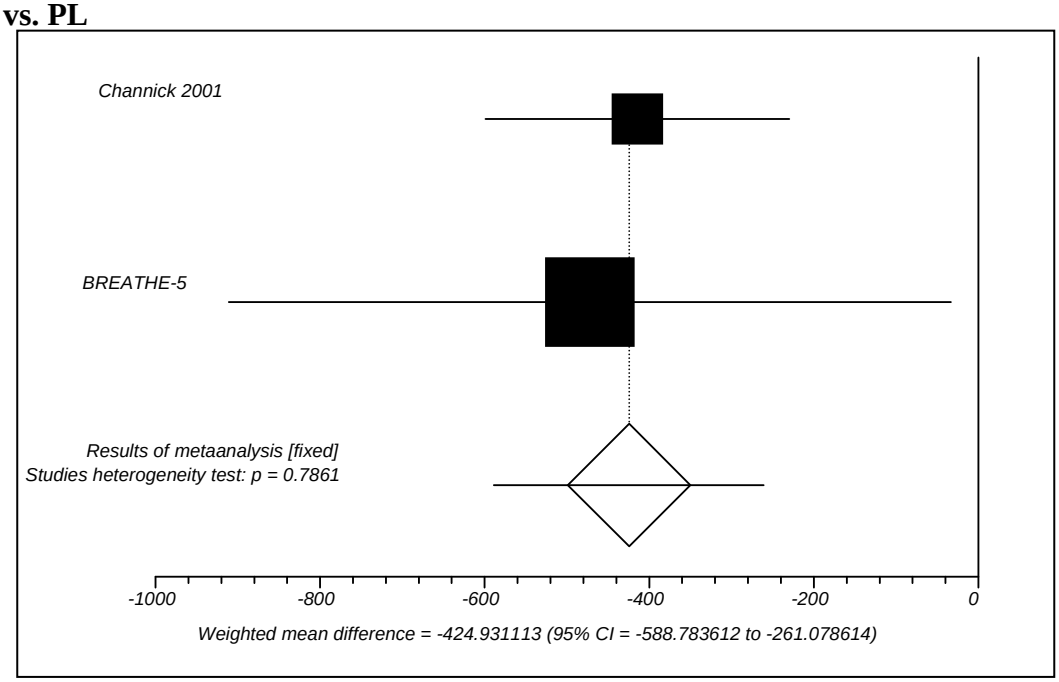
Study	Intervention	N	Baseline value (SD) [dyn*s*cm^{-5}]	Change from baseline (SD) [dyn*s*cm^{-5}]	Mean difference in change between the groups (95% CI)
Channick 2001	BOS	19	896 (425)	-223	-415 (-608 to -221)
	PL	10	942 (430)	191	
BREATHE-5	BOS	37	3425.10 (1410.50)	-316.90	-472.00 (-910.81 to -33.18)*
	PL	17	2870.00 (1209.30)	155.10	

* calculated from data reported in the study

In both studies reduction of pulmonary vascular resistance index was statistically significantly higher in the BOS group as compared to the PL group.

Weighted mean difference in change of pulmonary vascular resistance index between the BOS and PL groups is presented below.

Figure 9.
Weighted mean difference in change of value of pulmonary vascular resistance index; BOS vs. PL



In patients treated with BOS change of pulmonary vascular resistance index is greater by 424.93 dyn*s*cm^{-5} as compared with patients receiving placebo. Weighted mean difference in changes was -424.93 dyn*s*cm^{-5} (95% CI: -588.78 to -261.08; p = 0.0001). The result is statistically significant.

3.1.4.12.3. Cardiac index

Cardiac index, i.e. relation between cardiac output and the body surface area, was assessed only in the *Channick 2001* study. The observation period was 12 weeks.

Information presented in this clinical trial is summarized below.

Table 19.
Mean values of cardiac index; BOS vs. PL

Study	Intervention	N	Baseline value (SD) [L*min^{-1}m^{-2}]	Final value (SD)	Change from baseline	Mean difference in change between the groups (95% CI)
Channick 2001	BOS	20	2.4 (0.7)	n.d.	0.5 (0.45*)	1.0 (0.6 to 1.4)
	PL	10	2.5 (1.0)	n.d.	-0.5 (0.32*)	

* calculated from data reported in the study

Mean difference in change of cardiac index between the therapeutic groups is 1.0 (95% CI: 0.6 to 1.4), in favor of the BOS group. The result is statistically significant.

3.1.5. Assessment of safety

Information concerning adverse events was presented in all the studies included in the analysis. The most common adverse events were: headache, cough, palpitation, nausea, edema, syncope, sinus and nasal congestion, hepatic disorders, vertigo.

3.1.5.1. Any adverse event

Total number of patients, in whom any adverse event was observed, was reported in the trials of *Channick 2001* and *Barst 2006*. Numbers and percentages of patients, in whom this endpoint occurred, are presented in the table below.

Table 20.
Numbers and percentages of patients, in whom any adverse event was observed; BOS vs. PL

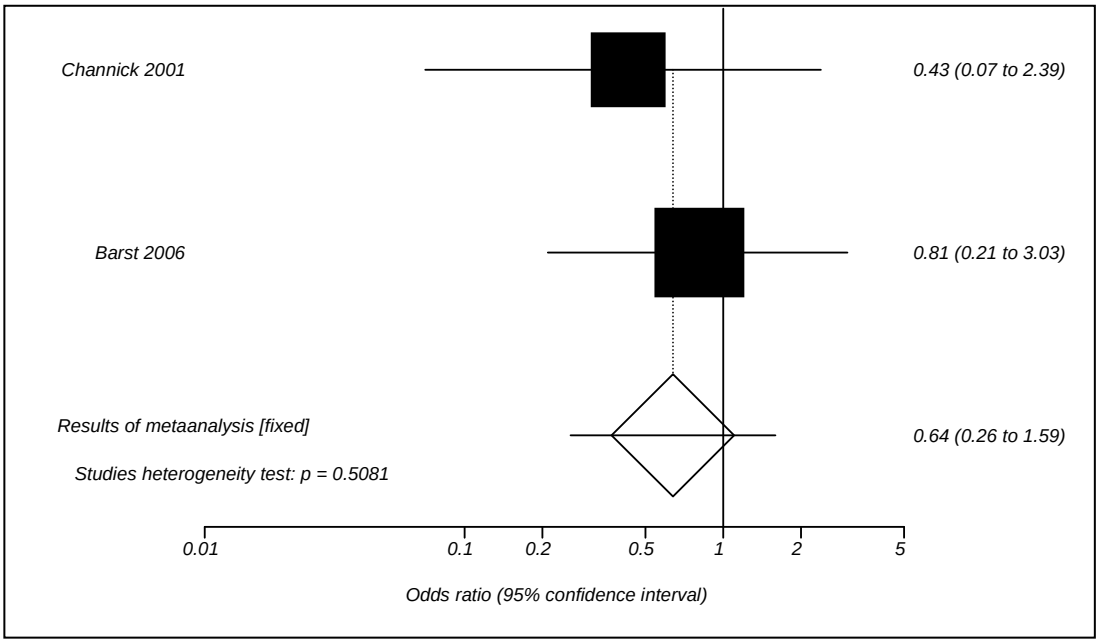
Study	BOS			PL			Statistical significance of differences between the groups; BOS vs. PL
	N	n	Percen-tage	N	n	Percen-tage	
Channick 2001	21	9	43%	11	7	64%	n.s. *
Barst 2006	60	53*	89%	62	56*	90%	n.s.*

* calculated from data reported in the study

From these data it may be concluded that adverse events occurred more often in the PL groups than in the BOS groups. However, differences between the experimental group and the control group were not statistically significant in any of the clinical trials.

A metaanalysis for the total number of patients, in whom any adverse event was observed, is presented below.

Figure 10.
Metaanalysis for the total number of patients, in whom any adverse event was observed; BOS vs. PL



The odds ratio for occurrence of any adverse event is 0.64 (95% CI: 0.26 to 1.59, p = 0.4629). It means that the odds of occurrence of any adverse event in the BOS group is 64% of this odds in the PL group. The result is not statistically significant.

3.1.5.2. Serious adverse events

Serious adverse events were reported in the *Barst 2006* and BREATHE-5 studies over an observation period of 16-18 weeks.

Detailed results are presented in the table below.

Table 21.
Numbers and percentages of patients, in whom serious adverse events were observed; BOS vs. PL

Study	BOS			PL			Statistical significance of differences between the groups; BOS vs. PL
	N	n	Percen-tage	N	n	Percen-tage	
Barst 2006	60	n.d.	n.d.	62	19*	31%	n.d.
BREATHE-5	37	5	14%	17	3	18%	n.s.*

* calculated from data reported in the study

Authors of the BREATHE-5 study reported one case of each of the following adverse events in the experimental group: biliary colic, cholelithiasis, vasovagal syncope, angina pectoris, sinus tachycardia. In the control group the following adverse events were observed (one case each): epigastric pain, respiratory failure, acute cholecystitis.

Due to incomplete data in the *Barst 2006* clinical trial it was not possible to perform a metaanalysis of the results of both studies.

From the results of the *BREATHE-5* study the odds ratio of 0.73 was calculated (95% CI: 0.12 to 5.38). It means that the odds of occurrence of a serious adverse event in the BOS group is 73% of this odds in the PL group. The result is not statistically significant.

3.1.5.3. Headache

Occurrence of headache was reported in the following studies: *Rubin 2002*, *Barst 2006*, and BREATHE-5. Data concerning this endpoint are summarized below. The observation period was 16-18 weeks.

Detailed data are summarized in the table below.

Table 22.
Numbers and percentages of patients, in whom headache was observed; BOS vs. PL

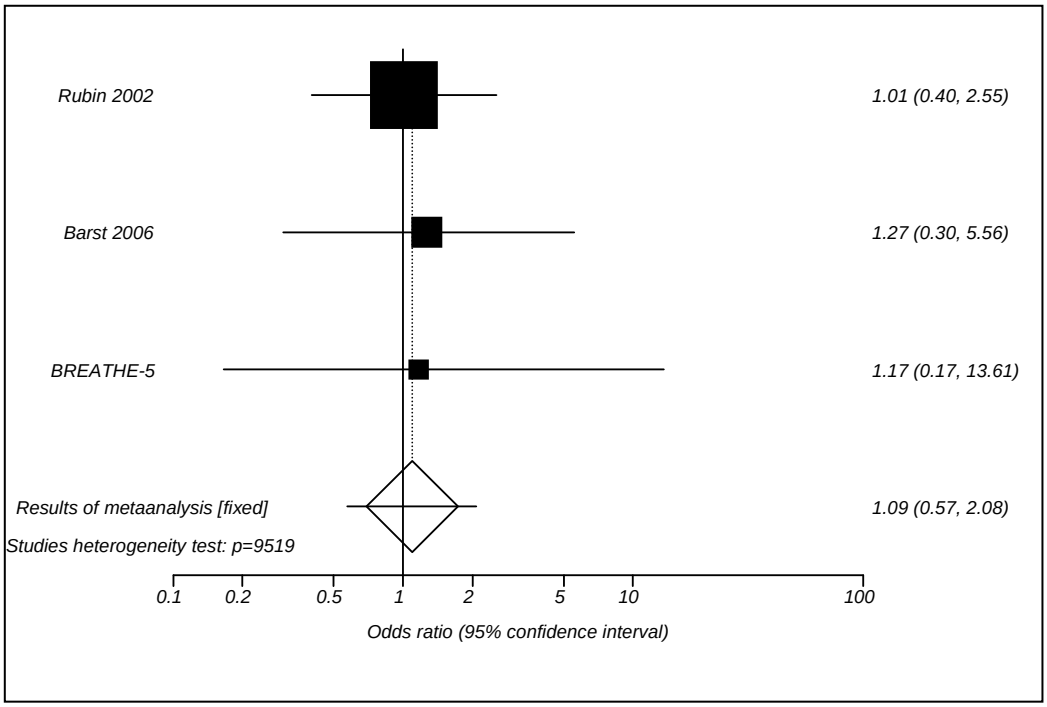
Study	BOS			PL			Statistical significance of differences between the groups; BOS vs. PL
	N	n	Percentage	N	n	Percentage	
Rubin 2002	74	14	19%	69	13	19%	p = 1.00
Barst 2006	60	6	10%*	62	5	8%*	n.s. *
BREATHE-5	37	5	14%	17	2	12%*	n.s. *

* calculated from data reported in the study

In all the studies differences between the groups concerning occurrence of headache were slight. They were not statistically significant in any of the trials.

A metaanalysis for the total number of patients, in whom such adverse events were observed, is presented in the figure below.

Figure 11.
Metaanalysis for the total number of patients, in whom headache was observed; BOS vs. PL



The odds ratio for occurrence of headache is 1.09 (95% CI: 0.57 to 2.08, p = 0.9163). It means that the odds of occurrence of adverse events of this kind in the BOS group is 109% of this odds in the PL group. The result is not statistically significant.

In the study of *Rubin 2002* the results for BOS 250 mg were presented separately. The odds ratio calculated from the results of this study is 1.28 (95% CI: 0.52 to 3.18), which means that the odds of occurrence of headache is higher in the group of patients treated with bosentan at a dose of 250 mg and is 128% of this odds in the PL group. The result is not statistically significant.

3.1.5.4. Cough

Numbers and percentages of patients, in whom cough was observed (in an observation period of 16 weeks), were reported only in the *Rubin 2002* clinical trial. Summary of the data is presented below.

Table 23.
Numbers and percentages of patients, in whom cough was observed; BOS vs. PL

Study	BOS			PL			Statistical significance of differences between the groups; BOS vs. PL
	N	n	Percen-tage	N	n	Percen-tage	
Rubin 2002	74	4	5%	69	8	12%	n.s.

The odds ratio for this endpoint is 0.44 (95% CI: 0.09 to 1.73); the odds of occurrence of cough in the group receiving BOS at a dose of 125 mg is therefore 44% of this odds in the PL group. The result is not statistically significant.

The odds of occurrence of cough in the group receiving BOS at a dose of 250 mg is 46% of this odds in the PL group. The odds ratio is 0.46 (95% CI: 0.10 to 1.89) and the result is not statistically significant.

3.1.5.5. Palpitations

Palpitations were assessed only in the BREATHE-5 study. Detailed numbers and percentages of patients, in whom this endpoint occurred, are presented in the table below.

Table 24.
Numbers and percentages of patients, in whom palpitations were observed; BOS vs. PL

Study	BOS			PL			Statistical significance of differences between the groups; BOS vs. PL
	N	n	Percentage	N	n	Percentage	
BREATHE-5	37	4	11%	17	0	0%	n.s.*

* calculated from data reported in the study

From these data it may be concluded that palpitation was observed more often among patients treated with bosentan as compared to the placebo group. However, differences between the therapeutic groups were not statistically significant.

3.1.5.6. Nausea

Adverse events of this kind were reported only in the study of *Barst 2006*. They were observed in only 4 patients in the PL group. Detailed summary of the data is presented below.

Table 25.
Numbers and percentages of patients, in whom nausea was observed; BOS vs. PL

Study	BOS			PL			Statistical significance of differences between the groups; BOS vs. PL
	N	n	Percen-tage	N	n	Percen-tage	
Barst 2006	60	0*	0%	62	4*	6%	s.s.*

* calculated from data reported in the study

The odds ratio calculated using the *Peto* method is 0.13 (95% CI: 0.02 to 0.97). It means that the odds of occurrence of nausea in the group treated with BOS is 13% of this odds in the PL group, and the result is statistically significant; NNT = 16 (95% CI: 7 to 28547).

3.1.5.7. Peripheral edema

Incidence of peripheral edema observed in the clinical trials of *Barst 2006* and BREATHE-5 is summarized below.

Table 26.
Numbers and percentages of patients, in whom edema was observed; BOS vs. PL

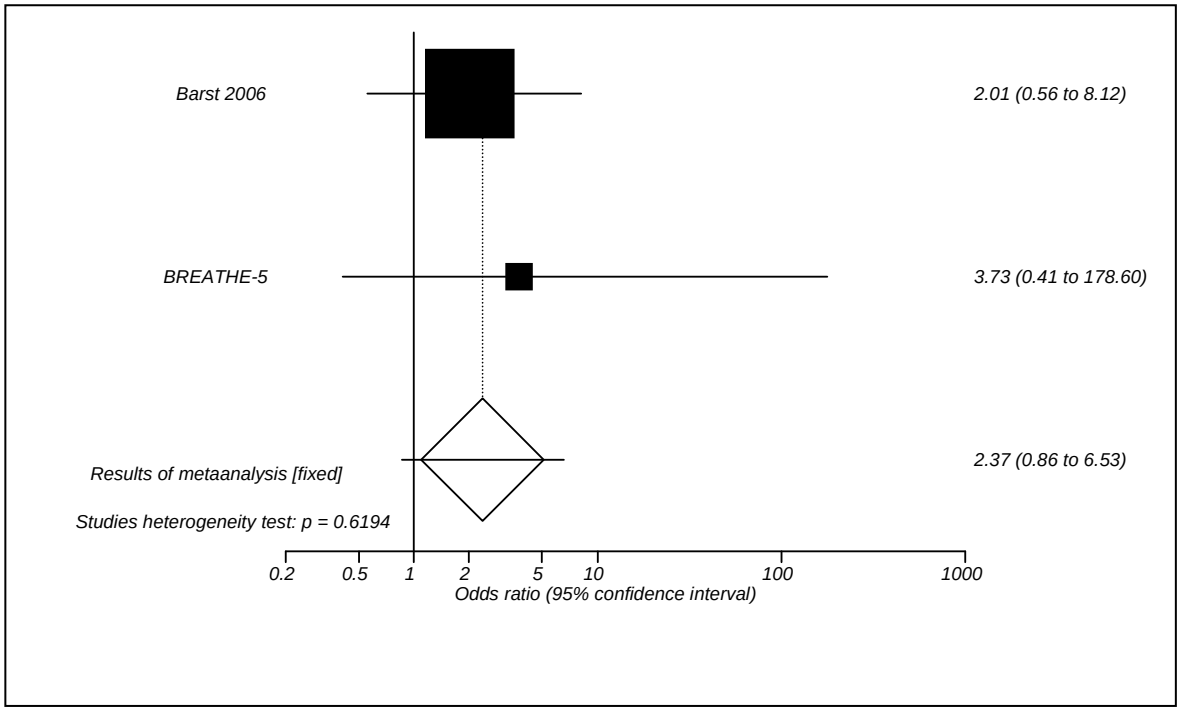
Study	BOS			PL			Statistical significance of differences between the groups; BOS vs. PL
	N	n	Percentage	N	n	Percentage	
Barst 2006	60	9	15%*	62	5	8%*	n.s.*
BREATHE-5	37	7	19%*	17	1	6%*	n.s.*

* calculated from data reported in the study

In both clinical trials peripheral edema was more frequent in the BOS group as compared to the PL group. However, the difference between the groups was not statistically significant in any of the studies.

A metaanalysis for the total number of patients, in whom peripheral edema was observed, is presented below.

Figure 12.
Metaanalysis for the total number of patients, in whom peripheral edema was observed; BOS vs. PL



The odds ratio is 2.37 (95% CI: 0.86 to 6.53, p = 0.145). It means that the odds of occurrence of peripheral edema in the BOS group is 237% of this odds in the PL group. However, the result is not statistically significant.

3.1.5.8. Syncope

Syncope was listed among adverse events only in the study of *Rubin 2002*.

Data concerning this endpoint for the groups of BOS 125 mg and PL are summarized below.

Table 27.
Numbers and percentages of patients, in whom syncope was observed; BOS vs. PL

Study	BOS			PL			Statistical significance of differences between the groups; BOS vs. PL
	N	n	Percentage	N	n	Percentage	
Rubin 2002	74	6	8%	69	4	6%	n.s.*

* calculated from data reported in the study

In the *Rubin 2002* study syncope was observed slightly more often in the BOS 125 mg group as compared with the control group: The odds of occurrence of syncope in the group receiving BOS at a dose of 125 mg is 143% of this odds in the PL group. The odds ratio is 1.43 (95% CI: 0.32 to 7.22). The result is not statistically significant.

The odds of occurrence of syncope in the BOS 250 mg group is 181% of this odds in the control group. The odds ratio is 1.81 (95% CI: 0.43 to 8.80). The result is not statistically significant.

3.1.5.9. Sinus congestion

Cases of sinus congestion were reported only in the study of *Barst 2006*.

Detailed data are summarized below.

Table 28.
Numbers and percentages of patients, in whom sinus congestion was observed; BOS vs. PL

Study	BOS			PL			Statistical significance of differences between the groups; BOS vs. PL
	N	n	Percentage	N	n	Percentage	
Barst 2006	60	5	8%*	62	4	6%*	n.s.*

* calculated from data reported in the study

In the *Barst 2006* study sinus congestion was observed slightly more often in the BOS group as compared to the PL group. The odds of occurrence of this endpoint in the BOS group was 132% of this odds in the PL group. The odds ratio is 1.32 (95% CI: 0.27 to 6.99). The result is not statistically significant.

3.1.5.10. Hepatic disorders

Information concerning hepatic disorders was provided in the studies of *Rubin 2002* and BREATHE-5. These data are summarized in the table below.

Table 29.
Numbers and percentages of patients, in whom hepatic disorders were observed; BOS vs. PL

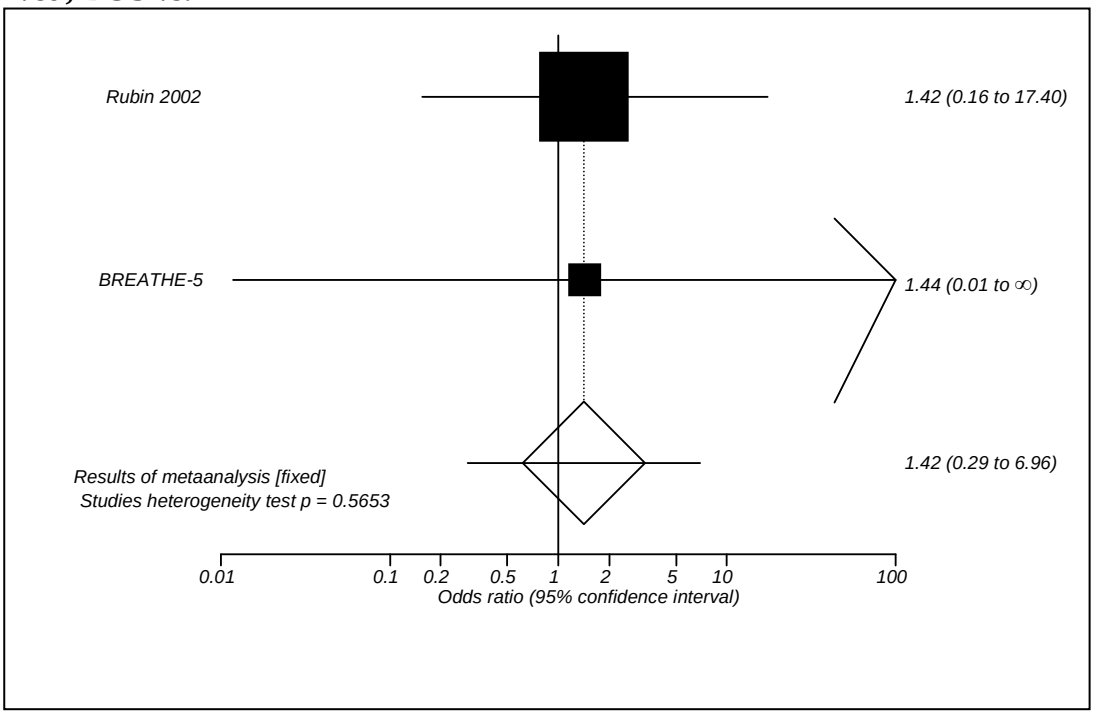
Study	BOS			PL			Statistical significance of differences between the groups; BOS vs. PL
	N	n	Percen-tage	N	n	Percen-tage	
Rubin 2002	74	3	4%	69	2	3%	n.s. *
BREATHE-5	37	1	3%*	17	0	0%*	n.s. *

* calculated from data reported in the study

Hepatic disorders were observed slightly more often in the BOS 125 mg group than in the PL group. However, differences between the BOS 125 mg group and the placebo group were not statistically significant.

A metaanalysis for the total number of patients, in whom this endpoint occurred, is presented in the figure below.

Figure 13.
Metaanalysis for the total number of patients, in whom hepatic disorders were observed; BOS vs. PL



The odds of occurrence of hepatic disorders in the group receiving BOS at a dose of 125 mg is 142% of this odds in the PL group. The odds ratio is 1.42 (95% CI: 0.29 to 6.96; p = 0.9655). The result is not statistically significant.

The odds of occurrence of hepatic disorders in the group receiving BOS at a dose of 250 mg is 558% of this odds in the control group. The odds ratio is 5.58 (95% CI: 1.11 to 53.84). The result is statistically significant.

The remaining EBM parameters for occurrence of hepatic disorders in the BOS 250 mg group as compared to the PL group are presented in the table below.

Table 30.
Hepatic disorders – additional EBM parameters; BOS 250 mg vs. PL

RR (95% CI)	RRI (95% CI)	ARI (95% CI)	NNH (95% CI)
4.93 (1.28 to 19.60)	3.93 (0.28 to 18.60)	0.11 (0.02 to 0.22)	9 (5 to 43)

The relative risk of occurrence of hepatic disorders is 4.93 (95% CI: 1.28 to 19.60). In the BOS 250 mg group the risk of this adverse event was 393% of this risk in the PL group. The relative risk increase is 3.93 (95% CI: 0.28 to 18.60). The absolute risk increase is 11 percentage points (95% CI: 0.02 to 0.22). Treatment of 9 patients with BOS at a dose of 250 mg instead of PL for a period of 12 weeks will result in additional development of hepatic disorders in one of them; NNH = 9 (95% CI: 5 to 43).

3.1.5.11. Flushing

In the study of *Rubin 2002* information concerning incidence of flushing (usually of the face) in patients receiving BOS at doses of 125 and 250 mg or placebo was provided. Detailed numeric data for patients receiving the drug at a dose of 125 mg or 250 mg and for the control group are summarized below.

Table 31.
Numbers and percentages of patients, in whom flushing was observed; BOS vs. PL

Study	BOS			PL			Statistical significance of differences between the groups; BOS vs. PL
	N	n	Percentage	N	n	Percentage	
Rubin 2002	74	7	9%	69	3	4%	p = 0.28*

* calculated from data reported in the study

The odds ratio for this endpoint is 2.30 (95% CI: 0.50 to 14.28), which means that the odds of occurrence of flushing in the group receiving BOS at a dose of 125 mg is 230% of this odds in the PL group. The result is not statistically significant.

The odds of occurrence of flushing in the BOS 250 mg group is 206% of this odds in the PL group. The odds ratio for flushing is 2.06 (95% CI: 0.42 to 13.22). The result is not statistically significant.

3.1.5.12. Vertigo

Data concerning vertigo were extracted from the studies of *Rubin 2002*, *Barst 2006* and BREATHE-5. Summary of the results pertaining to this endpoint is presented below.

Table 32.
Numbers and percentages of patients, in whom vertigo was observed; BOS vs. PL

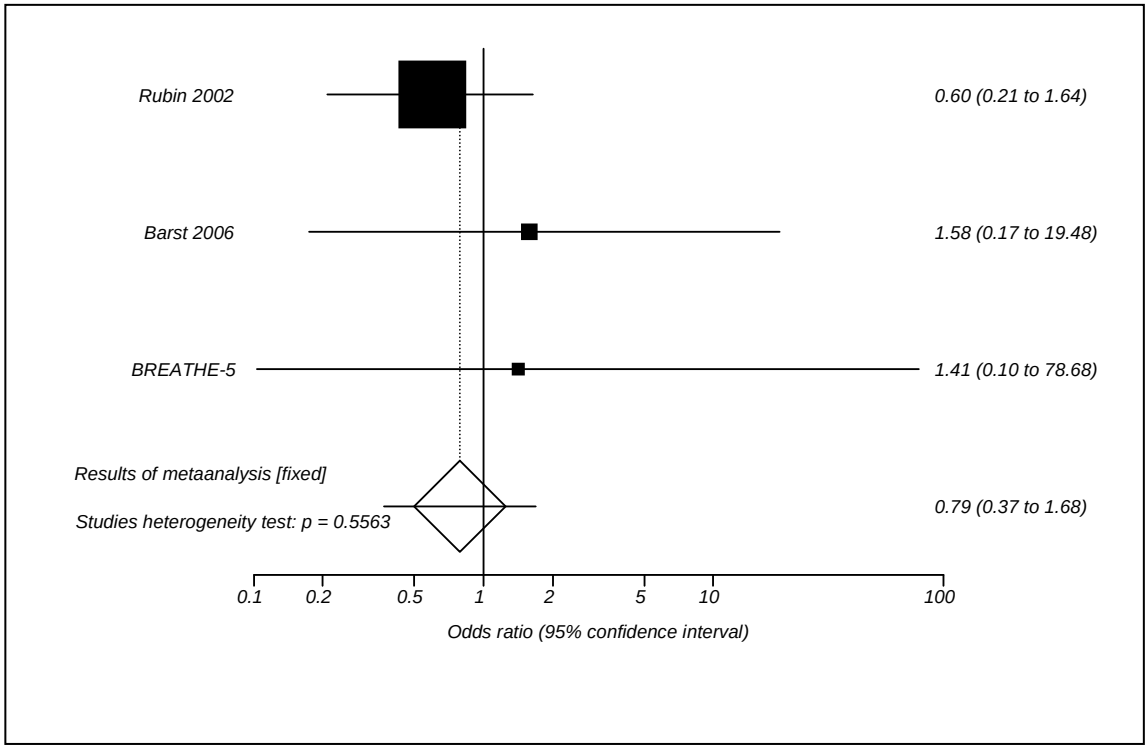
Study	BOS			PL			Statistical significance of differences between the groups; BOS vs. PL
	N	n	Percentage	N	n	Percentage	
Rubin 2002	74	9	12%	69	13	19%	p = 0.35*
Barst 2006	60	3	5%*	62	2	3%*	n.s.*
BREATHE-5	37	3*	8%	17	1*	6%	n.s.*

* calculated from data reported in the study

In the clinical trial of *Rubin 2002* vertigo was observed more frequently in the PL group as compared to the BOS group. In both remaining studies it was observed slightly more often in the BOS group than in the PL group.

A metaanalysis for the total number of patients, in whom vertigo was observed, is presented below.

Figure 14.
Metaanalysis for the total number of patients, in whom vertigo was observed; BOS vs. PL



The odds of occurrence of vertigo in the group receiving BOS at a dose of 125 mg is 79% of this odds in the PL group. The odds ratio is 0.79 (95% CI: 0.37 to 1.68; p = 0.6753). The result is not statistically significant.

The odds of occurrence of this adverse event in the BOS 250 mg group is 48% of this odds in the control group. The odds ratio is 0.48 (95% CI: 0.15 to 1.41). The result is statistically insignificant.

3.1.5.13. Chest pain or pressure

Incidence of chest pain was reported only by the authors of the BREATHE-5 study. Numbers and percentages of patients, in whom adverse events of this kind were observed, are presented below.

Table 33.
Numbers and percentages of patients, in whom chest pain was observed; BOS vs. PL

Study	BOS			PL			Statistical significance of differences between the groups; BOS vs. PL
	N	n	Percen-tage	N	n	Percen-tage	
BREATHE-5	37	3*	8%	17	0*	0%	**n.s.***

* calculated from data reported in the study

Chest pain was observed only in 3 patients in the experimental group. No such cases were reported in the PL group.

The odds of occurrence of chest pain in the BOS group is 3.45 higher than this odds in the PL group. The odds ratio with Haldane correction for this endpoint is 3.45 (95% CI: 0.30 to infinity). The result is not statistically significant.

3.1.5.14. Fatigue

Fatigue was observed in the *Barst 2006* study. Numbers and percentages of patients, in whom this adverse event occurred, are presented below.

Table 34.
Numbers and percentages of patients, in whom fatigue was observed; BOS vs. PL

Study	BOS			PL			Statistical significance of differences between the groups; BOS vs. PL
	N	n	Percen-tage	N	n	Percen-tage	
Barst 2006	60	3	5%*	62	2	3%*	n.s.

* calculated from data reported in the study

In this clinical trial fatigue was observed slightly more often in the BOS group than in the PL group.

The odds of occurrence of fatigue in the BOS group is 158% of this odds in the PL group. The odds ratio for this endpoint is 1.58 (95% CI: 0.17 to 19.48). The result is not statistically significant.

3.1.5.15. Exacerbation of symptoms of PAH

Incidence of exacerbation of symptoms of PAH was assessed in the study of *Rubin 2002*. Numbers and percentages of patients, in whom this adverse event occurred, are presented below.

Table 35.
Numbers and percentages of patients, in whom exacerbation of symptoms of PAH was observed; BOS vs. PL

Study	BOS			PL			Statistical significance of differences between the groups; BOS vs. PL
	N	n	Percentage	N	n	Percentage	
Rubin 2002	74	7	9%	69	13	19%	p = 0.15

The odds of exacerbation of symptoms of PAH in the group of patients receiving BOS at a dose of 125 mg is 45% of this odds in the PL group. The odds ratio for this endpoint is 0.45 (95% CI: 0.14 to 1.32). The result is not statistically significant.

The odds of exacerbation of symptoms of PAH in the group of BOS at a dose of 250 mg is 26% of this odds in the PL group. The odds ratio for this endpoint is 0.26 (95% CI: 0.06 to 0.92). The result is statistically significant.

The remaining EBM parameters for exacerbation of symptoms of PAH were calculated and are presented in the table below.

Table 36.
Additional EBM parameters for exacerbation of symptoms of PAH; BOS 250 mg vs. PL

RR (95% CI)	RRR (95% CI)	ARR (95% CI)	NNT (95% CI)
0.30 (0.11 to 0.83)	0.70 (0.17 to 0.89)	0.13 (0.02 to 0.25)	8 (5 to 43)

The relative risk of exacerbation of symptoms of PAH is 0.30 (95% CI: 0.11 to 0.83). In the BOS 250 mg group the risk of this adverse event was 70% lower as compared to the PL group. The relative risk reduction is 0.70 (95% CI: 0.17 to 0.89). The absolute risk reduction was 13 percentage points (95% CI: 0.02 to 0.25). Treatment of 8 patients with BOS at a dose of 250 mg instead of PL for a period of 12 weeks will make it possible to avoid one additional case of exacerbation of symptoms of PAH; NNT = 8 (95% CI: 5 to 43).

3.1.5.16. Dyspnea

This endpoint was assessed only in the study of *Rubin 2002*. Numbers and percentages of patients, in whom this adverse event was observed, are presented below.

Table 37.
Numbers and percentages of patients, in whom dyspnea was observed; BOS vs. PL

Study	BOS			PL			Statistical significance of differences between the groups; BOS vs. PL
	N	n	Percentage	N	n	Percentage	
Rubin 2002	74	2	3%	69	7	10%	p = 0.09

The odds of occurrence of dyspnea in the group receiving BOS at a dose of 125 mg is 25% of this odds in the PL group. The odds ratio for this endpoint is 0.25 (95% CI: 0.02 to 1.37). The result is not statistically significant.

The odds of occurrence of dyspnea in the group receiving BOS at a dose of 250 mg is 68% of this odds in the PL group. The odds ratio for this endpoint is 0.68 (95% CI: 0.16 to 2.65). The result is not statistically significant.

3.1.5.17. Withdrawal from the study due to adverse events

Withdrawal from the study due to adverse events was assessed in all the studies included in the analysis. Numbers and percentages of patients withdrawn from the study due to adverse events are summarized below.

Table 38.
Numbers and percentages of patients withdrawn from the study due to adverse events; BOS vs. PL

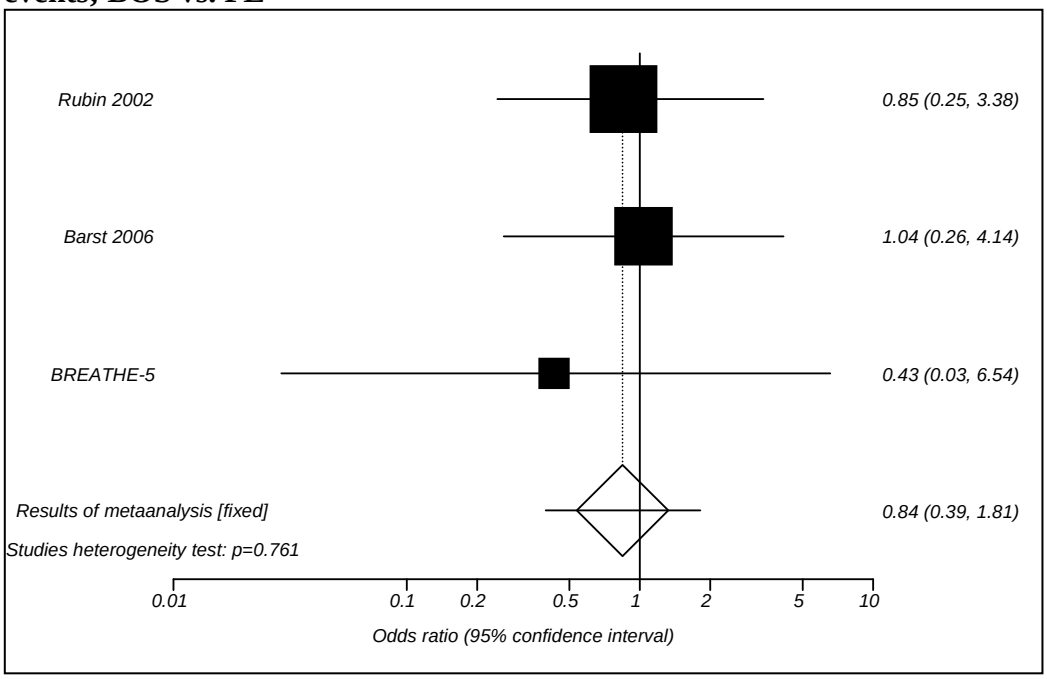
Study	BOS			PL			Statistical significance of differences between the groups; BOS vs. PL
	N	n	Percentage	N	n	Percentage	
Channick 2001	21	0	0%	11	0	0%	n.a.
Rubin 2002	144	9	6%	69	5	7%	
Barst 2006	60	6	10%	62	6	10%	n.s.*
BREATHE-5	37	2	5%	17	2	12%	n.s.*

* calculated from data reported in the study

In the studies of *Rubin 2002* and BREATHE-5 the percentage of patients withdrawn from the study due to adverse events was higher in the bosentan group as compared to the placebo group. In the *Barst 2006* study the percentage of patients withdrawn from the study due to adverse events was equal in both groups (BOS and PL). In the clinical trial of *Channick 2001* no patients were withdrawn due to adverse events in any of the compared groups.

A metaanalysis for the total number of patients withdrawn from the studies due to adverse events is presented below.

Figure 15.
Metaanalysis for the total number of patients withdrawn from the study due to adverse events; BOS vs. PL



The odds ratio is 0.84 (95% CI: 0.39 to 1.81, p = 0.811), which means that the odds of withdrawal of a patient due to adverse events is lower in the bosentan group and is 84% of the odds in the placebo group. The result is not statistically significant.

3.2. Epoprostenol vs. placebo

3.2.1. Results of the search for the studies

In searched medical databases three primary multicenter randomized clinical studies fulfilling the inclusion criteria were identified, in which epoprostenol (EPO) used in combination with conventional treatment (CT) was compared to CT alone: *Rubin 1990*, *Barst 1996* and *Badesch 2000*. None of the studies was double-blind. Detailed characteristics of the studies and publications related to them are presented in the table below.

Table 39.
Characteristics of the studies included in the analysis; EPO vs. CT

Study	Publications	Observation period	*Jadad* score
Rubin 1990	*Rubin 1990*	8 weeks	3
Barst 1996	*Barst 1996* *Hinderliter 1997* *Langleben 1999* *Raymond 2002*	12 weeks	3
Badesch 2000	*Badesch 2000*	12 weeks	3

Duration of the observation period in the included studies ranged from 8 weeks in the *Rubin 1990* study to 12 weeks in the trials of *Barst 1996* and *Badesch 2000*. Each of the trials mentioned above scored 3 points in the *Jadad* scale.

3.2.2. Description of the population

In all the analyzed studies patients with pulmonary arterial hypertension participated. In the *Rubin 1990* and *Barst 1996* studies patients with primary pulmonary arterial hypertension diagnosed according to the NIH *(National Institutes of Health)* were recruited, while in the study of *Badesch 2000* patients with pulmonary hypertension associated with collagenosis participated; the condition was defined as systemic or circumscribed scleroderma (deposition of calcium in the subcutaneous tissue *(calcinosis cutis)*, Rayanud's phenomenon, clinically defined disorders of esophageal function, scleroderma of the fingers or teleangiectases), systemic scleroderma accompanying other connective tissue diseases or presence of certain signs of systemic scleroderma, including Raynaud's phenomenon and positive test for antinuclear, antri-centromere or anti-Scl-70 antibodies, or fingernail capillary abnormalities.

The patients in the studies of *Rubin 1990* and *Badesch 2000* were in NYHA (*New York Heart Association*) class II-IV, while those in the *Barst 1996* trial – in NYHA class III or IV.

In the clinical trial of *Rubin 1990* patients who did not respond to treatment or did not tolerate one or more vasodilators commonly used in pulmonary hypertension were enrolled. All patients received stable doses of such drugs for a minimum of two weeks before enrollment. In the *Barst 1996* study all patients received standard treatment with anticoagulants, oral vasodilators, diuretics, cardiac glycosides and oxygen, while in the *Badesch 2000* trial the patients might remain on a long-term therapy for pulmonary hypertension, provided that this therapy was introduced at least a month before enrollment. Patients who discontinued such treatment (excepting anticoagulants) less than a week prior to enrollment as well as those receiving prostaglandins were excluded from the study.

Additional inclusion criteria for patients in the *Badesch 2000* trial were: age over 16 years, ability to walk at least 50 m within 6 minutes, moderate or severe pulmonary hypertension (mean pulmonary artery pressure ≥ 35 mmHg, pulmonary vascular resistance ≥ 3 mmHg/l/min, right atrial pressure ≤ 20 mmHg, no congenital heart disease, pulmonary capillary wedge pressure or left ventricular end-systolic pressure ≤ 15 mmHg; if these parameters could not be measured, disease of the left heart was excluded by means of echocardiography).

In two studies *(Rubin 1990, Badesch 2000)* thromboembolic disease was listed among the exclusion criteria for patients; this was diagnosed by means of pulmonary perfusion scintigraphy or, in case of doubts, pulmonary arteriography. From the study of *Badesch 2000* patients with interstitial lung disease other than mild were also excluded.

Detailed baseline characteristics of the patients enrolled in specific clinical trials are presented below.

Table 40.
Baseline characteristics of the patients enrolled in particular studies; EPO vs. CT

Study	Number of patients		Mean age (SD) [years]		Percentage of men		Percentage of patients with primary PAH/ PAH associated with collagenoses		Percentage of patients in NYHA functional class II/III/IV		Percentage of patients treated with oral vasodilators		Mean time from diagnosis (SD) [months]		Mean 6-minute walk distance (SD) [m]	
	EPO	CT	EPO	CT	EPO	CT	EPO	CT	EPO	CT	EPO	CT	EPO	CT	EPO	CT
Rubin 1990	11	12	38.4 (nd)*	35.0 (nd)*	36.4%*	25.0%*	100%/0%*	100%/0%*	9%/82%/9%*	8%/50%/42%*	nd	nd	nd	nd	246 (nd)	205 (nd)
Barst 1996	41	40	40 (19*)	40 (13*)	24%	30%	100%/0%	100%/0%	0%/76%/24%	0%/73%/28%	66%	60%	32 (51*)	25 (38*)	316 (115*)	272 (146*)
Badesch 2000	56	55	53.0 (13.1)	57.3 (10.3)	9%	18%	0%/100%	0%/100%	2%/75%/23%	7%/82%/11%	68%	69%	14.5 (17.9)	15.2 (20.1)	271.5**	240.0**
Total	108	107	46.6	48.3	17.5%	23.3%	-	-	2%/76%/22%	5%/75%/21%	67%	65%	21.9	19.3	301#	257#

* Calculation based on available data
** Median value
# Based on 2 studies

A total number of 215 patients participated in three investigated studies, of whom 108 were appointed to the epoprostenol group (EPO) and 107 to the conventional treatment group (CT). Mean age was 46.6 years in the epoprostenol group and 48.3 years in the conventional treatment group; the percentage of men was 17.5% and 23.3%, respectively, and the percentage of patients in NYHA functional class II: 2% and 5%, class III: 76% and 75% and class IV: 22% and 21%, respectively. Oral vasodilators were administered to 67% of patients in the epoprostenol group and 65% in the conventional treatment group, mean duration of the disease was 21.9 and 19.3 months and mean 6-minute walk distance: 301 m and 257 m, respectively.

From the above data it may be concluded that baseline characteristics of the patients with primary pulmonary hypertension in the studies of *Rubin 1990* and *Barst 1996* are similar as to mean age and the percentage of men, being different as to the NYHA functional class and mean 6-minute walk distance. In the *Badesch 2000* study, in which patients with PAH associated with connective tissue diseases took part, the percentage of men was lower and mean age was slightly higher as compared to the studies of *Rubin 1990* and *Barst 1996.*

The authors of two clinical trials *(Barst 1996* and *Badesch 2000)* did not find any statistically significant differences in the patients' baseline characteristics. This information was not provided in the *Rubin 1990* study.

3.2.3. Description of the interventions

In all three studies included in the analysis the patients were randomly assigned to the group receiving epoprostenol with conventional treatment (EPO) or the group, in which the patients received conventional treatment alone.

Details of dosage and the route of administration of epoprostenol as well as drugs used in conventional treatment are presented in the table below.

Table 41.
Description of the interventions; EPO vs. CT

Study	EPO	CT	Adjustments in concomitant treatments EPO and CT
Rubin 1990	Epoprostenol at the maximum tolerated dose, administered by intravenous infusion using a catheter and an infusion pump *(Autosyringe AS2F,Travenol Inc., Hooksett, New Hampshire).*	Anticoagulants, oral vasodilators, oxygen, glycosides and/or diuretics at the optimal dose	Warfarin dose adjustment to achieve a prothrombin time 1.3 to 2 times that of controls.
Barst 1996	Epoprostenol at the initial dose of 4 ng/kg of body mass/min below the maximum tolerated dose, which was then adjusted to signs and symptoms of the disease and adverse events. The drug was administered by intravenous infusion using a catheter and an infusion pump *(CADD-1 Model 5100 HF, Pharmacia Deltee, St. Paul, Minnesota*.).	Oral anticoagulants	Nd
Badesch 2000	Epoprostenol at the initial dose ≤ 2 ng/kg of body mass/min, then adjusted to signs and symptoms of the disease and adverse events. The drug was administered by intravenous infusion using a catheter and an infusion pump (*CADD-1 Model 5100 HF, Pharmacia Deltee, St. Paul, Minnesota.)*	Oral anticoagulants, calcium channel blockers	Adjustments in concomitant medications on the basis of clinical judgement.

In the studies of *Rubin 1990* and *Barst 1996* the maximum tolerated dose of epoprostenol was determined before randomization, during an initial period. The right ventricle was catheterized, hemodynamic measurements performed and then epoprostenol was infused at a dose of 1-2 ng/kg of body mass/min *(Rubin 1990)* or 2 ng/kg of body mass/min *(Barst 1996)*, which was increased every 5-15 minutes *(Rubin 1990)* or every 15 minutes *(Barst 1996)*. During infusion the hemodynamic parameters were assessed again. In both clinical trials the infusion was discontinued if peripheral blood pressure decreased by at least 40%, heart rate increased by at least 40% or other adverse events requiring discontinuation (in the physician's opinion) were observed. In the *Badesch 2000* study epoprostenol was administered at an initial dose not higher than 2 ng/kg of body mass/min, which was then increased and adjusted according to severity of signs and symptoms of pulmonary hypertension or possible adverse events during a treatment period of 12 weeks.

In all evaluated studies epoprostenol was administered intravenously into the jugular vein or the subclavian vein, in a continuous infusion using an infusion pump. Before discharge from the hospital the patients were trained in techniques of sterilization of the pump and preparation and administration of the drug.

All patients, both in the epoprostenol group and in the control group, received conventional treatment. In all studies anticoagulants were used, while in the *Rubin 1990* study apart from anticoagulants the patients were treated with oral vasodilators, oxygen, glycosides and/or diuretics and in Badesch 2000 with calcium channel blockers.

3.2.4. Analysis of efficacy

3.2.4.1. Mortality

Mortality was assessed in all studies included in the analysis: *Rubin 1990*, *Barst 1996* and *Badesch 2000*. The observation period ranged from 8 weeks in the *Rubin 1990* trial to 12 weeks in the studies of *Barst 1996* and *Badesch 2000*.
Numbers and percentages of patients who died are presented below.

Table 42.
Numbers and percentages of patients who died; EPO vs. CT

Study	EPO			CT			Statistical significance of differences between the groups; EPO vs. CT
	N	n	Percen-tage	N	n	Percen-tage	
Rubin 1990	10	1	10.0%*	9	3	33.3%*	n.s.*
Barst 1996	41	0	0%*	40	8	20.0%*	p = 0.003
Badesch 2000	56	4	7.1%*	55	5	9.1%*	n.s.

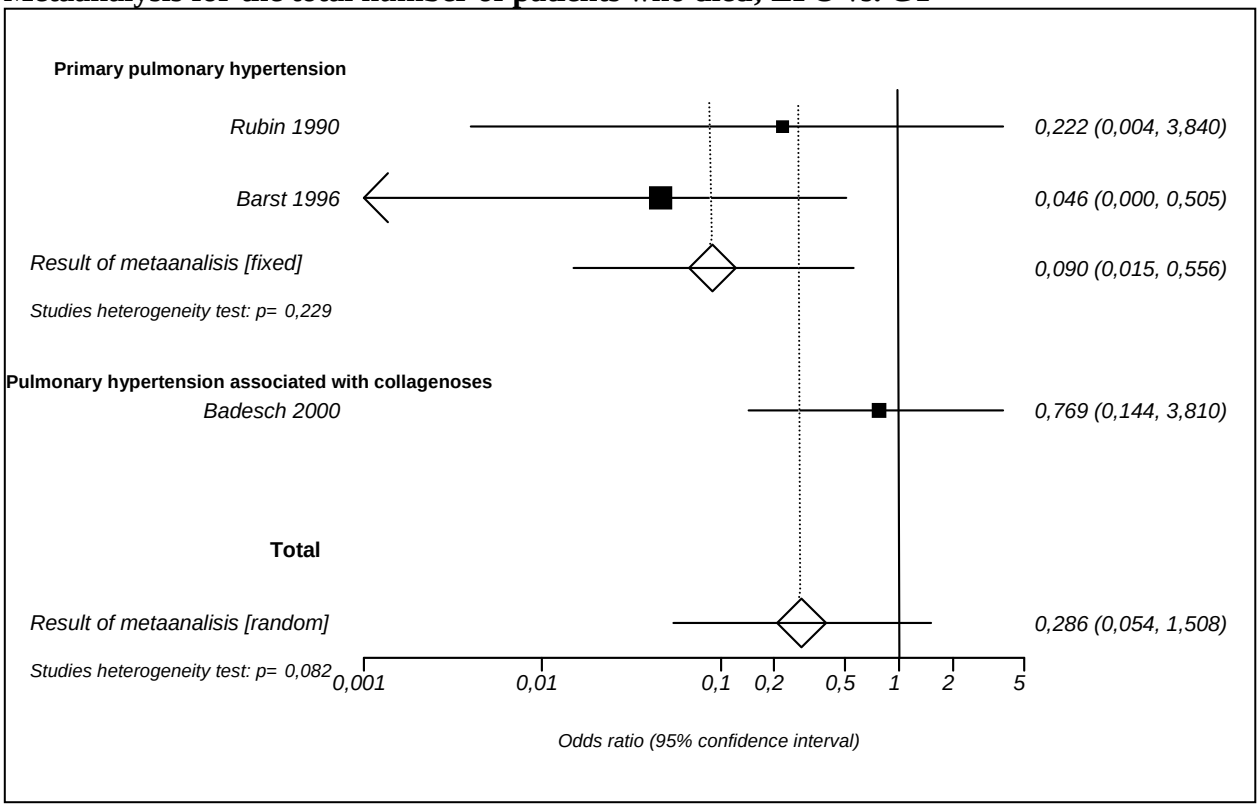
* Calculation based on available data

In all the clinical trials percentages of patients who died during an observation period of 8 or 12 weeks were lower in the EPO group than in the CT group Differences between the groups were statistically significant in the study of *Barst 1996;* in the trial of *Badesch 2000* they did not reach statistical significance and the authors of the *Rubin 1990* study provided no such information.

In the *Rubin 1990* study the cause of death of a patient in the EPO group was occlusion of small pulmonary veins, one of the patients assigned to the CT group died after introduction of treatment with nifedipin due to hypotension resistant to treatment and the two remaining patients in this group died of severe pulmonary hypertension. The causes of death of patients in the EPO group in the study of *Badesch 2000* were: progressive right ventricular failure, myocardial infarction, septic shock and sudden death, while in the conventional treatment group: respiratory failure (in 2 patients), progressive right ventricular failure, acute pulmonary edema and cardiac arrhythmia. The authors of the *Barst 1996* study did not specify the causes of death of patients in the conventional treatment group.

A metaanalysis for the total number of patients with primary hypertension, PAH associated with collagenoses and regardless of the type of hypertension, who died during an observation period of 8-12 weeks, is presented in the figure below.

Figure 16.
Metaanalysis for the total number of patients who died; EPO vs. CT



From this metaanalysis it may be concluded that the odds of death in both populations (the patients with primary PAH and PAH associated with connective tissue diseases) as well as for all patients is lower in the EPO group and is 9%, 77% and 29% of the respective odds in the conventional treatment group; the odds ratio is 0.09 (95% CI: 0.015 to 0.56); p = 0.006 for patients with primary PAH, 0.77 (95% CI: 0.14 to 3.81) for patients with PAH associated with collagenoses and 0.29 (95% CI: 0.05 to 1.51); p = 0.14 for both populations combined. However, the result reached statistical significance only for patients with primary pulmonary hypertension.

Additional EBM parameters calculated for patients with primary PAH are presented in the table below.

Table 43.
Mortality – additional EBM parameters; EPO vs. CT

RR (95% CI)	RRR (95% CI)	ARR (95% CI)	NNT (95% CI)
0.12 (0.02 to 0.64)	0.88 (0.36 to 0.98)	0.21 (0.08 to 0.33)	5 (4 to 13)

The relative risk is 0.12 (95% CI: 0.02 to 0.64), which means that the risk of death is lower in the EPO group and is 12% of this risk in the CT group. The result is statistically significant. The relative risk reduction is 88% (95% CI: 36 to 98), and the absolute risk reduction: 21 p.p. (8 to 33). In order to avoid one additional death epoprostenol must be administered (in addition to conventional treatment) to four patients with primary PAH for a period of 8-12 weeks; NNT = 5 (95% CI: 4 to 13).

3.2.4.2. Quality of life assessment according to the Chronic Heart Failure Questionnaire

Quality of life was assessed using the *Chronic Heart Failure Questionnaire* only in one of the studies included in the analysis: *Barst 1996.* This questionnaire assesses quality of life in four areas: dyspnea, fatigue, emotional function and control of the symptoms of disease. Higher score in this questionnaire reflects improved quality of life.

Median values of change from baseline scores in an observation period of 12 weeks reported by the authors of the *Barst 1996* study are presented in the table below.

Table 44.
Results of assessment of quality of life – *Chronic Heart Failure Questionnaire;* EPO vs. CT

Parameter	EPO		CT		Difference in median values between the groups (95% CI), EPO vs. CT*
	N	Median change	N	Median change	
Dyspnea	35	8.0	26	0.0	7.0 (4.0 to 10.0)
Fatigue	39	5.0	31	0.0	5.0 (3.0 to 7.0)
Emotional function	38	6.0	30	-1.0	7.0 (3.0 to 10.0)
Control of the symptoms	39	3.0	30	-0.5	2.5 (1.0 to 4.0)

* The authors of the study reported differences in median values between the therapeutic groups calculated using the *Hodges - Lehman* method

In the study of *Barst 1996* after 12 weeks of observation the patients in the EPO group reported statistically significant improvement from baseline with regard to all assessed areas.

The difference in median values between the assessed groups is 7.0 points (95% CI: 4.0 to 10.0) for dyspnea, 5.0 points (95% CI: 3.0 to 7.0) for fatigue, 7.0 points (95% CI: 3.0; 10.0) for emotional function and 2.5 points (95% CI: 1.0 to 4.0) for control of the

symptoms, in favor of the group receiving epoprostenol and conventional treatment. The results are statistically significant ($p < 0.01$).

3.2.4.3. Quality of life assessment according to the Nottingham Health Profile questionnaire

In the study of *Barst 1996* the *Nottingham Health Profile* questionnaire was used to assess: emotional reaction, energy level, pain, physical abilities, sleep and social isolation. Lower score reflected improved quality of life. The questionnaire was filled in after 12 weeks of observation.

Median values of change from baseline scores for all parts of the questionnaire are presented in the table below.

Table 45.
Results of assessment of quality of life – *Nottingham Health Profile;* EPO vs. CT

Parameter	EPO		CT		Difference in median values between the groups (95% CI), EPO vs. CT
	N	Median change	N	Median change	
Emotional reaction	37	-10.0	31	0.0	-14.7 (-24.5 to -4.9)
Energy level	39	-36.8	31	0.0	-36.8 (-60.8 to 0.0)
Pain	39	0.0	31	0.0	0.0 (-5.8 to 0.0)
Physical abilities	39	-11.2	30	-6.4	-9.2 (-19.9 to 2.0)
Sleep	41	-16.1	31	0.0	-21.7 (-34.3 to -9.1)
Social isolation	40	0.0	31	0.0	0.0 (-20.1 to 0.0)

* The authors of the study reported differences in median values between the therapeutic groups calculated using the *Hodges - Lehman* method

From these data it may be concluded that improvement in quality of life assessed using the *Nottingham Health Profile* questionnaire was statistically significantly higher in the EPO group as compared to the CT group with regard to emotional reaction and sleep.

The difference in median values between the groups was -14.7 points (95% CI: -24.5 to -4.9) for emotional reaction and -21.7 points (95% CI: -34.3 to -9.1) for sleep in favor of the EPO group; $p < 0.01$.

Differences between the therapeutic groups did not reach statistical significance in the following areas: energy level, pain, physical abilities and social isolation.

3.2.4.4. Increase of exercise capacity according to the NYHA classification (reclassification into a lower NYHA functional class)

In all the studies included in the analysis improvement in exercise capacity as measured by the NYHA *(New York Heart Association)* classification was assessed both in patients receiving epoprostenol with conventional treatment and in patients receiving conventional treatment alone. This endpoint was defined as reclassification of a patient with pulmonary arterial hypertension into a lower NYHA class. The observation period in this regard was 8 weeks in the *Rubin 1990* study and 12 weeks in the trials of *Barst 1996* and *Badesch 2000*.

The numbers and percentages of patients in specific treatment groups, whose exercise capacity as measured by the NYHA classification increased by at least one class, are presented in the table below.

Table 46.
Numbers and percentages of patients, whose exercise capacity as measured by the NYHA classification increased; EPO vs. CT

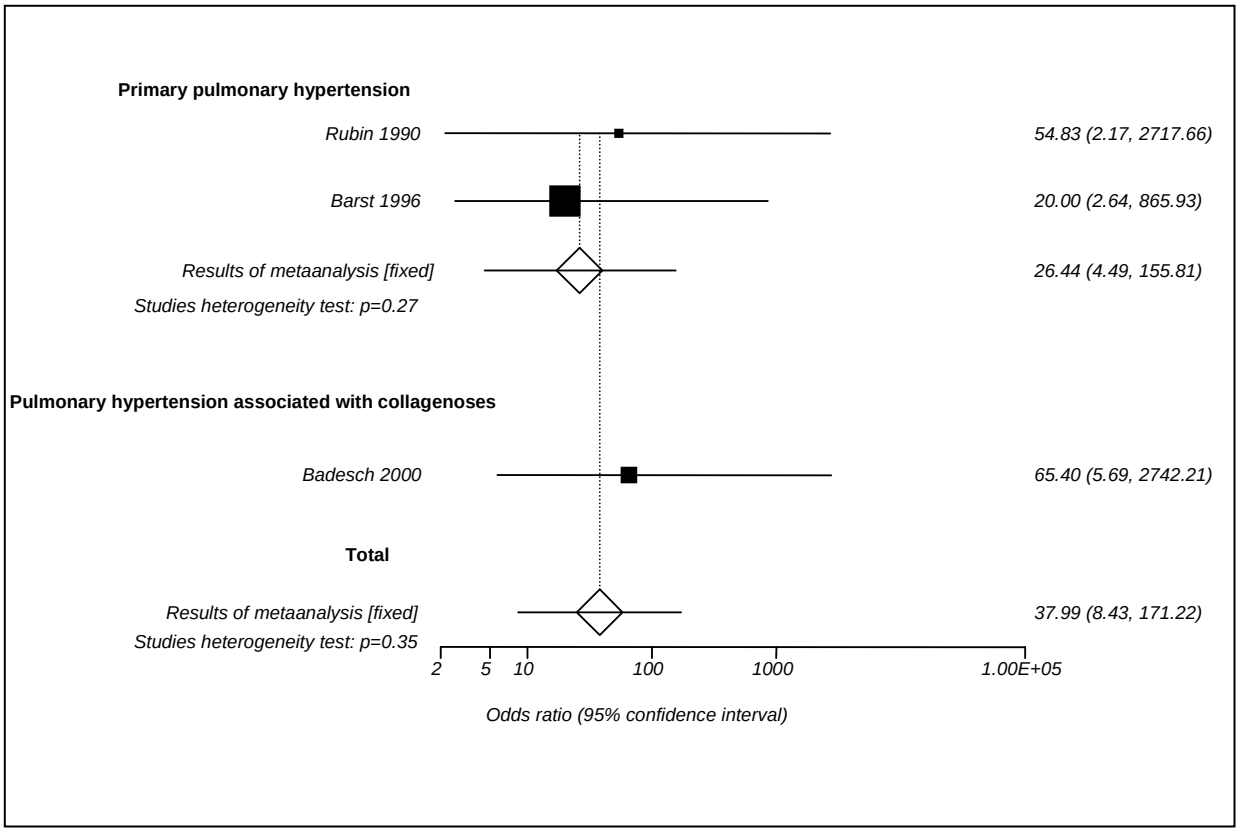
Study	EPO			LCT			Statistical significance of differences between the groups; EPO vs. CT
	N	n	Percen-tage	N	n	Percen-tage	
Rubin 1990	10	10	100%*	9	2	22%*	$p < 0,05$*
Barst 1996	40	16	40%	31	1	3%	$p < 0.02$
Badesch 2000	56	21	38%	55	0	0%	$p < 0,05$*

* Calculation based on available data

In all the studies included in the analysis improvement in exercise capacity according to the NYHA classification was higher in the EPO group than in the CT group. In the study of *Barst 1996* the difference between the groups reached statistical significance ($p < 0.02$). Authors of the remaining clinical trials provided no information concerning statistical significance.

A metaanalysis for the total number of patients, who were reclassified into a lower NYHA functional class after 8-12 weeks of treatment, is presented in the figure below.

Figure 17.
Metaanalysis for all patients with increase of exercise capacity according to the NYHA classification; EPO vs. CT



The odds ratio calculated from the metaanalysis of two studies, in which patients with primary PAH participated, is 26.44 (95% CI: 4.49 to 155.81); $p < 0.0001$, which means that the odds of reclassification into a lower NYHA class is 26.44 times higher in the EPO group than in the CT group. The result is statistically significant.

The odds ratio for this endpoint in patients with PAH associated with connective tissue diseases is 65.40 (95% CI: 5.69 to 160.00); the odds of increase of exercise capacity according to the NYHA classification is therefore more than 65 times higher in the EPO group than in the CT group. The result reached statistical significance.

In the population of all patients the odds of increase of exercise capacity according to the NYHA classification is nearly 38 times higher in the EPO group than in the CT group; OR = 37.99 (95% CI: 8.43 to 171.22); $p < 0.0001$. The result is statistically significant.

The table below presents additional EBM parameters: relative benefit (RB), relative benefit increase (RBI), absolute benefit increase (ABI) and the number of patients needed to treat in order to achieve one additional case of increase of exercise capacity; the parameters are calculated for patients with primary PAH, PAH associated with collagenoses and regardless of the type of the disease, respectively.

Table 47.
Increase of exercise capacity – additional EBM parameters; EPO vs. CT

Population of patients	RB (95% CI)	RBI (95% CI)	ABI (95% CI)	NNT (95% CI)
Primary pulmonary arterial hypertension	6.22 (2.29 to 16.89)	5.22 (1.29 to 16.89)	0.46 (0.31 to 0.60)	3 (2 to 4)

Pulmonary arterial hypertension associated with collagenoses	41.25 (4.52 to 399.53)	40.25 (3.52 to 398.53)	0.37 (0.26 to 0.51)	3 (2 to 4)
Total	10.30 (4.03 to 26.33)	9.3 (3.03 to 25.33)	0.41 (0.31 to 0.51)	3 (2 to 4)

The relative benefit is 6.22 (95% CI: 2.29 to 16.89), 41.25 (95% CI: 4.52 to 399.53), 10.30 (95% CI: 4.03 to 26.33) for patients with primary PAH, PAH associated with connective tissue diseases and regardless of the type of the disease, respectively; the probability of increase of exercise capacity is therefore 6.22, 41.25 and 10.30 times higher in the EPO group as compared with the CT group. The results are statistically significant. The relative benefit increase is 5.22 (95% CI: 1.29 to 16.89); 40.25 (3.52 to 398.53) and 9.3 (95% CI: 3.03 to 25.33), respectively. The absolute benefit increase is 0.46 (95% CI: 0.31 to 0.60), 0.37 (95% CI: 0.26 to 0.51) and 0.41 (95% CI: 0.31 to 0.51), which means that the probability of reclassification into a lower functional class was increased in the EPO group as compared to the CT group by 46 percentage points (p.p.) for patients with primary PAH, by 31 p.p. for patients with PAH associated with collagenoses and by 41 p.p. in the population of all patients regardless of the type of PAH. In order to achieve one additional case of increase of exercise capacity according to the NYHA classification, epoprostenol must be administered with conventional treatment instead of conventional treatment alone to 3 patients with PAH, either primary or associated with collagenoses, or regardless to its type, for a period of 8-12 weeks; NNT = 3 (95% CI: 2 to 4).

3.2.4.5. Decrease of exercise capacity according to the NYHA classification (reclassification into a higher NYHA functional class)

This endpoint was analyzed in the *Barst 1996* study only, in which patients with primary PAH took part. The observation period was 12 weeks.

Numbers and percentages of patients, in whom decrease of exercise capacity according to the NYHA classification was observed, are presented in the table below.

Table 48.
Numbers and percentages of patients, whose exercise capacity as measured by the NYHA classification decreased; EPO vs. CT

Study	EPO			CT			Statistical significance of differences between the groups; EPO vs. CT
	N	n	Percen-tage	N	n	Percen-tage	
Barst 1996	40	5	13%	31	3	10%	n.s.*

* Calculation based on available data

From the above data it may be concluded that the percentages of patients reclassified into a higher NYHA functional class after 12 weeks of treatment are similar in the compared therapeutic groups. The authors of the *Barst 1996* study provided no information concerning statistical significance of differences between the EPO group and the CT group.

The odds ratio is 1.33 (95% CI: 0.24 to 9.29), which means that the odds of decrease of exercise capacity according to the NYHA classification is higher in the EPO group and is 133% of this odds in the CT group. The result is not statistically significant.

3.2.4.6. No change in exercise capacity according to the NYHA classification

No change in exercise capacity according to the NYHA classification was assessed as an endpoint in the *Barst 1996* study only. The observation period with regard to this endpoint was 12 weeks.

Numbers and percentages of patients in the EPO group and in the CT group, in whom no change in the NYHA functional class was observed, are presented below.

Table 49.
Numbers and percentages of patients, whose exercise capacity as measured by the NYHA classification did not change; EPO vs. CT

Study	EPO			CT			Statistical significance of differences between the groups; EPO vs. CT
	N	n	Percen-tage	N	n	Percen-tage	
Barst 1996	40	19	48%	31	27	87%	s.s.*

* Calculation based on available data

After 12 weeks of treatment of patients with primary PAH there was no change in the NYHA functional class in 48% of patients in the group receiving epoprostenol with conventional treatment and in 87% of patients in the group of conventional treatment alone. The authors of the analyzed study provided no information concerning statistical significance of differences between the therapeutic groups.

3.2.4.7. Results of the 6-minute walk test

In all the studies included in the analysis exercise capacity of patients with PAH was assessed using the 6-minute walk test. The aim of this test is to measure the distance walked by the patient in 6 minutes.

In the study of *Rubin 1990* this endpoint was assessed during an observation period of 8 weeks, while in both remaining clinical trials *(Barst 1996 and Badesch 2000)* the observation period with regard to results of the 6-minute walk test was 12 weeks.

The results of the evaluated studies were presented as median or mean values of change in the distance walked in 6 minutes as compared to baseline distance.

Detailed results of specific studies are presented below.

Table 50.
Results of the 6-minute walk test; EPO vs. CT

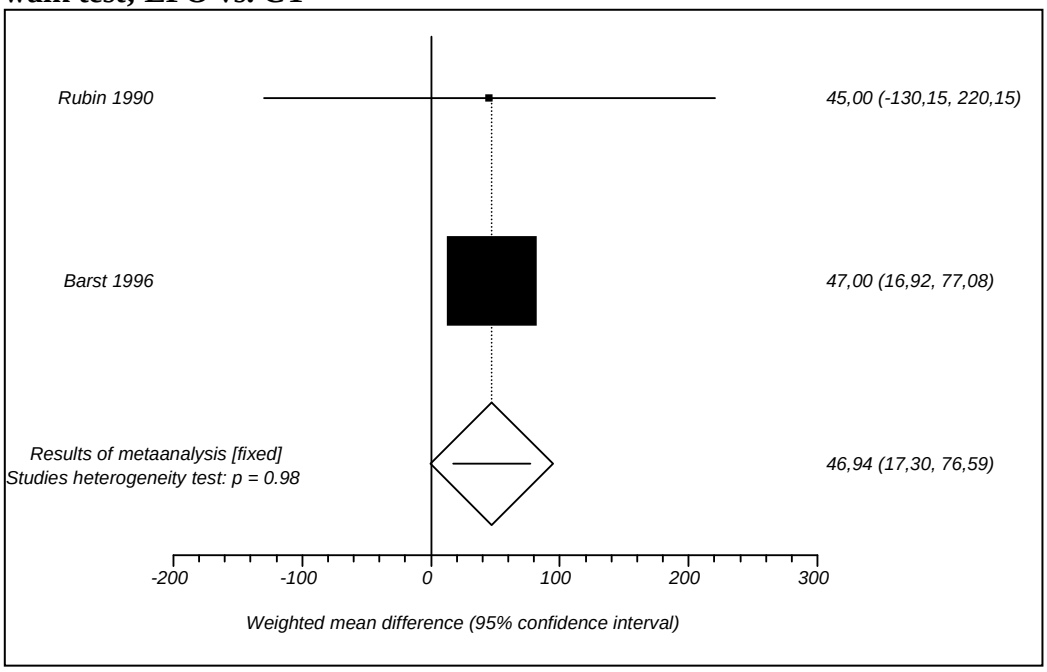
Study	Intervention	N	Baseline distance [m]		Final distance [m]		Change from baseline [m]		Mean difference in change between the groups (95% CI); EPO vs. CT
			Mean	SD	Mean	SD	Mean	SD	
Rubin 1990	EPO	10	246	nd	378	nd	132*	228*	45 (-130.15 to 220.15)
	CT	9	205	nd	292	nd	87*	148*	
Barst 1996	EPO	41	316	115	348	109	32	nd	47 (16.92 to 77.08) p < 0.003
	CT	40	272	145	257	152	-15	nd	
Badesch 2000	EPO	56	271.5	nd	316**	nd	63.50**	nd	99.5** (nd)
	CT	55	240.0	nd	192**	nd	-36.00**	nd	

* Calculation based on available data
** Median value

In all the studies improvement in exercise capacity as measured by the 6-minute walk test was higher in the EPO group than in the CT group. However, the differences between the compared therapeutic groups were statistically significant only in the study of *Barst 1996.* This information was not presented in *Badesch 2000* trial.

Due to different methods of presentation of the results of the 6-minute walk test (mean values in the trials of *Rubin 1990* and *Barst 1996* and median values in the *Badesch 2000* study), the metaanalysis concerning weighted mean difference in change between the assessed interventions was based on the results of two studies: *Rubin 1990* and *Barst 1996*.

Figure 18.
Weighted mean difference in change of exercise capacity evaluated using the 6-minute walk test; EPO vs. CT



Weighted mean difference in change of the 6-minute walk distance between the EPO group and the CT group is 46.94 m (95% CI: 17.30 to 76.59); p = 0.002; improvement in exercise capacity of patients with primary PAH as measured by the 6-minute walk test is therefore higher by 46.9 m in the EPO group as compared to the CT group. The result is statistically significant.

In the *Badesch 2000* study, in which patients with PAH associated with connective tissue diseases took part, the difference in median 6-minute walk distance was 108 m (95% CI: 55.2 to 180.0), in favor of the EPO group. The result is statistically significant.

3.2.4.8. Assessment of dyspnea and fatigue

Severity of dyspnea and fatigue was assessed in two studies included in the analysis: *Barst 1996* and *Badesch 2000*. In the scale used for assessment of dyspnea and fatigue higher score reflected decreased severity of these symptoms. In both studies this endpoint was assessed after 12 weeks of observation of patients with pulmonary arterial hypertension.

Median values of change from baseline scores are presented in the table below.

Table 51.
Results of assessment of severity of dyspnea and fatigue; EPO vs. CT

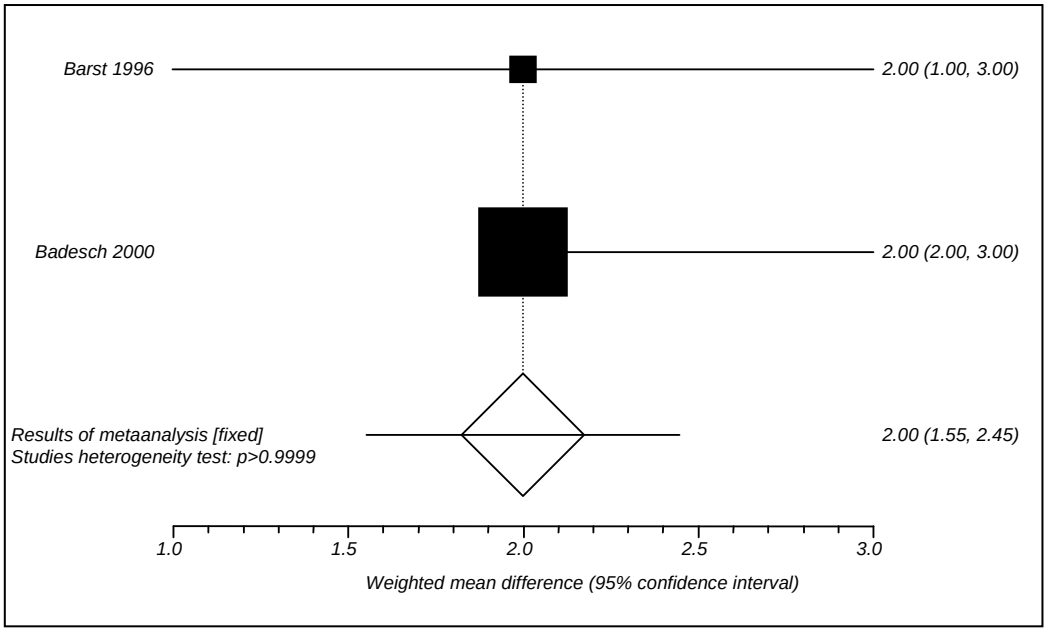
Study	EPO		CT		Difference in median values between the groups (95% CI), EPO vs. CT*
	N	Median change	N	Median change	
Barst 1996	41	1.0	31	0.0	2.0 (1.0 to 3.0)
Badesch 2000	56	1.0	55	-1.0	2.0 (2.0 to 3.0)

* The authors of the study reported differences in median values between the therapeutic groups calculated using the *Hodges - Lehman* method

In both analyzed studies the difference in median values of change of the score in the scale used for assessment of dyspnea and fatigue between the EPO group and the CT group was 2.0 points in favor of the EPO group. The results were statistically significant.

A metaanalysis of the results of two studies is presented below.

Figure 19.
Weighted mean difference in median values of change of the dyspnea and fatigue assessment score in an observation period of 12 weeks; EPO vs. CT



Weighted mean difference is 2.00 points (95% CI: 1.55 to 2.45); $p < 0.0001$; reduction of severity of dyspnea and fatigue is therefore higher by 2 points in the EPO group as compared to the CT group. The result is statistically significant.

3.2.4.9. Borg Dyspnea Score

Severity of dyspnea was assessed using the Borg Dyspnea Score only in the study of *Badesch 2000*. In this scale lower score reflects less severe dyspnea. The observation period with regard to this endpoint was 12 weeks.

Median values of change from baseline scores in both therapeutic groups are presented in the table below.

Table 52.
Borg Dyspnea Score; EPO vs. CT

Study	EPO		CT		Difference in median values between the groups (95% CI), EPO vs. CT*
	N	Median change	N	Median change	
Badesch 2000	56	-2.0	55	1.0	-2.5 (-3.5 to -1.5)

* The authors of the study reported differences in median values between the therapeutic groups calculated using the *Hodges - Lehman* method

The difference in median values of change between the EPO group and the CT group is 2.5 points (95% CI: -3.5 to -1.5); reduction of severity of dyspnea is therefore higher by 2.5 points in the Borg Dyspnea Score in the EPO group as compared to the CT group. The result is statistically significant.

3.2.4.10. Pulmonary transplantation

Pulmonary transplantation was assessed as an endpoint only in the study of *Barst 1996*. The period of observation of patients with primary PAH was 12 weeks in this trial.

Numbers and percentages of patients in both therapeutic groups, in whom this endpoint occurred, are presented in the table below.

Table 53.
Numbers and percentages of patients, in whom pulmonary transplantation was performed; EPO vs. CT

Study	EPO			CT			Statistical significance of differences between the groups; EPO vs. CT
	N	n	Percen-tage	N	n	Percen-tage	
Barst 1996	41	1	2.4*	40	2	5%*	n.s.*

* Calculation based on available data

The odds ratio calculated from the above data is 0.48 (0.01 to 9.56); the odds of pulmonary transplantation is therefore lower in the EPO group and is 48% of this odds in the CT group. The result is not statistically significant.

3.2.4.11. Severity of Raynaud's phenomenon

Severity of *Raynaud's* phenomenon was assessed only in one of the clinical studies included in the analysis, in which patients with PAH associated with collagenoses took part: *Badesch 2000*. The patients were asked to assess severity of *Raynaud's* disease, taking into account the number of episodes daily, duration of an episode, specific symptoms (such as numbness, burning or tingling sensation and pain), impairment of function of the hands due to an episode (excluding such factors as pain, ulceration, arthritis or scleroderma) and the effect of cold and stress on daily activities and well-being. The patients evaluated severity of the symptoms over the previous week using a scale from 1 (no problems) to 10 (severe symptoms).

The mean values of change from baseline score for severity of *Raynaud's* phenomenon in an observation period of 12 weeks are presented below.

Table 54.
Mean values of change from baseline score for severity of *Raynaud's* phenomenon; EPO vs. CT

Study	Intervention	N	Change from baseline		Mean difference in change between the groups (95% CI); EPO vs. CT
			Mean	SD	
Badesch 2000	EPO	56	1.69	3.1*	2.19 (0.86 to 3.52)*
	CT	55	-0.50	4.0*	

* Calculation based on available data

Mean difference in change from baseline score for severity of *Raynaud's* phenomenon between the assessed therapeutic groups was 2.19 points (95% CI: 0.86 to 3.52); p = 0.038, in disfavor of the EPO group. The result was statistically significant.

3.2.4.12. New digital ulcers or ischemic demarcation

New digital ulcers or ischemic demarcation events were assessed only in one clinical trial, in which patients with PAH associated with collagenoses took part: *Badesch 2000.*

Numbers and percentages of patients, in whom this endpoint occurred, are presented in the table below.

Table 55.
Numbers and percentages of patients, in whom new digital ulcers or ischemic demarcation events were observed; EPO vs. CT

Study	EPO			CT			Statistical significance of differences between the groups; EPO vs. CT
	N	n	Percen-tage	N	n	Percen-tage	
Badesch 2000	52	10	19%	52	11	20%	n.s.

* Calculation based on available data

Percentages of patients, in whom new digital ulcers or ischemic demarcation events were observed, were similar in both assessed therapeutic groups.

The odds ratio calculated from the above data is 0.89 (95% CI: 0.30 to 2.59). It means that the odds of occurrence of this endpoint is lower in the EPO group and is 89% of this odds in the CT group. The result is not statistically significant.

3.2.4.13. Hemodynamic parameters

3.2.4.13.1. Mean pulmonary artery pressure

Mean pulmonary artery pressure was assessed in all three clinical trials included in the analysis. The observation period was 8 weeks in the *Rubin 1990* study and 12 weeks in the trials of *Barst 1996* and *Badesch 2000*.

In addition, in the clinical trial of *Rubin 1990* the number of patients, in whom mean pulmonary artery pressure decreased by 10 mmHg, was presented.

Mean values reported by the authors of specific studies are presented below.

Table 56.
Mean pulmonary artery pressure; EPO vs. CT

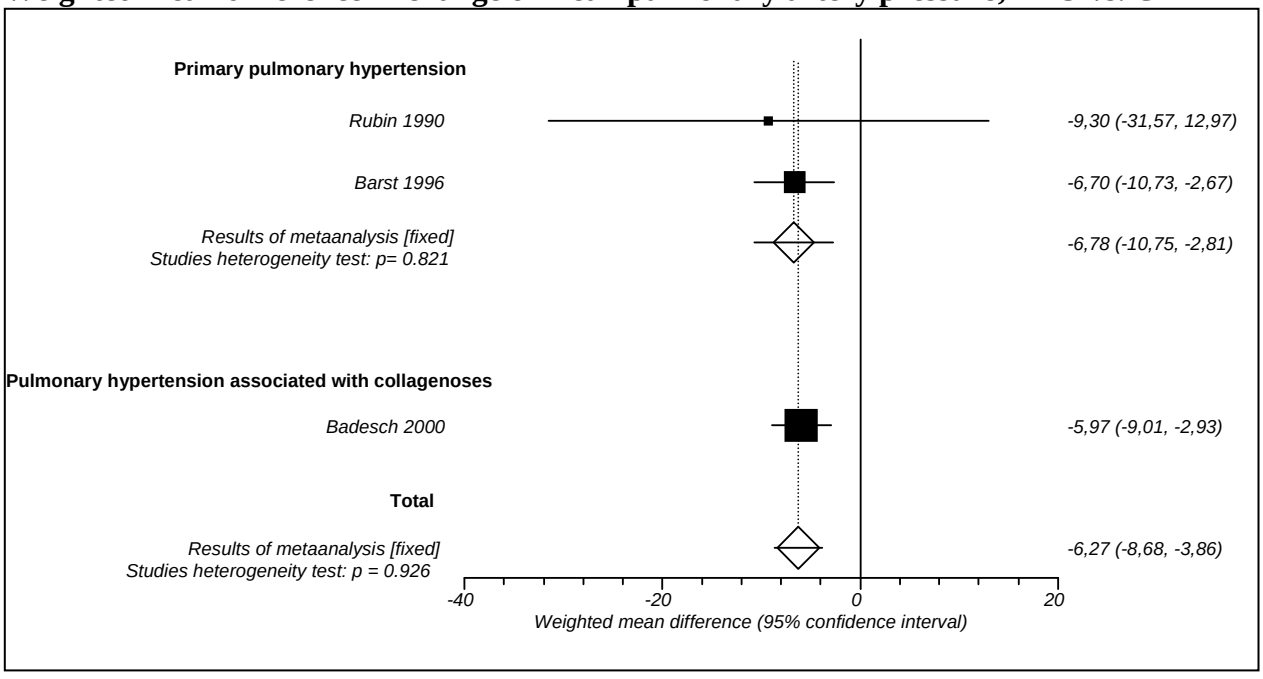
Study	Intervention	N	Baseline value [mmHg]		Final value [mmHg]		Change from baseline [mmHg]		Mean difference in change between the groups (95% CI); EPO vs. CT
			Mean	SD	Mean	SD	Mean	SD	
Rubin 1990	EPO	10	58.6	nd	49.3	nd	-9.3*	26.02*	-9.3* (n.s.)
	CT	9	62.2	nd	62.2	nd	0.0*	23,18*	
Barst 1996	EPO	41	61	12.81	nd	nd	-4.8	8.3*	-6.7 (-10.7 to -2.6)
	CT	40	59	12.81	nd	nd	1.9	10.12*	
Badesch 2000	EPO	56	50.9	10.6	nd	nd	-5.03	8.16*	-5.97 (-8.98 to -2.96)
	CT	55	49.1	10.2	nd	nd	0.94	8.16*	

* Calculation based on available data

In all clinical trials there was a reduction of mean pulmonary artery pressure in the EPO group and increase in CT group. Differences between the therapeutic groups were statistically significant in the studies of *Barst 1996* and *Badesch 2000*, while in the trial of *Rubin 1990* they did not reach statistical significance.

A metaanalysis of differences in change of mean pulmonary artery pressure between the EPO group and the CT group for patients with primary PAH, PAH associated with connective tissue diseases and regardless of the type of PAH is presented in the figure below.

Figure 20.
Weighted mean difference in change of mean pulmonary artery pressure; EPO vs. CT



Weighted mean difference in change of mean pulmonary artery pressure for patients with primary PAH is -6.78 mmHg (95% CI: -10.75 to -2.81); p < 0.001, in the favor of EPO group. The result is statistically significant.

Weighted mean difference in change of mean pulmonary artery pressure for patients with PAH associated with connective tissue diseases is -5.97 mmHg (95% CI: -9.01 to -2.93), in favor of the EPO group. The result is statistically significant.

For the population of all patients weighted mean difference in change of mean pulmonary artery pressure between the groups (EPO and CT) calculated in the metaanalysis is -6.27 mmHg (95% CI: -8.68 to -3.86), p < 0.001; in favor of the EPO group as compared to the CT group. The result reached statistical significance.

Numbers and percentages of patients participating in the *Rubin 1990* study, in whom pulmonary artery pressure decreased by more than 10 mmHg after an observation period of 8 weeks, are presented in the table below.

Table 57.
Numbers and percentages of patients, in whom pulmonary artery pressure decreased by more than 10 mmHg; EPO vs. CT

Study	EPO			CT			Statistical significance of differences between the groups; EPO vs. CT
	N	n	Percentage	N	n	Percentage	
Rubin 1990	10	6	60%*	9	1	11%*	p = 0.057

* Calculation based on available data

From the above data it may be concluded that the percentage of patients, in whom mean pulmonary artery pressure decreased by at least 10 mmHg, was higher in the EPO group than in the CT group. However, the result was not statistically significant (p = 0.057).

The odds ratio calculated from the results of the *Rubin 1990* study is 12.00 (95% CI: 0.83 to 619.03), which means that the odds of reduction of pulmonary artery pressure is 12 times higher in the EPO group than in the CT group. The result is statistically significant.

Administration of epoprostenol with conventional treatment instead of conventional treatment alone to 3 patients will result in reduction of pulmonary artery pressure by more than 10 mmHg in one additional patient; NNT = 3 (95% CI: 2 to 23).

3.2.4.13.2. Pulmonary vascular resistance

In all three clinical studies included in the analysis pulmonary vascular resistance was estimated. The observation period was 8 weeks in the *Rubin 1990* trial and 12 weeks in the studies of *Barst 1996* and *Badesch 2000*.

The table below presents mean final values of pulmonary vascular resistance and mean values of change from baseline for this parameter as reported by the authors of the studies.

Table 58.
Mean pulmonary vascular resistance; EPO vs. CT

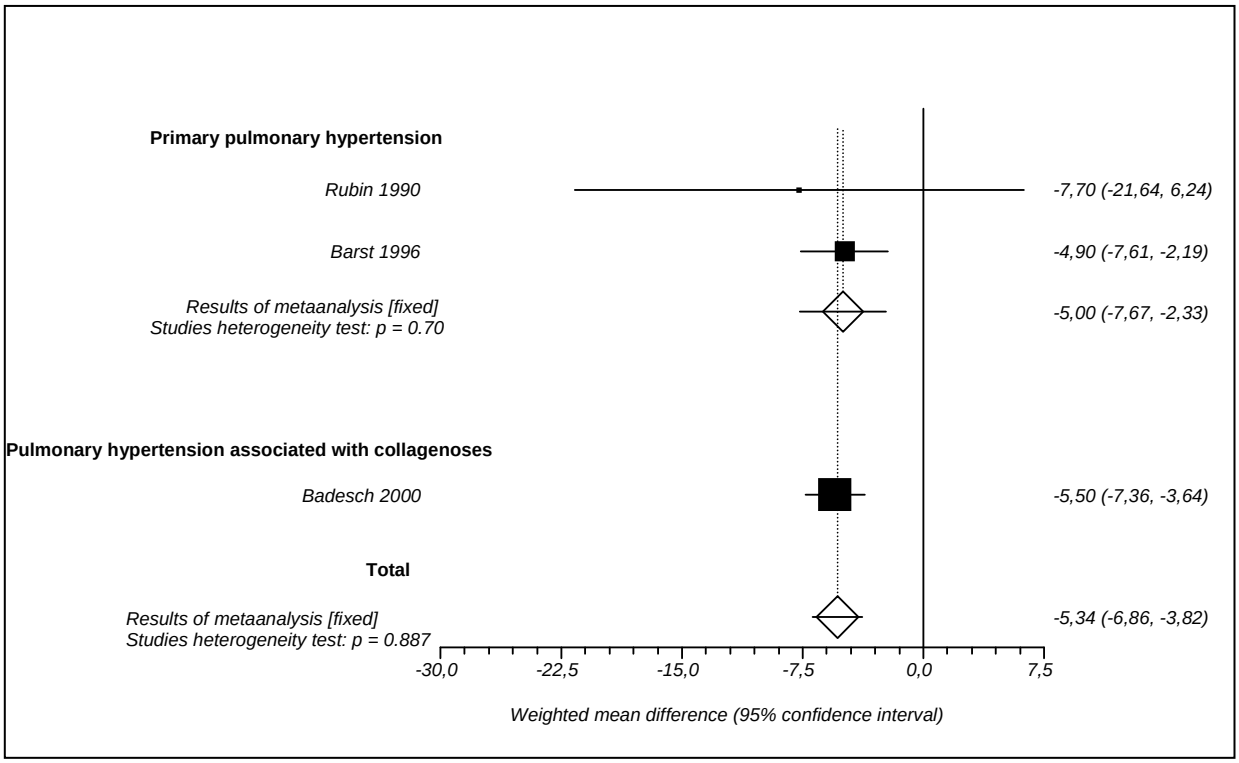
Study	Intervention	N	Baseline value [mmHg/l/min]		Final value [mmHg/l/min]		Change from baseline [mmHg/l/min]		Mean difference in change between the groups (95% CI); EPO vs. CT
			Mean	SD	Mean	SD	Mean	SD	
Rubin 1990	EPO	10	21.6	nd	13.9	nd	-7.9	15.24*	-7.70 (-21.64 to 6.24)*
	CT	9	20.6	nd	20.4	nd	-0.2*	15.74*	
Barst 1996	EPO	41	16	6.40	nd	nd	-3.4	4.48*	-4.9 (-7.61 to -2.19)*
	CT	40	16	6.32	nd	nd	1.5	7.59*	
Badesch 2000	EPO	56	14.2	7.1	nd	nd	-4.58	5.69*	-5.50 (-7.36 to -3.64)*
	CT	55	11.2	5.3	nd	nd	0.92	4.15*	

* Calculation based on available data

In studies of *Barst 1996* and *Badesch 2000* there was a decrease of mean pulmonary vascular resistance in the EPO groups and increase in CT groups. Differences between treatment groups were statistically significant. The result was not statistically significant only in *Rubin 1990* trial.

A metaanalysis for difference in change of pulmonary vascular resistance between the assessed therapeutic groups is presented below.

Figure 21.
Weighted mean difference in change of value of pulmonary vascular resistance; EPO vs. CT



For patients with primary PAH weighted mean difference in change from baseline values of pulmonary vascular resistance is -5,00 mmHg/l/min (95% CI: -7.67 to -2.33); $p < 0.001$. It means that reduction of pulmonary vascular resistance is higher by 5.00 mmHg/l/min in the EPO group as compared to the group of patients, who received conventional treatment alone. The result is statistically significant.

For patients with PAH associated with connective tissue diseases mean difference in change of pulmonary vascular resistance between the therapeutic groups is -5.50 mmHg/l/min (95% CI: -7.36 to -3.64), in favor of the EPO group.

Weighted mean difference of change in values of pulmonary vascular resistance in the population of all patients is -5.34 mmHg/l/min (95% CI: -6.86 to -3.82); $p < 0.001$. It means that reduction of this parameter is higher by 5.34 mmHg/l/min in the EPO group than in the CT group and the result reached statistical significance.

3.2.4.13.3. Cardiac index

Cardiac index was evaluated in two of the analyzed clinical trials: *Barst 1996* and *Badesch 2000*. The observation period was 12 weeks.

Table 59.
Mean values of cardiac index; EPO vs. CT

Study	Intervention	N	Baseline value [l/min/m^2]		Change from baseline [l/min/m^2]		Mean difference in change between the groups (95% CI); EPO vs. CT
			Mean	SD	Mean	SD	
Barst 1996	EPO	41	2.0	0.6*	0.3	0.6*	0.5 (0.2 to 0.9)
	CT	40	2.1	1.3*	-0.2	1.3*	
Badesch 2000	EPO	56	1.9	0.6	0.50	0.6*	0.60 (0.39 to 0.81)
	CT	55	2.2	0.7	-0.10	0.6*	

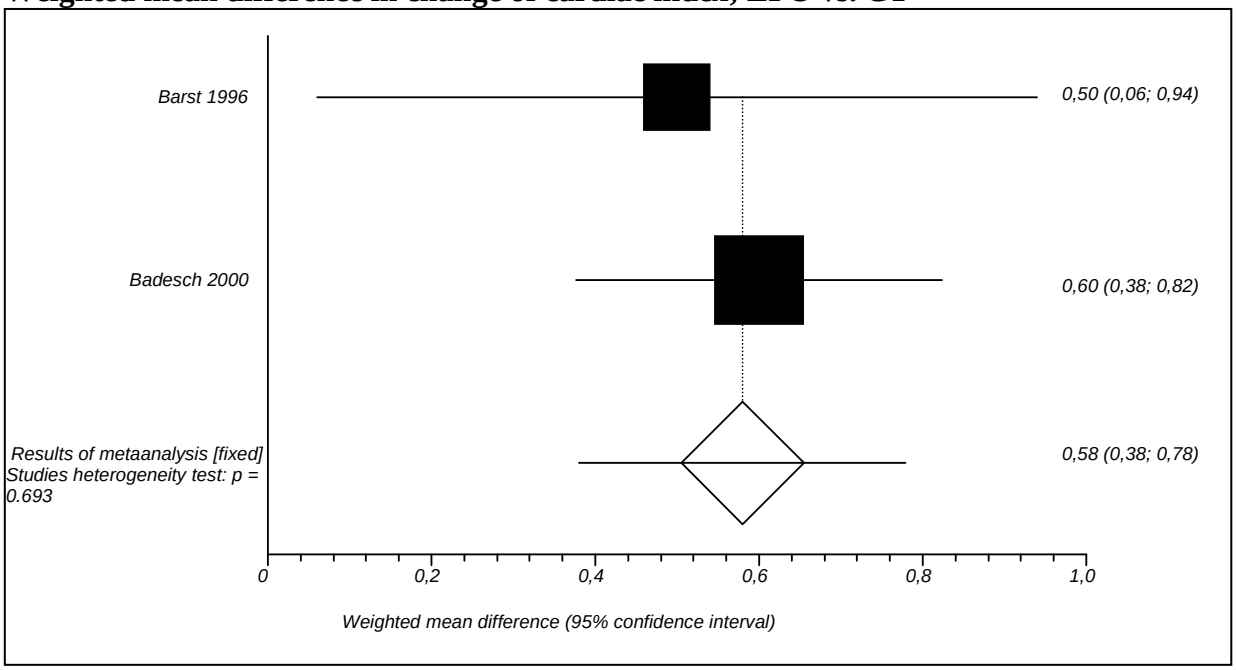
* Calculation based on available data

In both studies increase of the value of cardiac index was statistically significantly higher in the group of patients, who received epoprostenol with conventional treatment as compared to patients receiving conventional treatment alone. The results were statistically significant.

Difference in change of the value of cardiac index between the groups (EPO and CT) in patients with primary PAH was 0.5 l/min/m^2 and in patients with PAH associated with collagenoses – 0.60 l/min/m^2, in favor of the EPO group.

Weighted mean difference in change of the value of cardiac index in an observation period of 12 weeks calculated form a metaanalysis of the results of both studies is presented below.

Figure 22.
Weighted mean difference in change of cardiac index; EPO vs. CT



Weighted mean difference of change in values of cardiac index calculated for the population of all patients is 0.58 l/min/m^2 (95% CI: 0.38 to 0.78); p < 0.001, in favor of epoprostenol and the result is statistically significant.

3.2.4.13.4. Cardiac output

Cardiac output was assessed in the *Rubin 1990* study only. Patients with primary PAH were observed for 8 weeks with regard to this parameter.

Mean baseline and final values of cardiac output reported by the authors and calculated changes from baseline values of this parameter are presented in the table below.

Table 60.
Mean values of cardiac output; EPO vs. CT

Study	Intervention	N	Baseline value [l/min]		Final value [l/min]		Change from baseline [l/min]		Mean difference in change between the groups (95% CI); EPO vs. CT
			Mean	SD	Mean	SD	Mean	SD	
Rubin 1990	EPO	10	3.3	nd	3.9	nd	0.6*	0.92*	0.2 (-1.11 to 1.51)*
	CT	9	3.5	nd	3.9	nd	0.4*	1.89*	

* Calculation based on available data

Mean difference in change between the groups (EPO and CT) calculated from data presented by the authors of the *Rubin 1990* study is 0.2 l/min (95% CI: -1.11 to 1.51); increase of cardiac output is therefore higher by 0.2 l/min in the EPO group as compared to patients receiving conventional treatment alone. However, the result is not statistically significant.

3.2.4.13.5. Arterial blood oxygen saturation

Arterial blood oxygen saturation was assessed in one study, in which patients with primary PAH took part *(Barst 1996)*, and one, in which patients with PAH associated with collagenoses were enrolled *(Badesch 2000)*. The observation period was 12 weeks.

The table below presents mean baseline values of arterial blood oxygen saturation and changes from baseline values observed in both clinical trials.

Table 61.
Mean arterial blood oxygen saturation; EPO vs. CT

Study	Intervention	N	Baseline value		Change from baseline		Mean difference in change between the groups (95% CI); EPO vs. CT
			Mean	SD	Mean	SD	
Barst 1996	EPO	41	91%	13*	2.0%	10.3*	2.6 (-1.8 to 7.1)
	CT	40	92%	6*	-0.6%	8.9*	
Badesch 2000	EPO	56	92.7%	6.8	-0.33%	8.16*	-0.02 (-2.45 to 2.42)
	CT	55	92.5%	6.6	-0.31%	4.52*	

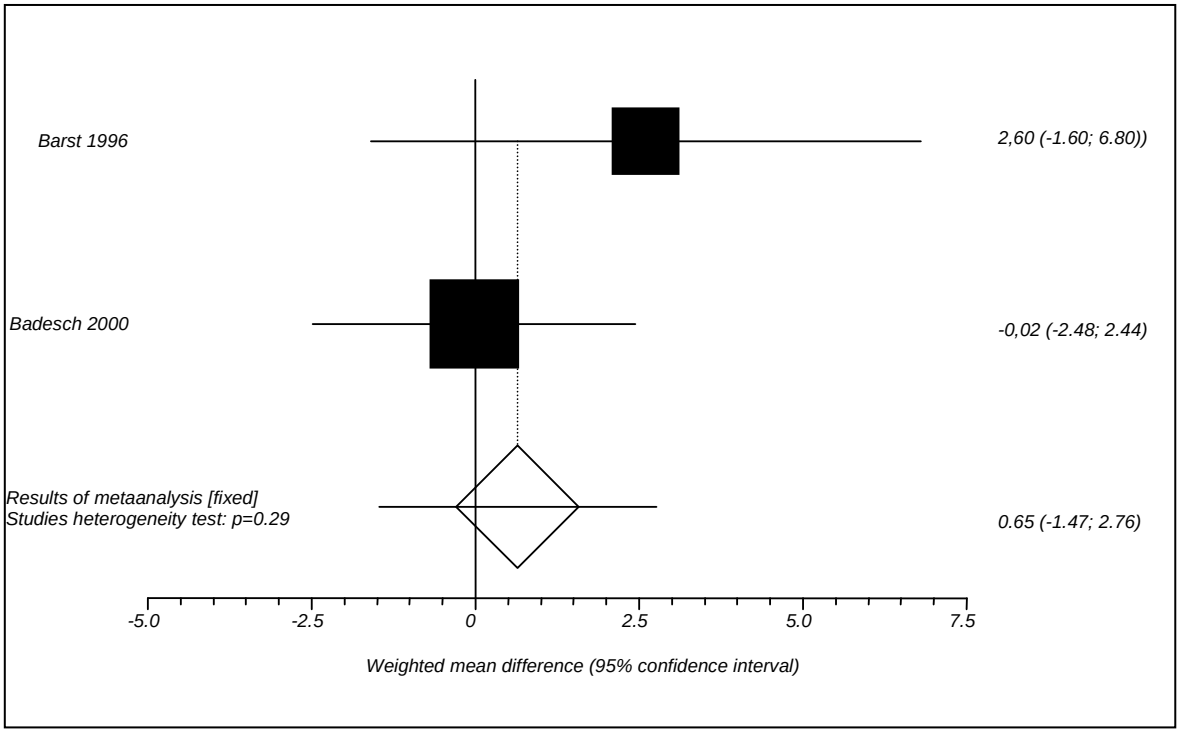
* Calculation based on available data

In patients with primary PAH *(Barst 1996)* increase in arterial blood oxygen saturation was higher by 2.6 p.p. in the EPO group as compared to the CT group. Mean difference in change was 2.6 p.p. (95% CI: -1.8 to 7.1); however, the result was not statistically significant.

For patients with PAH associated with connective tissue diseases mean difference of change in arterial blood oxygen saturation between the therapeutic groups was -0.02 p.p. (95% CI: -2.45 to 2.42). It means that decrease of this parameter was higher by 0.02 p.p. in the EPO group as compared to the CT group. The result did not reach statistical significance.

Weighted mean difference in change of arterial blood oxygen saturation between the assessed groups calculated for the population of all patients is presented in the figure below.

Figure 23.
Weighted mean difference in change of arterial blood oxygen saturation; EPO vs. CT



Weighted mean difference in change of arterial blood oxygen saturation between the assessed therapeutic groups is 0.65 p.p. (95% CI: -1.47 to 2.76); p = 0.55. It means that increase of this parameter is higher by 0.65 p.p. in the EPO group than in the CT group. However, the result is not statistically significant.

3.2.4.13.6. Mixed venous blood oxygen saturation

This parameter was evaluated in two clinical trials with an observation period of 12 weeks. In the study of *Barst 1996* patients with primary PAH took part, while in the *Badesch 2000* trial patients with PAH associated with collagenoses participated.

Detailed results of both studies are presented below.

Table 62.
Mean mixed venous blood oxygen saturation; EPO vs. CT

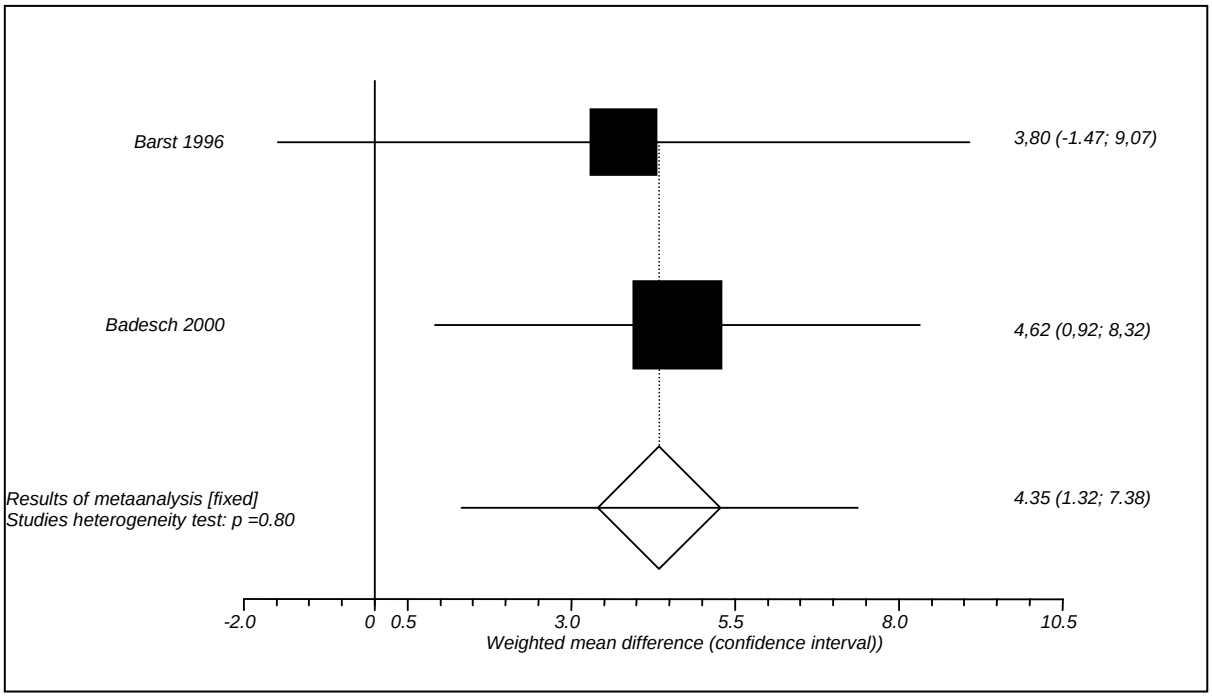
Study	Intervention	N	Baseline value		Change from baseline		Mean difference in change between the groups (95% CI); EPO vs. CT
			Mean	SD	Mean	SD	
Barst 1996	EPO	41	62%	13*	1.2%	11.5*	3.8 (-1.6 to 9.2)
	CT	40	59%	13*	-2.6%	12.7*	
Badesch 2000	EPO	56	57.4%	10.8	3.55%	10.63*	4.69 (0.94 to 8.30)
	CT	55	58.8%	9.9	-1.07%	9.20*	

* Calculation based on available data

For patients with primary PAH *(Barst 1996)* as well as those with PAH associated with collagenoses *(Badesch 2000)* increase in mean mixed venous blood oxygen saturation in the group of patients treated with epoprostenol and decrease in groups of patients receiving conventional treatment alone was observed. However, differences between therapeutic groups were statistically significant only for patients with PAH associated with connective tissue diseases. Mean difference in change between the assessed groups was 3.8 p.p. (95% CI: -1.6 to 9.2) for patients with primary PAH and 4.69 p.p. (95% CI: 0.94 to 8.30) for patients with PAH associated with collagenoses, in both cases in favor of the EPO group.

The figure below presents weighted mean difference in change of mixed venous blood oxygen saturation between the groups (EPO and CT) for the population of all patients.

Figure 24.
Weighted mean difference in change of mixed venous blood oxygen saturation; EPO vs. CT



Weighted mean difference in change of mixed venous blood oxygen saturation between the assessed therapeutic groups calculated from a metaanalysis is 4.35 p.p. (95% CI: 1.32 to 7.38); p = 0.0049. It means that increase of this parameter is higher by 4.35 p.p. in the EPO group as compared to the CT group. The result is statistically significant.

3.2.5. Assessment of safety

3.2.5.1. Adverse events

Safety of the compared treatment options was assessed in all three studies included in the analysis; however, detailed numeric data for both groups were presented only by the authors of the *Badesch 2000* study. In this study adverse events were classified into one of the three groups: related to the disease (syncope, pallor, ascites), related to treatment (anorexia, nausea,

diarrhea, jaw pain, depression) and related to the route of administration (sepsis, cellulites, hemorrhage, pneumothorax).

The observation period was 8 weeks in the *Rubin 1990* study and 12 weeks in the trials of *Barst 1996* and *Badesch 2000*.

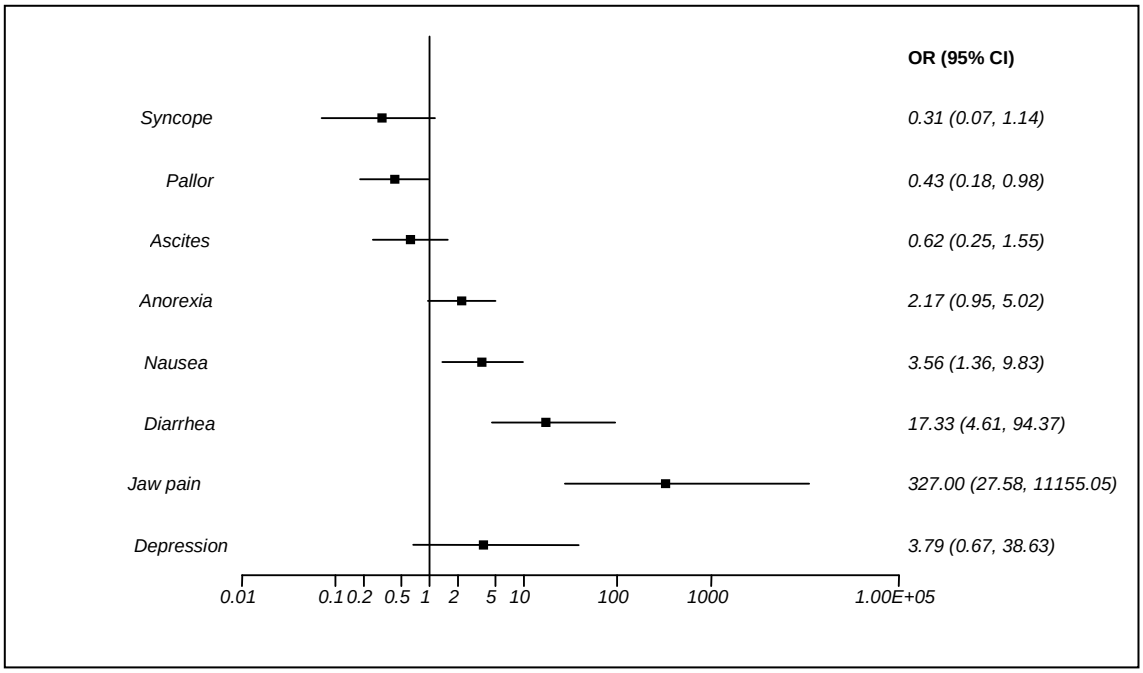
The table below presents numbers and percentages of patients participating in the *Badesch 2000* trial, in whom specific adverse events were observed.

Table 63.
Numbers and percentages of patients in the *Badesch 2000* study, in whom specific adverse events were observed; EPO vs. CT

Adverse event	EPO			CT			Statistical significance of differences between the groups; EPO vs. CT
	N	n	Percen-tage	N	n	Percen-tage	
Syncope	56	4	7%	55	11	20%	s.s.
Pallor	56	18	32%	55	29	53%	s.s.
Ascites	56	13	23%	55	18	33%	n.s.
Anorexia	56	37	66%	55	26	47%	s.s.
Nausea	56	23	41%	55	9	16%	s.s.
Diarrhea	56	28	50%	55	3	5%	s.s.
Jaw pain	56	42	75%	55	0	0%	n.s.
Depression	56	7	13%	55	2	4%	n.s.
Sepsis	56	2	4%	55	-	-	-
Cellulitis	56	2	4%	55	-	-	-
Hemorrhage	56	2	4%	55	-	-	-
Pneumothorax	56	2	4%	55	-	-	-

In the clinical trial of *Badesch 2000* incidence of adverse events related to the disease was lower in the group of patients treated with epoprostenol as compared with the conventional treatment group, while adverse events related to epoprostenol were observed more often in the EPO group as compared to the CT group. However, differences between the assessed therapeutic groups reached statistical significance only with regard to the following adverse events: syncope, pallor, anorexia, nausea and diarrhea.

Figure 25.
Odds ratios for specific adverse events calculated from the results of the *Badesch 2000* study; EPO vs. CT



The odds of occurrence of syncope, pallor and ascites is lower in the EPO group and is 31%, 43% and 62% of the respective odds in the conventional treatment group. The odds ratio for syncope is 0.31 (95% CI: 0.07 to 1.14), for pallor: 0.43 (95% CI: 0.18 to 0.98) and for ascites: 0.62 (95% CI: 0.25 to 1.55). However, the result reached statistical significance for pallor only.

In order to avoid one additional case of pallor, epoprostenol must be administered with conventional treatment instead of conventional treatment alone to 5 patients with PAH associated with connective tissue diseases for a period of 12 weeks; NNT = 5 (95% CI: 3 to 48).

The respective odds ratios and NNH values are: OR = 2.17 (95% CI: 0.95 to 5.02) for anorexia, OR = 3.56 (95% CI: 1.36 to 9.83), NNH = 5 (95% CI: 3 to 13) for nausea, 17.33 (95% CI: 4.61 to 94.37), NNH = 3 (95% CI: 2 to 4) for diarrhea, 327.00 (95% CI: 27.58 to 11155.05), NNH = 2 (95% CI: 2 to 2) for jaw pain and 3.79 (95% CI: 0.67 to 38.63) for depression. It means that the odds of occurrence of anorexia, nausea, diarrhea, jaw pain and depression in the EPO group as compared with the CT group is 2.17, 3.56, 17.33, 327.00 and 3.79 times higher, respectively. However, the results are statistically significant only for nausea, diarrhea and jaw pain.

In the study of *Rubin 1990* among the most common adverse events in the epoprostenol group were: loose stools (observed in 100% of patients), jaw pain (57% of patients) and photophobia (36% of patients). In addition in two patients flushing was observed, one third of the patients reported dyspnea and in a few patients thrombophlebitis and ascites occurred. Failure of the infusion pump requiring discontinuation of the infusion was observed in five cases and four patients required replacement of the catheter. In one patient a reversible neurological ischemic event was reported. In two patients relapse of the symptoms was observed, including syncope; this was due to inappropriate (i.e. too low) epoprostenol dosage after a new type of the syringe was applied. None of the adverse events listed above was life-threatening.

In the *Barst 1996* clinical trial the following adverse events related to treatment were observed in the epoprostenol group: jaw pain, diarrhea, flushing, headache, nausea and vomiting. Among serious adverse events, mainly related to the route of administration of the drug, sepsis and a thrombotic event were reported. Twenty-six cases of failure of the drug administering system with subsequent discontinuation of the infusion were reported, these were due to occlusion, perforation or damage to the infusion pump. After discontinuation of epoprostenol administration increase of severity of symptoms of pulmonary hypertension was observed. In addition, irritation or infection at the site of the catheter insertion was observed in 7 patients, bleeding in 4 patients and 4 patients reported pain.

3.2.5.2. Withdrawal from the study

This endpoint was assessed in the study of *Barst 1996* only. Numbers and percentages of patients withdrawn from the clinical trial during an observation period of 12 weeks are presented below.

Table 64.
Numbers and percentages of patients withdrawn from the study; EPO vs. CT

Study	EPO			CT			Statistical significance of differences between the groups; EPO vs. CT
	N	n	Percen-tage	N	n	Percen-tage	
Barst 1996	41	2	5%*	40	0	0%	n.s.*

* Calculation based on available data

The odds ratio calculated using the *Peto* method is 7.39 (95% CI: 0.45 to 120.32), which means that the odds of a patient being withdrawn from the study is 7.39 times higher in the EPO group than in the CT group. The result is not statistically significant.

Among the causes of withdrawal the authors of the *Barst 1996* study reported jaw pain, diarrhea and inability to operate the drug administering system.

3.3. Iloprost vs. placebo

3.3.1. Results of search for the studies

Two primary clinical studies fulfilling the inclusion criteria, in which patients with pulmonary arterial hypertension participated, were included in the comparative analysis of efficacy and safety of iloprost (ILO) vs. placebo (PL): *Thurm 1991* and *Olschewski 2002*. The clinical trial of *Thurm 1991* was conducted in one treatment center, while the *Olschewski 2002* study was carried out in 37 European centers. Only the *Thurm 1991* study was double-blind. The table below presents detailed characteristics of the studies included in the analysis.

Table 65.
Characteristics of the studies included in the analysis; ILO + PL vs. PL

Study	Publications	Observation period	*Jadad* score
Thurm1991	*Thurm 1991*	3 days	3
Olschewski 2002	*Olschewski 2002*	12 weeks	2

The observation period was 3 days in the *Thurm 1991* study and 12 weeks in the *Olschewski 2002* trial. The *Jadad* credibility score was 3 points for the *Thurm 1991* study and 2 points for the study of *Olschewski 2002*.

3.3.2. Description of the population

In both clinical studies patients with pulmonary hypertension were enrolled. However, in the trial of *Thurm 1991* patients with PAH associated with collagenoses (diagnosed according to the *American College of Rheumatology* criteria) took part, while for the *Olschewski 2002* trial both patients with primary and secondary PAH (i.e. associated with use of appetite suppressant drugs, collagenoses or inoperable chronic thromboembolic disease) were qualified.

The participants of the *Thurm 1991* study were classified according to the degree of skin involvement (assessed using the *Barnett* method) into one of three groups: digital scleroderma (type I), scleroderma proximal to the metacarpophalangeal joints but not involving the trunk (type II) or diffuse skin involvement including the trunk (type III). Among the inclusion criteria the authors of the *Thurm 1991* study listed also occurrence of at least eight episodes of *Raynaud's* phenomenon a week.

In the trial of *Olschewski 2002* the patients, whose mean pulmonary artery pressure exceeded 30 mmHg, were able to walk from 50 to 500 m during a 6-minute walk test and were classified in NYHA *(New York Heart Association)* functional class III or IV, in spite of conventional treatment with anticoagulants, diuretics, digitalis glycosides, calcium channel blockers or oxygen, were enrolled. Patients receiving the investigated drugs, prostanoids or β-blockers could not participate in the clinical trial; use of calcium channel blockers was admitted provided that the dose of these drugs remained stable for at least 6 weeks prior to enrollment. Among the exclusion criteria pulmonary artery wedge pressure at rest over 15 mmHg, cardiac index at rest below 1.5 or over 4 l/min/m^2 of the body surface area, bleeding disorders, bilirubin concentration over 3 mg/dl (51 µmol/l), creatinine clearance below 30 ml/min, forced vital capacity (FVC) below 50%, forced expiratory volume in one second (FEV_1) below mean normal value minus twice the standard deviation and clinical instability were listed.

Detailed baseline characteristics of the patients enrolled in the *Thurm 1991* and *Olschewski 2002* studies are presented in the table below.

Table 66.
Baseline characteristics of the patients enrolled in particular studies; ILO vs. PL

Study	Number of patients		Mean age (SD) [years]		Percentage of men		Percentage of patients with primary PAH/ PAH associated with other diseases		Percentage of patients in NYHA functional class III/IV		Percentage of patients treated with oral vasodilators		Mean time from diagnosis (SD) [years]		Mean 6-minute walk distance (SD) [m]	
	ILO	PL	ILO	PL	ILO	PL	ILO	PL	ILO	PL	ILO	PL	ILO	PL	ILO	PL
Thurm 1991	6	7	55.2 (14.5)	45.7 (8.7)	16.7%*	28.6%*	0%/100%	0%/100%	nd	nd	0%	0%	16.0 (13.2)	12.3 (5.8)	nd	nd
Olschewski 2002	101	102	51.2 (13.2)	52.8 (12.0)	31.7%	33.3%	50.5%/49.5%	50.0%/50.0%	59.4%/40.6%	57.8%/42.2%	51.5%	56.9%	nd	nd	332 (93)	315 (96)
Total	107	109	51.4	52.3	30.9%	33.0%	47.7%/52.8%	46.8%/53.2%	-	-	48.6%	53.3%	-	-	-	-

* Calculation based on available data

A total number of 216 patients with PAH were enrolled in these two clinical trials, 107 assigned to the iloprost group and 109 to the placebo group. Mean age of patients in both studies was 51.4 in the ILO group and 52.3 in the PL group, the percentage of men: 30.9% and 33.0%, respectively, the percentage of patients with primary PAH: 47.7% and 46.8% and those with PAH associated with other diseases: 52.8% and 53.2%, respectively.

The populations of patients enrolled in both studies were relatively similar as to mean age and the percentage of men but were different with respect to the percentage of patients with primary PAH and PAH associated with other diseases.

In the study of *Thurm 1991* only patients with PAH associated with collagenoses were enrolled, while in the *Olschewski 2002* trial PAH associated with other diseases was diagnosed only in a half of the patients. The patients enrolled in the *Thurm 1991* trial received no additional treatment during the study, while in the *Olschewski 2002* study 52% of patients in the ILO group and 57% of patients in the placebo group received oral vasodilators.

The authors of the *Thurm 1991* study stated that despite random assignment of patients their baseline characteristics differed between the therapeutic groups. Mean age of patients in the iloprost group was higher and duration of the disease longer as compared to the placebo group. Moreover, in the placebo group more patients were classified in stage III of the disease (diffuse skin involvement including the trunk) than in the iloprost group (43% vs. 0%).

3.3.3. Description of the interventions

Patients enrolled in both studies *(Thurm 1991* and *Olschewski 2002)* were randomly assigned to the iloprost (ILO) or placebo (PL) group.

The table below presents detailed description of the interventions used in both clinical trials.

Table 67.
Description of the interventions; ILO vs. PL

Study	ILO	PL	Additional treatment
Thurm 1991	Iloprost administered in intravenous infusion at the maximum tolerated dose – from 0.5 to 2.0 ng/kg/min.	Placebo in intravenous infusion	nd
Olschewski 2002	Iloprost (Ilomedin) administered in inhalation by means of a nebulizer *(HaloLite, MedicAid)* at a dose of 2.5 or 5.0 µg/ml in one inhalation (depending on tolerance of the first dose).	Inhaled placebo	Oral vasodilators

In the study of *Thurm 1991* in case of adverse events the dose was tapered until the maximum tolerated dose was found. In an observation period of 3 days mean tolerated dose of iloprost was 0.96 mg/kg/min (range: 0.46 – 1.61).

In the *Olschewski 2002* trial the drug remaining in the nebulizer was discarded after each inhalation. This action was repeated 6-9 times a day. Frequency of inhalations and the dose administered was adjusted individually during the first 8 days of treatment, according to a pre-defined dosage algorithm. The authors of the study reported that average frequency of iloprost inhalations was 7.5/day and median dose inhaled was 30 µg/day with 91% of patients using a dose of 5.0 µg/inhalation and 9% – 2.5 µg/inhalation.

3.3.4. Analysis of efficacy

3.3.4.1. Mortality

Mortality was assessed in the *Olschewski 2002* study only. The authors presented the results separately for the patients with primary PAH, those with PAH associated with other diseases and for the whole population of patients.

Numbers and percentages of patients in both groups (iloprost and placebo), who died during an observation period of 12 weeks, are presented below.

Table 68.
Numbers and percentages of patients who died; ILO vs. PL

Population	ILO			PL			Statistical significance of differences between the groups; ILO vs. PL
	N	n	Percen-tage	N	n	Percen-tage	
Primary hypertension	51	1*	1.9%	51	2*	3.6%	n.s.
Hypertension associated with other diseases	50	0*	0.0%	51	2*	4.3%	n.s.
Total	101	1*	1.0%	102	4*	3.9%	p = 0.37

* Calculation based on available data

In all the analyzed populations the percentages of patients who died during an observation period of 12 weeks were lower in the iloprost group as compared to the placebo group. However, differences between the therapeutic groups did not reach statistical significance.

The odds ratio for death was 0.49 (95% CI: 0.01 to 9.76) for patients with primary PAH, 0.25 (95% CI: 0.00 to 3.97) for patients with PAH associated with other diseases and 0.24 (95% CI: 0.01 to 2.55) for the whole population. It means that the odds of death is lower in the iloprost group and is 49%, 25% and 24% of this odds in the placebo group for patients with primary PAH, those with PAH associated with other diseases and regardless of the type, respectively. The results are not statistically significant.

3.3.4.2. Exacerbation of symptoms of the disease

This endpoint in the study of *Olschewski 2002* was defined as refractory systolic arterial hypotension (blood pressure below 85 mmHg), worsening of right ventricular failure (e.g. ascites or pulmonary edema resistant to treatment), progressive heart, liver or kidney failure, reduction of the 6-minute walk distance by at least 30%, worsening of hemodynamic parameters, e.g. central blood pressure and mixed venous blood oxygen saturation.

The table below presents the numbers and percentages of patients, in whom exacerbation of symptoms of the disease was observed during an observation period of 12 weeks.

Table 69.
Numbers and percentages of patients, in whom exacerbation of symptoms of the disease was observed; ILO vs. PL

Population	ILO			PL			Statistical significance of differences between the groups; ILO vs. PL
	N	n	Percentage	N	n	Percentage	
Total	101	5*	4.9%	102	9*	8.8%	p = 0.41

* Calculation based on available data

The percentage of patients, in whom exacerbation of symptoms of PAH was observed, was lower in the iloprost group as compared to the placebo group; however, the difference between the assessed groups did not reach statistical significance (p = 0.41).

The odds ratio is 0.54 (95% CI: 0.14 to 1.87), which means that the odds of occurrence of this endpoint is lower in the iloprost group and is 54% of this odds in the placebo group. The result is not statistically significant.

3.3.4.3. Death or exacerbation of symptoms of the disease

Incidence of this composite endpoint was assessed in the trial of *Olschewski 2002* only.

Detailed results reported by the authors of the study for an observation period of 12 weeks are presented below.

Table 70.
Numbers and percentages of patients, who died or in whom exacerbation of symptoms of the disease was observed; ILO vs. PL

Population	ILO			PL			Statistical significance of differences between the groups; ILO vs. PL
	N	n	Percen-tage	N	n	Percen-tage	
Total	101	5*	4.9%	102	12*	11.8%	p = 0.09

* Calculation based on available data

The percentage of patients who died or suffered from exacerbation of symptoms of the disease was lower in the iloprost group as compared to the placebo group. However, the difference between the groups was not statistically significant (p = 0.09).

The odds ratio calculated from the above data is 0.39 (95% CI: 0.1 to 1.26), the odds of death or exacerbation of symptoms of the disease in the iloprost group is therefore 39% of this odds in the placebo group. The result is not statistically significant.

3.3.4.4. Quality of life

Quality of life was assessed in the clinical trial of *Olschewski 2002* using *EuroQol* – a tool consisting of a 5-part questionnaire and a visual analogue scale (VAS) from 0 to 100, where 0 represented the worst possible condition and 100 – the best. A 12-part *Medical Outcomes Study Short-Form General Health Survey* was also used. The observation period was 12 weeks.

Mean baseline and final scores are presented below.

Table 71.
Quality of life – EuroQol; ILO vs.PL

EuroQol	Intervention	N	Baseline value		Final value		Mean difference in change between the groups (95% CI); ILO vs. PL
			Mean	SD	Mean	SD	
Questionnaire	ILO	101	0.49	0.28	0.58	0.27	0.02 (-0.06 to 0.1)*
	PL	102	0.56	0.29	0.56	0.31	
VAS	ILO	101	46.9	15.9	52.8	19.1	5.4 (-0.14 to 10.94)*
	PL	102	48.6	16.9	47.4	21.1	

* Calculation based on available data

Quality of life assessed with the *EuroQol* questionnaire improved after 12 weeks of observation of patients with PAH in the iloprost group and remained the same in the placebo group. No statistically significant difference between the assessed therapeutic groups was noted (p = 0.11). Mean difference between the groups is 0.02 (95% CI: -0.06 to 0.1) in favor of the ILO group.

Mean quality of life score in the VAS *EuroQol* scale was statistically significantly improved in the iloprost group and slightly worsened in the placebo group. The authors of the *Olschewski 2002* study reported a statistically significant difference between the groups (p = 0.026). Mean difference between the groups (ILO and PL) calculated from the above results is 5.4 (95% CI: -0.14 to 10.94) and the result did not reach statistical significance. That discrepancy in statistical significance might be a result of analysis of covariance used in Olschewski 2002, which took into account the difference in baseline values.

No statistically significant differences in quality of life assessed using a 12-part form designed for assessment of general condition *(Medical Outcomes Study Short-Form General Health Survey)* were found between the groups.

3.3.4.5. Exercise capacity according to the NYHA classification

Only in the study of *Olschewski 2002* exercise capacity was assessed according to the NYHA *(New York Heart Association)* classification. Authors of the study reported the percentage of patients, in whom improvement in exercise capacity by one or two NYHA classes was

observed (reclassification into a lower NYHA class), that of patients whose functional class did not change and the percentage of patients, in whom this parameter worsened (reclassification into a higher NYHA class). The observation period was 12 weeks.

Detailed results of the *Olschewski 2002* trial are presented below.

Table 72.
Numbers and percentages of patients, in whom change in exercise capacity according to the NYHA classification was observed; ILO vs. PL

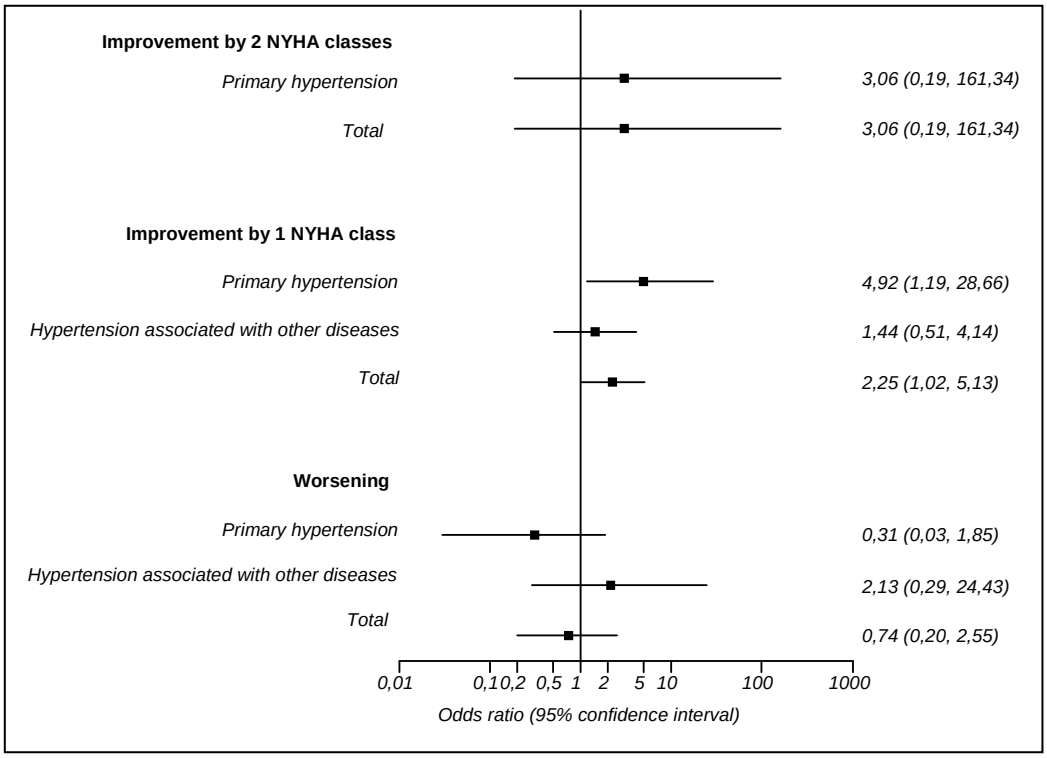
Change in the NYHA class	Population	ILO			PL			Statistical significance of differences between the groups; ILO vs. PL
		N	n	Percentage	N	n	Percentage	
Improvement by 2 classes	**Primary hypertension**	51	1*	1.9%	51	0	0%	n.s.
	Hypertension associated with other diseases	50	0*	0.0%	51	0	0%	n.s.
	Total	101	1*	1.0%	102	0	0%	p = 0.03
Improvement by 1 class	**Primary hypertension**	51	12*	22.6%	51	3*	7.3%	n.s.
	Hypertension associated with other diseases	50	13*	25.0%	51	10*	19.1%	n.s.
	Total	101	25*	23.8%	102	13*	12.7%	p = 0.03
No change	**Primary hypertension**	51	34*	66.0%	51	35*	69.1%	n.s.
	Hypertension associated with other diseases	50	31*	62.5%	51	32*	61.7%	n.s.
	Total	101	65*	64.4%	102	67*	65.7%	n.s.
Worsening	**Primary hypertension**	51	2*	3.8%	51	6*	10.9%	n.s.
	Hypertension associated with other diseases	50	4*	8.3%	51	2*	4.3%	n.s.
	Total	101	6*	5.9%	102	8*	7.8%	n.s.

* Calculation based on available data

For the whole population of patients in the ILO group the percentage of patients, in whom exercise capacity improved, either by one or by two NYHA classes, was statistically significantly higher as compared to the PL group. Differences between the therapeutic groups did not reach statistical significance for exercise capacity assessment according to the NYHA either remaining the same or worsening.

Odds ratios calculated from data reported by the authors of the *Olschewski 2002* study are presented in the figure below.

Figure 26.
Odds ratios for changes in exercise capacity according to the NYHA classification; ILO vs. PL



The odds of increase of exercise capacity by two NYHA functional classes is more than three times higher in the ILO group as compared to the PL group; OR = 3.06 (95% CI: 0.02 to infinity) both for patients with primary PAH and for the whole population of patients. None of the results reached statistical significance, in spite of the fact that in Olschewski 2002 trial the difference reached statistical significance (p=0.03).

The odds ratio for increase of exercise capacity by one NYHA functional class is 4.92 (95% CI: 1.19 to 28.66) for patients with primary PAH, 1.44 (95% CI: 0.51 to 4.14) for patients with PAH associated with other diseases and 2.25 (95% CI: 1.02 to 5.13) for both populations combined. It means that the odds of occurrence of this endpoint is 4.92, 1.44 and 2.25 times higher in the ILO group as compared to the respective odds in the PL group. However, the result reached statistical significance only for the population of patients with primary PAH and for both populations combined.

The odds ratio for decrease of exercise capacity according to the NYHA classification is 0.31 (95% CI: 0.03 to 1.85) for patients with primary PAH, 2.13 (95% CI: 0.29 to 24.43) for patients with PAH associated with other diseases and 0.74 (95% CI: 0.20 to 2.55) for both populations combined. It means that the odds of reclassification into a higher NYHA class in the ILO group is 31%, 213% and 74% of this odds in the PL group, respectively. The results are not statistically significant.

For increase of exercise capacity according to the NYHA classification in patients with primary PAH and in the whole population of patients additional EBM parameters were calculated: relative benefit (RB), relative benefit increase (RBI), absolute benefit increase (ABI) and the NNT.

Table 73.
Additional EBM parameters for increase of exercise capacity by one NYHA class; ILO vs. PL

Population of patients	RB (95% CI)	RBI (95% CI)	ABI (95% CI)	NNT (95% CI)
Primary pulmonary arterial hypertension	4.00 (1.31 to 12.7)	3.00 (0.31 to 11.7)	0.18 (0.04 to 0.32)	6 (4 to 24)
Total	1.94 (1.07 to 3.57)	0.94 (0.07 to 2.57)	0.12 (0.01 to 0.23)	9 (5 to 79)

For patients with primary PAH the relative benefit is 4.00 (95% CI: 1.31 to 12.7); the probability of increase of exercise capacity by one NYHA class is therefore four times higher in the ILO group than in the PL group. The result is statistically significant. The relative benefit increase is 3.00 (95% CI: 0.31 to 11.7), which means that the probability of reclassification into a lower NYHA class is higher by 300% in the ILO group than in the CT group. The absolute benefit increase is 18 p.p. (95% CI: 4 to 32). In order to achieve one additional case of improvement in exercise capacity by one NYHA class, iloprost instead of placebo must be administered to 6 patients with primary PAH for 12 weeks; NNT = 6 (95% CI: 4 to 24).

The probability of occurrence of this endpoint in the whole population of patients is nearly twice higher in the ILO group than in the PL group; RB = 1.94 (95% CI: 1.07 to 3.57). The relative benefit increase is 94% (95% CI: 7 to 257) and the absolute benefit increase: 12 p.p. (95% CI: 1 to 23). It should be expected that administration of iloprost instead of placebo to 9 patients with PAH (primary or associated with other diseases) will result in improvement in exercise capacity by one NYHA class in one additional patient.

3.3.4.6. Results of the 6-minute walk test

In the clinical trial of *Olschewski 2002* exercise capacity was assessed using the 6-minute walk test. The authors of the study reported percentages of patients, for whom the 6-minute walk distance increased by at least 10%, increased or decreased by less than 10% or decreased by at least 10%. The observation period was 12 weeks.

Numbers and percentages of patients, in whom specific endpoints occurred, are presented in the table below.

Table 74.
Numbers and percentages of patients, in whom change in exercise capacity measured using the 6-minute walk test was observed; ILO vs. PL

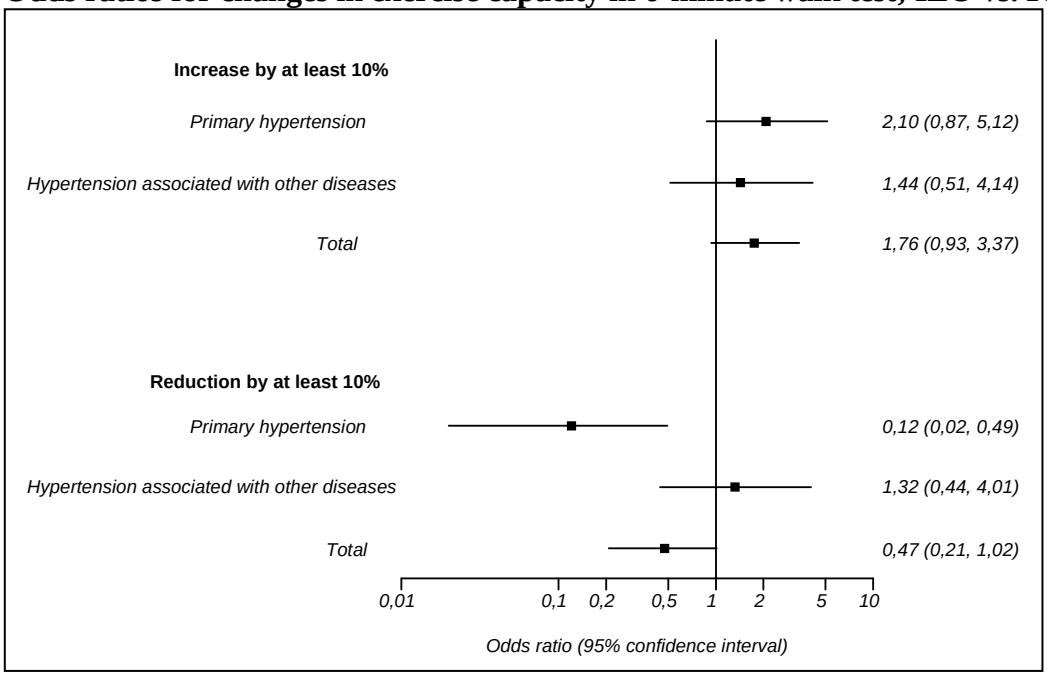
Change of walk distance	Population	ILO			PL			Statistical significance of differences between the groups; ILO vs. PL
		N	n	Percentage	N	n	Percentage	
Increase ≥ 10%	**Primary hypertension**	51	25*	49.1%	51	16*	30.9%	n.s.
	Hypertension associated with other diseases	50	13*	25.0%	51	10*	19.1%	n.s.
	Total	101	38*	37.6%	102	26*	25.5%	p = 0.06
Increase < 10% or reduction < 10%	**Primary hypertension**	51	19*	37.7%	51	10*	20.0%	n.s.
	Hypertension associated with other diseases	50	24*	47.9%	51	23*	46.8%	n.s.
	Total	101	43*	42.6%	102	33*	32.4%	n.s.
Reduction ≥ 10%	**Primary hypertension**	51	3*	5.7%	51	17*	32.7%	n.s.
	Hypertension associated with other diseases	50	11*	22.9%	51	9*	17.0%	n.s.
	Total	101	14*	13.9%	102	26*	25.5%	n.s.

* Calculation based on available data

From these results it may be concluded that the percentages of patients, in whom increase of exercise capacity by at least 10% as measured by the 6-minute walk test was observed, were higher in the ILO group than in the PL group. However, differences between the therapeutic groups were not statistically significant (p = 0.06). In the ILO group increase or decrease of exercise capacity by less than 10% was observed in a higher percentage of patients with PAH as compared to the placebo group. Reduction of exercise capacity by at least 10% was observed less often in the ILO group than in the PL group. The results did not reach statistical significance.

The figure below presents odds ratios calculated from the results of the *Olschewski 2002* study for increase of exercise capacity in the 6-minutes walk test by at least 10%, increase or reduction of this parameter by < 10% and reduction of exercise capacity by at least 10%.

Figure 27.
Odds ratios for changes in exercise capacity in 6-minute walk test; ILO vs. PL



The odds ratios for increase of exercise capacity by at least 10% in the 6-minute walk test are 2.10 (95% CI: 0.87 to 5.12), 1.44 (95% CI: 0.51 to 4.14) and 1.76 (95% CI: 0.93 to 3.37) for patients with primary PAH, those with PAH associated with other diseases and for both populations combined, respectively. It means that the odds of increase of this parameter is higher in the ILO group and is 210%, 144% and 176% of the respective odds in the PL group. None of the results reached statistical significance.

Both for patients with primary PAH and the whole population of patients the odds of reduction of exercise capacity by at least 10% in the 6-minute walk test is lower in the group of patients treated with iloprost and is 12% and 47% of this odds in the placebo group, respectively. The odds ratio is 0.12 (95% CI: 0.02 to 0.49) for patients with primary PAH and 0.47 (95% CI: 0.21 to 1.02) for the whole population of patients. However, the result is statistically significant only for patients with primary PAH. The odds ratio for this endpoint in patients with PAH associated with other diseases is 1.32 (95% CI: 0.44 to 4.01); the odds of decrease of exercise capacity by at least 10% is therefore higher in the ILO group and is 132% of this odds in the placebo group; the result is not statistically significant.

For reduction of exercise capacity by at least 10% in the 6-minute walk test in patients with primary PAH additional EBM parameters were calculated: relative risk (RR), relative risk reduction (RRR), absolute risk reduction (ARR) and the NNT.

Table 75.
Additional EBM parameters for reduction of exercise capacity by at least 10%; ILO vs. PL

Population of patients	RR (95% CI)	RRR (95% CI)	ARR (95% CI)	NNT (95% CI)
Primary pulmonary arterial hypertension	0.18 (0.06 to 0.52)	0.82 (0.48 to 0.94)	0.27 (0.13 to 0.42)	4 (3 to 8)

The relative risk is 0.18 (95% CI: 0.06 to 0.52); the risk of reduction of exercise capacity by at least 10% is therefore lower in the ILO group and is 18% of this risk in the placebo group; the result is statistically significant. The relative risk reduction is 82% (95% CI: 48% to 94%). The absolute risk reduction is 27 p.p. (95% CI: 13 to 42), which means that the risk of this endpoint in the iloprost group is lower by 27 p.p. as compared to the placebo group. Administration of iloprost instead of placebo for 12 weeks to 4 patients with primary PAH will make it possible to avoid reduction of exercise capacity in the 6-minute walk test by at least 10% in one additional patient; NNT = 4 (95% CI: 3 to 8).

The authors of the *Olschewski 2002* study reported also that mean difference in change of exercise capacity in the 6-minute walk test between the groups (ILO and placebo) was 58.8 m for patients with primary PAH, 12.0 m for those with PAH associated with other diseases and 36.4 m for the whole population of patients, in favor of iloprost. The result was statistically significant only for the whole population of patients (p = 0.004).

3.3.4.7. Increase of exercise capacity according to the NYHA classification and the 6-minute walk test

In the trial of *Olschewski 2002* a composite endpoint was assessed – increase of exercise capacity by at least 10% in the 6-minute walk test and reclassification into a lower NYHA class with no exacerbation of the symptoms or death during an observation period of 12 weeks.

Numbers and percentages of patients in both therapeutic groups, in whom this endpoint occurred, are presented in the table below.

Table 76.
Numbers and percentages of patients, in whom increase of exercise capacity both in the 6-minute walk test and according to the NYHA classification was observed; ILO vs. PL

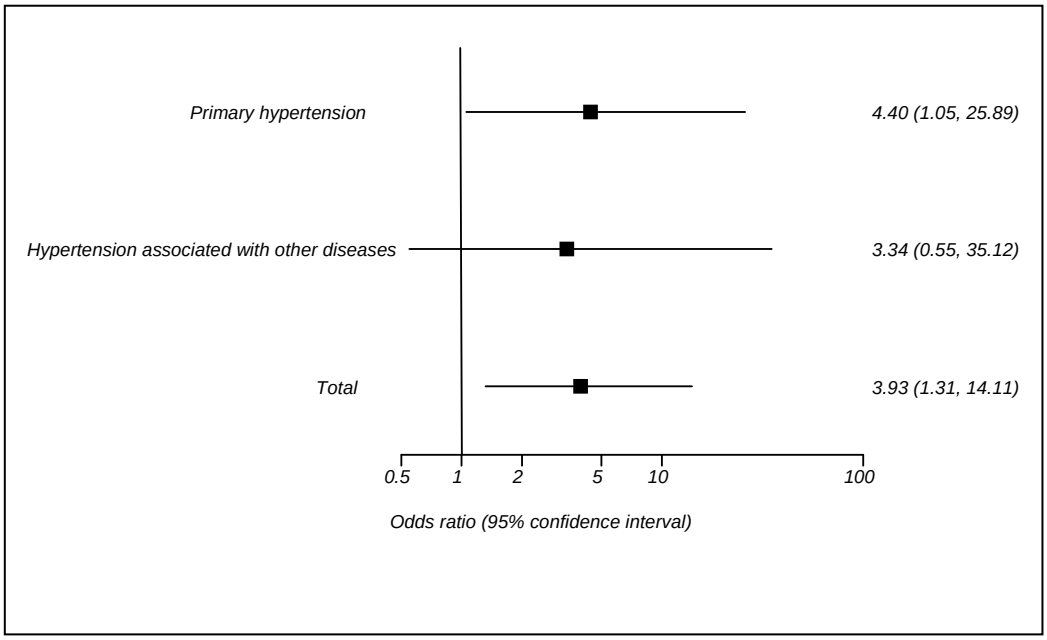
Population	ILO			PL			Statistical significance of differences between the groups; ILO vs. PL
	N	n	Percentage	N	n	Percentage	
Primary hypertension	51	11*	20.8%	51	3*	5.5%	n.s.
Hypertension associated with other diseases	50	6*	12.5%	51	2*	4.3%	n.s.
Total	101	17*	16.8%	102	5*	4.9%	p = 0.007

* Calculation based on available data

Increase of exercise capacity by at least 10% in the 6-minute walk test and according to the NYHA classification was observed more often in the ILO group than in the placebo group. Differences between the groups were statistically significant only for the whole population of patients (p = 0.007).

The figure below presents the odds ratios for increase of exercise capacity calculated for specific populations of patients.

Figure 28.
Odds ratios for increase of exercise capacity both in the 6-minute walk test and according to the NYHA; ILO vs. PL



The odds ratio for increase of exercise capacity in patients with primary PAH is 4.40 (95% CI: 1.05 to 25.89), which means that the odds of occurrence of this endpoint is 4.40 times higher in the ILO group than in the placebo group. The result is statistically significant.

For patients with PAH associated with other diseases the odds of increase of exercise capacity is 3.34 times higher in the iloprost group than in the placebo group; OR = 3.34 (95% CI: 0.55 to 35.12); however, the result is not statistically significant.

For the whole population of patients the odds of increase of exercise capacity is 3.93 times higher in the iloprost group than in the placebo group and the result is statistically significant; OR = 3.93 (95% CI: 1.31 to 14.11).

Additional EBM parameters calculated for the population of patients with primary PAH and regardless of the type of PAH: relative benefit (RB), relative benefit increase (RBI), absolute benefit increase (ABI) and the NNT are presented below.

Table 77.
Additional EBM parameters for increase in exercise capacity both in the 6-minute walk test and according to the NYHA; ILO vs. PL

Population of patients	RB (95% CI)	RBI (95% CI)	ABI (95% CI)	NNT (95% CI)
Primary pulmonary arterial hypertension	3.67 (1.19 to 11.75)	2.67 (0.19 to 10.75)	0.16 (0.02 to 0.30)	7 (4 to 41)
Total	3.43 (1.38 to 8.72)	2.43 (0.38 to 7.72)	0.12 (0.04 to 0.21)	9 (5 to 28)

The relative benefit is 3.67 (95% CI: 1.19 to 11.75) for patients with primary PAH and 3.43 (95% CI: 1.38 to 8.72) for the whole population of patients; the probability of increase of exercise capacity in the iloprost group is therefore 3.67 and 3.43 times higher than this

probability in the placebo group, respectively. The results are statistically significant. The absolute benefit increase is 2.67 (95% CI: 0.19 to 10.75) for patients with primary PAH and 2.43 (95% CI: 0.38 to 7.72) for the whole population. The absolute benefit increase is 16 p.p. (95% CI: 2 to 30) and 12 p.p. (95% CI: 4 to 21), which means that the probability of occurrence of this endpoint in the ILO group as compared to the placebo group is higher by 16 p.p. and 12 p.p., respectively. In order to achieve one additional case of increase of exercise capacity iloprost instead of placebo must be administered to 7 patients with primary PAH or 9 patients regardless of the type of PAH for a period of 12 weeks; NNT = 7 (95% CI: 4 to 41) for patients with primary PAH and 9 (95% CI: 5 to 28) for the whole population of patients.

3.3.4.8. Mahler Dyspnea Index

In the *Olschewski 2002* study severity of dyspnea was assessed using the Mahler Dyspnea Index consisting of two tools, of which the first allows for baseline assessment of dyspnea (in a scale 0-12, where 0 represents the most severe dyspnea and 12 – no symptoms), while the second is used for evaluation of change from baseline assessment (from -9 to 9, where -9 represents severe exacerbation of dyspnea and 9 – significant improvement) in three categories: functional impairment, magnitude of task and magnitude of effort.[2] The observation period with regard to this endpoint was 12 weeks.

Baseline scores and changes from baseline assessment for the whole population of patients with PAH are presented below.

Table 78.
The Mahler Dyspnea Index; ILO vs. PL

Intervention	N	Baseline score		Change from baseline score		Mean difference in change between the groups (95% CI); ILO vs. PL
		Mean	SD	Mean	SD	
ILO	101	4.14	1.8	1.42	2.59	1.12 (0.43 to 1.81)*
PL	102	4.27	1.8	0.30	2.45	

* Calculation based on available data

The authors of the *Olschewski 2002* study reported statistically significantly higher reduction of severity of dyspnea in the iloprost group as compared with the placebo group (p = 0.015). Mean difference in change from baseline score for this parameter calculated from the above results is 1.12 points (95% CI: 0.43 to 1.81), in favor of the iloprost group. The result is statistically significant.

[2] Mahler DA, Weinberg DH, Wells CK, Feinstein AR; "The measurement of dyspnea. Contents, interobserver agreement, and physiologic correlates of two new clinical indexes"; Chest. 1984 Jun;85(6):751-8

3.3.4.9. Pulmonary transplantation

Frequency of pulmonary transplantation was assessed in the *Olschewski 2002* trial in an observation period of 12 weeks. During this time an operation of this kind was not necessary in any of the assessed therapeutic groups.

3.3.4.10. Hemodynamic parameters

In the study of *Olschewski 2002* mean changes from baseline values for such hemodynamic parameters as mean pulmonary artery pressure, pulmonary vascular resistance, cardiac output and arterial as well as mixed venous blood oxygen saturation were presented. The results were reported for the whole population of patients, regardless of the type of pulmonary hypertension. The observation period with regard to these endpoints was 12 weeks.

Hemodynamic parameter were measured both before and after the administration of iloprost in the trial of Olschewski 2002. However, pre-inhalation values, which reflect the chronic effects of administering iloprost over 12 weeks, are took into account as a main results.

Detailed results reported by the authors of the study are presented in the table below.

Table 79.
Mean values of hemodynamic parameters; ILO vs. PL

Parameter	Intervention	N	Baseline value		Change from baseline (before inhalation)		Statistical significance of differences between the groups; ILO vs. PL
			Mean	SD	Mean	SD	
Mean pulmonary artery pressure [mmHg]	ILO	101	52.8	11.5	-0.1	7.3	n.s.
	PL	102	53.8	14.1	-0.2	6.9	
Pulmonary vascular resistance [dyn · sec · cm $^{-5}$]	ILO	101	1029	390	-9	275	p<0.01
	PL	102	1041	493	96	322	
Cardiac output [l/min]	ILO	101	3.8	1.1	0.05	0.86	n.s.
	PL	102	3.8	0.9	-0.19	0.81	
Arterial blood oxygen saturation [%]	ILO	101	92.6	4.4	-0.4	3.7	n.s.
	PL	102	92.2	5.0	-1.6	4.4	
Mixed venous blood oxygen saturation [%]	ILO	101	60.4	7.5	-1.1	7.6	n.s.
	PL	102	60.5	8.2	-3.2	6.7	

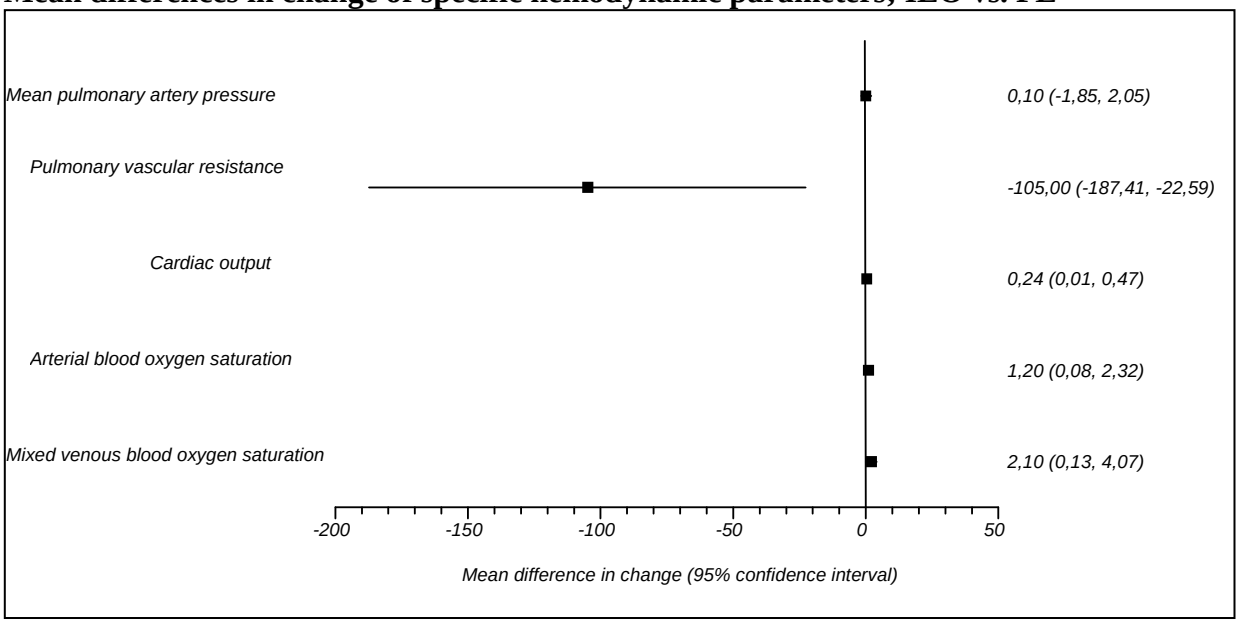
* Calculation based on available data

Hemodynamic parameters changes from baseline values were not statistically significant in iloprost group. In the placebo group pulmonary vascular resistance increased while cardiac output and arterial as well as mixed venous blood oxygen saturation decreased. Changes from

baseline values were statistically significant; however, differences in change between the assessed therapeutic groups were statistically significant only for mean pulmonary vascular resistance.

Mean differences in change of specific hemodynamic parameters measured before inhalations, between the assessed therapeutic groups calculated from the results of the *Olschewski 2002* study are presented in the figure below.

Figure 29.
Mean differences in change of specific hemodynamic parameters; ILO vs. PL



Mean difference in changes of pulmonary artery pressure between the ILO group and the placebo group is 0,10 mmHg (95% CI: -1,85; 2,05), in favor of placebo. The result is not statistically significant. As far as pulmonary pulmonary vascular resistance is concerned, mean difference in changes is statistically significant, in favor of iloprost group: -105 dyn · s · cm^{-5} (95% CI: -187,41; -22,59).
Mean differences in changes of cardiac output, arterial blood oxygen saturation and mixed venous blood oxyden saturation are 0,24 l/min (95% CI: 0,01; 0,47); 1,20 p.p. (95% CI: 0,08; 2,32); 2,10 p.p. (95% CI: 0,13; 4,07); respectively. It means that decrease of above mentioned parameters is lower in the ILO group as compared to the placebo group. Results are staistically significant.

Taking into account hemodynamic parameters mesured after administration of iloprost, mean differences in change of pulmonary artery pressure and pulmonary vascular resistance between the ILO group and the placebo group are -4.40 mmHg (95% CI: -6.65 to -2.15) and -335 dyn · s · cm^{-5} (95% CI: -417.92 to -252.08), respectively. Both results are statistically significant, despite the fact that the authors of the *Olschewski 2002* study did not report statistically significant differences between the groups.

Increase of such parameters as cardiac output, arterial blood oxygen saturation and mixed venous blood oxygen saturation, mesured after iloprost inhalation, was higher in the ILO group as compared to the placebo group by 0.74 l/min, 20 p.p. and 500 p.p., respectively. Mean difference in change between the therapeutic groups is 0.74 l/min (95% CI: 0.47 to 1.01) for cardiac output, 20 p.p. (95% CI: -92 to 132) for arterial blood oxygen saturation and 500 p.p. (95% CI: 293 to 707) for mixed venous blood oxygen saturation.

3.3.4.11. Pulmonary function tests

In the study of *Thurm 1991* pulmonary function tests were used in order to assess vital capacity (VC) and diffusion capacity (DL_{CO}), i.e. the amount of carbon oxide that may diffuse across the alveolar-capillary barrier in a given unit of time and under a specific difference in partial pressure of this gas in blood and the alveoli. The observation period with regard to these parameters was 3 days.

Detailed results reported by the authors of the study are presented in the table below.

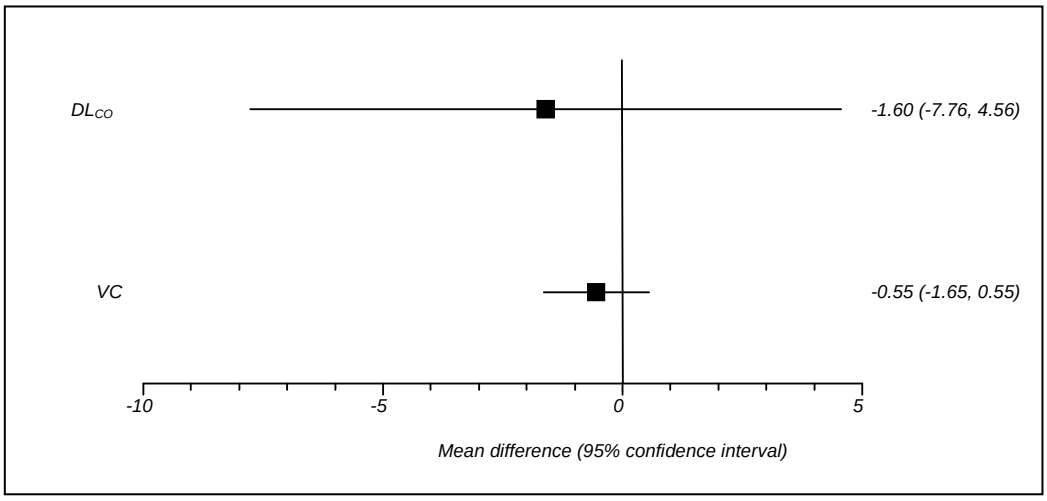
Table 80.
Mean values of DL_{CO} and VC; ILO vs. PL

Parameter	Intervention	N	Baseline value		Final value		Statistical significance of differences between the groups; ILO vs. PL
			Mean	SD	Mean	SD	
DL_{CO} [ml/min/mmHg]	ILO	6	11.3	5.7	11.1	5.2	n.s.
	PL	7	12.9	5.4	12.7	6.0	
VC [l]	ILO	6	2.30	0.73	2.28	0.91	n.s.
	PL	7	2.73	1.00	2.83	1.08	

In an observation period of 3 days no statistically significant differences between the groups (iloprost and placebo) were found, either for lung diffusion capacity or vital capacity.

Mean differences in lung diffusion capacity and vital capacity between the assessed therapeutic groups calculated from the above data are presented in the figure.

Figure 30.
Mean differences in DL_{CO} and VC; ILO vs. PL



Mean difference in lung diffusion capacity between the therapeutic groups after 3 days of observation of patients with PAH associated with collagenoses is -1.60 ml/min/mmHg

(95% CI: -7.76 to 4.56), in disfavor of the iloprost group. The result is not statistically significant.

Vital capacity was lower by 0.55 l in the iloprost group than in the placebo group. Mean difference between the groups is -0.55 l (95% CI: -1.65 to 0.55). The result is not statistically significant.

3.3.5. Assessment of safety

3.3.5.1. Serious adverse events

Incidence of the most common serious adverse events was assessed in the trial of *Olschewski 2002* in an observation period of 12 weeks.

Numbers and percentages of patients, in whom specific serious adverse events were observed, are presented below.

Table 81.
Numbers and percentages of patients, in whom serious adverse events were observed; ILO vs. PL

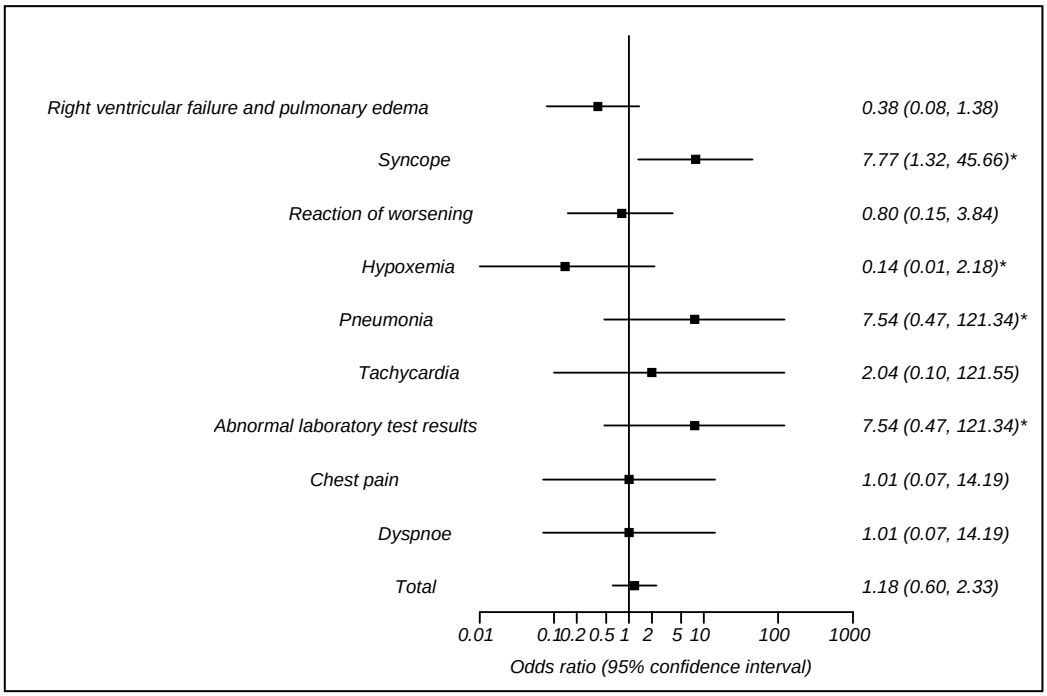
Adverse event	ILO			PL			Statistical significance of differences between the groups; ILO vs. PL
	N	n	Percen-tage	N	n	Percen-tage	
Right ventricular failure and pulmonary edema	101	4	4.0%	102	10	9.8%	p = 0.16
Syncope	101	5	5.0%	102	0	0%	p = 0.03
Reactive worsening (an event which may result in worsening)	101	4	4.0%*	102	5	5.0%*	n.s.
Hypoxemia	101	0	0%	102	2	2.0%*	n.s.
Pneumonia	101	2	2.0%*	102	0	0%	n.s.
Tachycardia	101	2	2.0%*	102	1	1.0%*	n.s.
Abnormal laboratory test results	101	2	2.0%*	102	0	0%	n.s.
Chest pain	101	2	2.0%*	102	2	2.0%*	n.s.
Dyspnea	101	2	2.0%*	102	2	2.0%*	n.s.
Total	101	28	27.7%	102	25	24.5%	p = 0.63

* Calculation based on available data

Incidence of serious adverse events was similar in both assessed therapeutic groups and for most endpoints no statistically significant differences were found between the groups. The exception was syncope, which occurred statistically significantly higher in the iloprost group as compared to the placebo group (p = 0.03).

The odds ratios for specific serious adverse events calculated from the results of the *Olschewski 2002* study are presented in the figure below.

Figure 31.
Odds ratios for serious adverse events; ILO vs. PL



* Odds ratio calculated using the *Peto* method

The odds ratios are 0.38 (95% CI: 0.08 to 1.38) for right ventricular failure and pulmonary edema, 0.80 (95% CI: 1.32 to 45.66) for reactive worsening and 0.14 (95% CI: 0.01 to 2.18) for hypoxemia. It means that the odds of occurrence of these adverse events in lower the ILO group and is 38%, 80% and 14% of the respective odds in the placebo group. The results are not statistically significant.

The odds of occurrence of the remaining serious adverse events is higher in the ILO group as compared to the PL group. The odds ratios are 7.77 (95% CI: 1.32 to 45.66) for syncope, 7.54 (95% CI: 0.47 to 121.34) for pneumonia, 2.04 (95% CI: 0.10 to 121.55) for tachycardia, 7.54 (95% CI: 0.47 to 121.34) for abnormal laboratory test results, 1.01 (95% CI: 0.07 to 14.19) for chest pain, 1.01 (95% CI: 0.07 to 14.19) for dyspnea and 1.18 (95% CI: 0.60 to 2.33) for all serious adverse events combined. However, the result is statistically significant for syncope only; NNH = 23 (10 to 83), which means that treatment of 23 patients with PAH with iloprost instead of placebo for a period of 12 weeks will result in syncope occurring in one additional patient.

3.3.5.2. Other adverse events

In the study of *Olschewski 2002* other adverse events were assessed, such as severe cough, headache, flushing, flu-like symptoms, peripheral edema, nausea, jaw pain, hypotension, diarrhea, vertigo and syncope. The observation period was 12 weeks.

Numbers and percentages of patients, in whom specific serious adverse events were observed, are presented below as reported by the authors of the study.

Table 82.
Numbers and percentages of patients, in whom adverse events were observed; ILO vs. PL

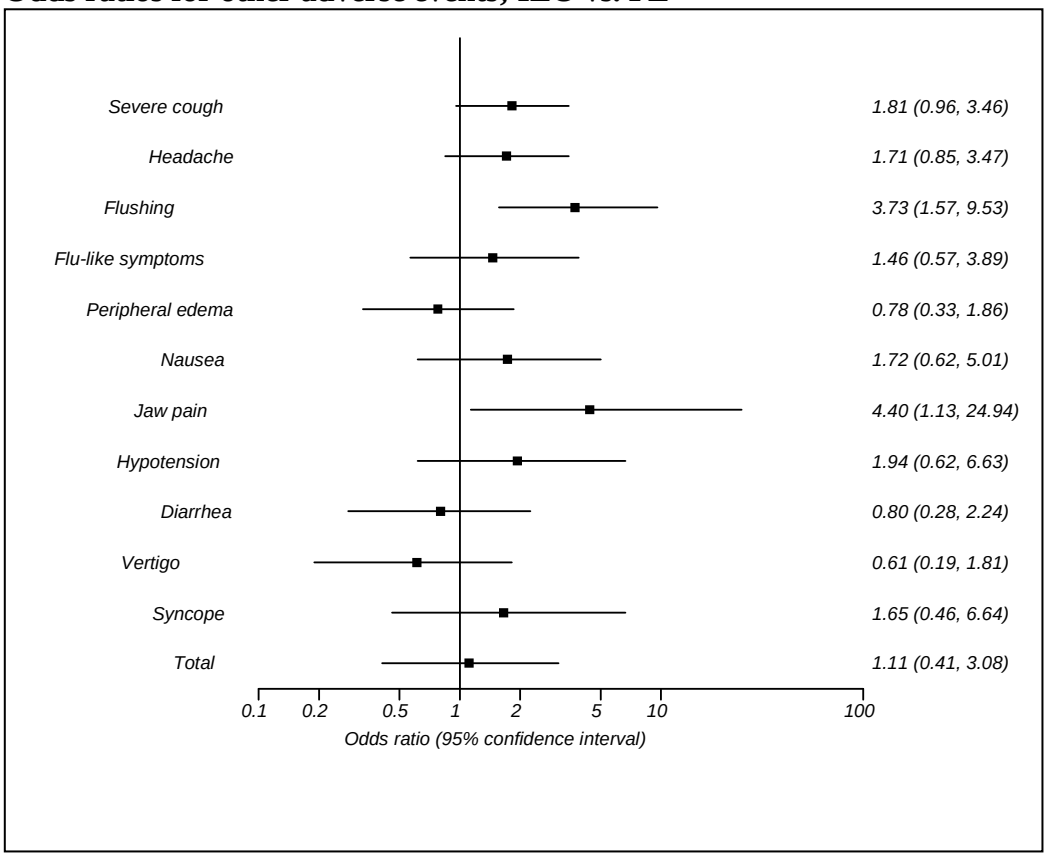
Adverse event	ILO			PL			Statistical significance of differences between the groups; ILO vs. PL
	N	n	Percen-tage	N	n	Percen-tage	
Severe cough	101	39	38.6%	101	26	25.5%	p = 0.05
Headache	101	30	29.7%	101	20	29.6%	p = 0.11
Flushing	101	27	26.7%	101	9	8.8%	p = 0.001
Flu-like symptoms	101	14	13.9%	101	10	9.8%	p = 0.39
Peripheral edema	101	13	12.9%	101	16	15.7%	p = 0.69
Nausea	101	13	12.9%	101	8	7.8%	p = 0.26
Jaw pain	101	12	11.9%	101	3	2.9%	p = 0.02
Hypotension	101	11	10.9%	101	6	5.9%	p = 0.22
Diarrhea	101	9	8.9%	101	11	10.8%	p = 0.81
Vertigo	101	7	6.9%	101	11	10.8%	p = 0.46
Syncope	101	8	7.9%	101	5	4.9%	p = 0.41
Total	101	91	90.1%	101	90	89.2%	p = 0.82

Most of the adverse events assessed in the *Olschewski 2002* trial (severe cough, headache, flu-like symptoms, nausea, jaw pain, hypotension, syncope and all adverse events combined) occurred more often in the ILO group as compared to the PL group; however, the differences reached statistical significance only for flushing (p = 0.001) and jaw pain (p = 0.02).

Incidence of peripheral edema, diarrhea and vertigo was lower in the ILO group as compared to the placebo group and the differences between the groups were not statistically significant.

The figure presents odds ratios calculated from the above data.

Figure 32.
Odds ratios for other adverse events; ILO vs. PL



The odds ratio for any adverse event is 1.11 (95% CI: 0.41 to 3.08), which means that the odds of occurrence of this endpoint in the ILO group is 111% of this odds in the placebo group. The result is not statistically significant.

The odds of occurrence of peripheral edema, diarrhea or vertigo is lower in the iloprost group and is 78%, 80% and 61% of the respective odds in the placebo group. The odds ratios are 0.78 (95% CI: 0.33 to 1.86) for peripheral edema, 0.80 (95% CI: 0.28 to 2.24) for diarrhea and 0.61 (95% CI: 0.19 to 1.81) for vertigo. The results are not statistically significant.

The odds ratios for flushing and jaw pain are 3.73 (95% CI: 1.57 to 9.53) and 4.40 (95% CI: 1.13 to 24.94), respectively. It means that the odds of occurrence of these endpoints in the iloprost group as compared to the placebo group is 3.73 and 4.40 times higher, respectively; the results are statistically significant. The NNH for flushing is 6 (95% CI: 4 to 14) and for jaw pain – 12 (95% CI: 6 to 54); administration of iloprost instead of placebo to 6 and 12 patients with PAH will therefore result in one additional case of flushing and jaw pain, respectively.

For the remaining adverse events: severe cough, headache, flu-like symptoms, nausea, hypotension and syncope it was observed that chances of their occurrence are higher in the ILO group as compared to the PL group; however, none of the results reached statistical significance.

3.3.5.3. Withdrawal from the study

This endpoint was assessed in the study of *Olschewski 2002* in an observation period of 12 weeks. The authors reported the numbers and percentages of patients withdrawn from the trial both due to death and to other reasons, such as discontinuation of treatment or withdrawal of consent for participation in the study.

Detailed results are presented in the table below.

Table 83.
Numbers and percentages of patients withdrawn from the study; ILO vs. PL

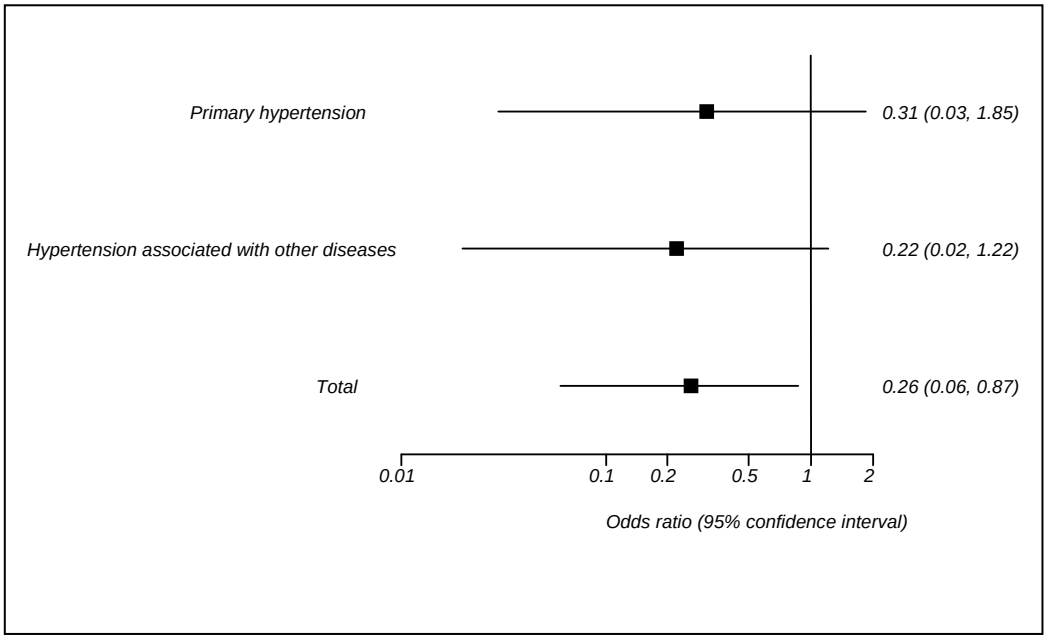
Population	ILO			PL			Statistical significance of differences between the groups; ILO vs. PL
	N	n	Percen-tage	N	n	Percen-tage	
Primary hypertension	51	2*	3.8%	51	6*	12.7%	n.s.
Hypertension associated with other diseases	50	2*	4.2%	51	8*	14.9%	n.s.
Total	101	4*	4.0%	102	14*	13.7%	n.s.

* Calculation based on available data

From the above data it may be concluded that regardless of the population investigated the percentage of patients withdrawn from the study was lower in the iloprost group as compared to the placebo group. However, the authors of the *Olschewski 2002* study did not report statistically significant differences between the assessed therapeutic groups.

The calculated odds ratios are presented in the figure below.

Figure 33.
Odds ratios for withdrawal from the study; ILO vs.PL



The odds ratio for withdrawal from the study is 0.31 (95% CI: 0.03 to 1.85) for patients with primary PAH and 0.22 (95% CI: 0.02 to 1.22) for patients with PAH associated with other diseases. It means that the odds of occurrence of this endpoint is lower in the ILO group and is 31%, and 22% of the respective odds in the placebo group. The results are not statistically significant.

For the whole population of patients the odds of a patient being withdrawn from the study in the ILO group is 26% of this odds in the placebo group; OR = 0.26 (95% CI: 0.06 to 0.87) and the result is statistically significant. In order to avoid one additional case of the patient's withdrawal from the study iloprost must be administered instead of placebo to 11 patients with PAH (primary or associated with other diseases); NNT = 11 (95% CI: 6 to 48).

3.4. Sildenafil vs. placebo – adult patients

3.4.1. Results of search for the studies

Four randomized clinical studies, in which sildenafil (SIL) was compared to placebo (PL) in adult patients with pulmonary arterial hypertension, were identified during the search and included in the analysis. All the studies were double-blind. In the SUPER-1 study the interventions were compared in parallel groups; the three remaining trials *(Bharani 2003, Sastry 2004* and *Singh 2006)* were cross-over studies.

The SUPER-1 study was multicenter; the other trials were carried out in single centers.

Duration of the observation period varied between the studies. The shortest *(Bharani 2003)* lasted 2 weeks, while the blinded phase of the longest (SUPER-1) was terminated after 12 weeks.

Publications related to the included studies, duration of the observation period and the *Jadad* scores for specific studies are presented in the table below.

Table 84.
Characteristics of the clinical trials included in the analysis; SIL vs. PL

Study	Publications	Observation period	*Jadad* score
Bharani 2003	*Bharani 2003*	2 weeks	4
Sastry 2004	*Sastry 2004*	6 weeks	4
Singh 2006	*Singh 2006*	6 weeks	3
SUPER-1	*Badesch 2005* *Galie 2005a* *Pepke-Zaba 2005* *Rubin 2005* *SUPER-1*	12 weeks	4

Each study was assessed using the 0-5 *Jadad* scale. The lowest score was that of the *Singh 2006* study – 3 points; the remaining studies scored 4 points.

3.4.2. Population

Adult patients or children above 3 years of age with PAH participated in all studies included in this part of the analysis. In one study *(Sastry 2004)* patients with primary PAH were enrolled, while in three clinical trials *(Bharani 2003*, SUPER-1, *Singh 2006)* participated patients, in whom primary or secondary (associated with other diseases, such as thromboembolic disease, interstitial lung disease *(Bharani 2003)*, Eisenmenger's syndrome *(Bharani, 2003, Singh 2006),* collagenoses, e.g. scleroderma or systemic lupus erythematosus, or hypertension after surgical intervention due to congenital systemic-to-pulmonary shunt performed within previous 5 years (SUPER-1)) PAH was diagnosed. Children aged from three to twelve years were enrolled in the *Singh 2006* study only; however, the authors did not specify the percentage of such patients among the participants.

Among the inclusion criteria NYHA *(New York Heart Association)* class ≥ II was listed in the *Bharani 2003* study and class II or III – in the trial of *Sastry 2004.*

For the *Bharani 2003* study only those patients were qualified, in whom mean pulmonary artery pressure was at least 35 mmHg; in the trial of *Sastry 2004* the threshold value was 30 mmHg and in the SUPER-1 trial – 25 mmHg, with mean pulmonary capillary wedge pressure at rest not exceeding 15 mmHg. The authors of the studies of *Bharani 2003* and SUPER-1 stated that patients with poorly controlled pulmonary hypertension in spite of conventional treatment were enrolled.

The exclusion criteria were: contraindications to treatment with sildenafil *(Bharani 2003, Singh 2006),* PAH due to reversible causes, such as heart valve diseases *(Bharani 2003, Sastry 2004),* NYHA functional class IV, impaired left ventricular systolic function, severe left-to-right shunt, systemic hypertension, secondary PAH, other serious concomitant diseases *(Sastry 2004),* treatment with intravenous epoprostenol, oral bosentan, intravenous or inhaled iloprost or subcutaneous treprostinil, 6-minute walk distance below 100 m or over 450 m (SUPER-1), coronary heart disease, severely impaired renal or hepatic function and pulmonary hypertension associated with diseases other than Eisenmenger's syndrome *(Singh 2006).*

Baseline characteristics of the population of patients in particular studies are presented in the table below.

Table 85.
Baseline characteristics of the patients enrolled in particular studies; SIL vs. PL

Study	Number of patients		Mean age (SD) [years]		Percentage of men		Percentage of patients with primary PAH/ PAH associated with other diseases		Percentage of patients in NYHA/WHO functional class II/III/IV		Percentage of patients receiving conventional treatment		Mean time from diagnosis (SD) [months]		Mean 6-minute walk distance (SD) [m]	
	SIL	PL	SIL	PL	SIL	PL	SIL	PL	SIL	PL	SIL	PL	SIL	PL	SIL	PL
Bharani 2003	9		32.11 (15.06)		44.4%*		33.3%/66.7%*		33.3%/55.6%/11.1%*		100%		nd		163.9 (110.7)	
Sastry 2004	22		16-55§		45.5%*		100%/0%		81.8%/18.2%/0%*		nd		30 (1-180)‡		nd	
Singh 2006	20		3-45§		25.0%*		50%/50%*		40%/55%/5%*		100%		nd		262* (nd)	
SUPER-1	207	70	51*	49 (17)	27%*	19%*	64%/36%*	60%/40%*	36%/61%/3%*	46%/49%/4%	100%	100%	nd	nd	344*	344 (79)
Total**	**258**	**121**	**50.21**	**47.1**	**29.0%**	**26.7%**	**65%/35%**	**64%/36%**	**40%/57%/3%**	**51%/45%/4%**	**100%**	**100%**	**nd**	**nd**	**330.2**	**311.1**

* calculation based on available data
§ range
‡ median (range)
** mean value weighted with the numbers of patients in particular studies

Sildenafil was administered to a total number of 258 patients and placebo – to 121 patients with PAH. Mean age in the SIL and PL groups was 50 and 47 years, respectively; mean 6-minute walk distance was 330 and 311 m, the percentage of men: 29% and 27%, the percentage of patients with primary PAH: 65% and 64%, those with PAH associated with other diseases: 35% and 36%, those in NYHA/WHO functional class II: 40% and 51%, class III: 57% and 45% and class IV: 3% and 4%, respectively.

From the above data it may be concluded that the populations of patients in specific studies differed as to the percentage of male participants, which was slightly higher in the *Bharani 2003* and *Sastry 2004* studies as compared to the trials of *Singh 2006* and SUPER-1. The studies of *Singh 2006* and SUPER-1 were also similar with regard to the percentage of patients with primary PAH and mean 6-minute walk distance. The population of patients in the *Bharani 2003* trial differed from the others both with regard to the percentage of patients with primary PAH and mean 6-minute walk distance, which were significantly lower than those in the remaining studies. In the *Sastry 2004* study only patients with primary PAH were enrolled. The percentage of patients in NYHA/WHO functional class II, III or IV was similar in the studies of *Bharani 2003*, *Singh 2006* and *SUPER-1*; it was different from that in the *Sastry 2004* trial, in which most patients were classified in NYHA class II.

In the study of *Bharani 2003* 33.3% of the enrolled patients suffered from pulmonary hypertension other than arterial: in 22.2% of the patients diagnosed hypertension was associated with interstitial lung disease and in 11.1% – with thromboembolic disease. Nevertheless, since majority of the population (66.7%) consisted of patients with pulmonary arterial hypertension, the study was included in the analysis.

3.4.3. Interventions

Patients enrolled in specific clinical trials were randomly assigned to the sildenafil (SIL) group or the placebo (PL) group.

Detailed dosage of sildenafil and additional treatment received by the patients are presented in the table below.

Table 86.
Description of the interventions; SIL vs. PL

Study	SIL			PL	Additional treatment
Bharani 2003	SIL at a dose of 25 mg every 8 h			placebo	Warfarin, nifedipin, diuretics, digoxin
Sastry 2004	SIL at a dose adjusted to body mass: below 25 kg - SIL at a dose of 25 mg 3 times daily, 26 to 50 kg - SIL at a dose of 50 mg 3 times daily, over 50 kg - SIL at a dose of 100 mg 3 times daily.			PL	Digoxin, diuretics and oral anticoagulants (at the physician's discretion)
Singh 2006	Adults: SIL at an initial dose of 25 mg repeated after 6 h; if no hypotension was observed, the dose was increased to 100 mg 3 times daily. Children with a body mass of less than 30 kg: initial dose – 3.125 mg, then 25 mg 3 times daily. Children with a body mass > 30 kg: initial dose – 6.25 mg, then 50 mg 3 times daily.			PL	Admissible: digitalis glycosides, diuretics and oral anticoagulants
SUPER-1	SIL at a dose of 20 mg 3 times daily	SIL at a dose of 40 mg 3 times daily	SIL at an initial dose of 40 mg 3 times daily, increased after 7 days to 80 mg 3 times daily.	PL	n.d.

The studies included in the analysis differed with regard to dosage of sildenafil. SIL at the dose registered in Poland, i.e. 20 mg three times daily, was assessed only in one group in the SUPER-1 trial. In the study of *Bharani 2003* all patients received the drug at a dose of 25 mg 3 times daily, while in the trials of *Sastry 2004* and *Singh 2006* the dose of sildenafil was adjusted to the patients' body mass and age: 25 mg 3 times daily for children with a body mass below 25 kg *(Sastry 2004)* or 30 kg *(Singh 2006),* 40 mg 3 times daily for patients with a body mass 26-50 kg *(Sastry 2004)* or over 30 kg *(Singh 2006)* and 100 mg 3 times daily in adult patients or those with a body mass at least 51 kg. In the SUPER-1 study three groups of patients were compared, receiving sildenafil at different doses: 20 mg, 40 mg and 80 mg three times daily; however, since the authors of the study noted no significant differences between the sildenafil groups, in further analysis results for all those therapeutic groups combined were presented.

In three studies *(Bharani 2003*, *Sastry 2004*, *Singh 2006)*, apart from the treatment investigated in the study, patients in both groups (experimental and control) underwent so-called conventional therapy. This treatment included drugs such as: anticoagulants, vasodilators, diuretics, digitalis glycosides and oxygen. In the study of *Bharani 2003* previously used vasodilators were discontinued for one week prior to randomization. The authors of the SUPER-1 study provided no information concerning additional treatment.

In three included studies *(Bharani 2003*, *Sastry 2004*, *Singh 2006)* cross-over design was adopted. In the studies of *Bharani 2003* and *Singh 2006* between the periods (of 2 and 6 weeks, respectively) of treatment with SIL or PL a wash-out period of 2 weeks was introduced. No such information was provided for the *Sastry 2004* trial.

3.4.4. Analysis of efficacy

3.4.4.1. Mortality

Deaths were reported in the studies of *Bharani 2003*, *Sastry 2004* and SUPER-1. The observation period in this regard was 2 weeks in the *Bharani 2003* study, 6 weeks in the *Sastry 2004* study and 12 weeks in the trial of SUPER-1.

Numbers and percentages of patients, in whom this endpoint occurred, are presented in the table below.

Table 87.
Numbers and percentages of patients who died; SIL vs. PL

Study	SIL			PL			Statistical significance of differences between the groups; SIL vs. PL
	N	n	Percen-tage	N	n	Percen-tage	
Bharani 2003	9	0	0%	9	0	0%	n.s.
Sastry 2004	22	0	0%	22	1	4.6%*	n.s.
SUPER-1	207*	3*	1.5%*	70	1	1.4%*	n.s.

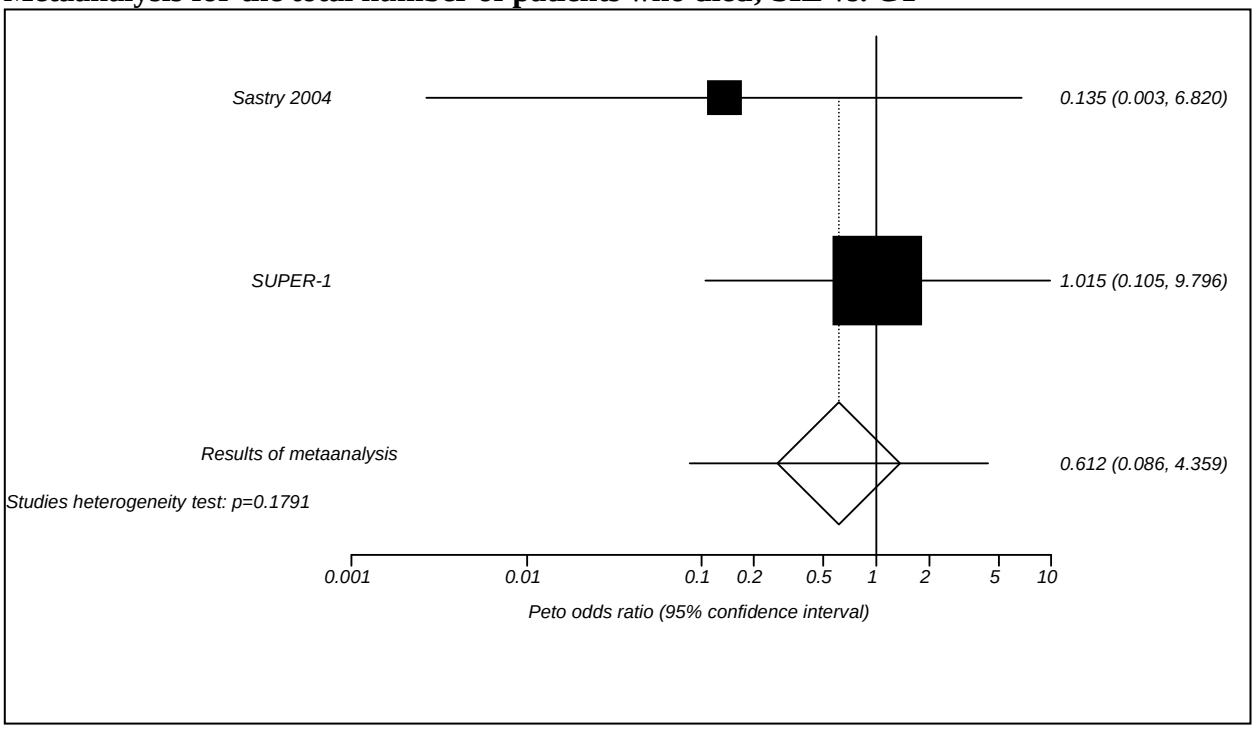
* Calculation based on available data

In the SUPER-1 study one patient assigned to the placebo group died due to right ventricular failure; the causes of death of the patients in the sildenafil group included: acute pulmonary embolism and urosepsis, myocardial infarction and pneumonia. The authors of the *Sastry 2004* study did not specify the cause of reported death of a patient in the placebo group.

In the study of *Bharani 2003* no deaths in the compared therapeutic groups were observed during an observation period of 2 weeks.

A metaanalysis for the total number of patients, who died during an observation period of 6-12 weeks, is presented below.

Figure 34.
Metaanalysis for the total number of patients who died; SIL vs. CT



The odds ratio calculated in the metaanalysis using the *Peto* method is 0.61 (95% CI: 0.09 to 4.36). It means that the odds of death for patients with PAH (primary or associated with other diseases) is lower in the sildenafil group and is 61% of this odds in the placebo group. However, the result is not statistically significant.

For patients with primary PAH the odds ratio calculated from the results of the *Sastry 2004* trial is 0.14 (95% CI: 0.00 to 6.82), the odds of death in the sildenafil group is therefore 14% of this odds in the placebo group. The result is not statistically significant.

3.4.4.2. Quality of life assessment using the Chronic Heart Failure Questionnaire

Quality of life was assessed only in one study included in the analysis: *Sastry 2004.* This endpoint was analyzed using the *Chronic Heart Failure Questionnaire* consisting of 16 questions, of which 5 are related to assessment of dyspnea, 4 – fatigue and 7 – emotional function. Each question was scored from 1 (the best result) to 7 (the worst result).

Mean baseline and final scores (after 6 weeks of observation) for specific aspects of quality of life reported in the sildenafil and placebo groups are presented in the table below.

Table 88.
Results of assessment of quality of life – *Chronic Heart Failure Questionnaire;* SIL vs. PL

Aspect	Intervention	N	Baseline value		Final value		Difference in mean values between the groups (95% CI); SIL vs. PL
			Mean	SD	Mean	SD	
Dyspnea	SIL	22	21.86	6.47	21.95	6.02	4.33* p = 0.009
	PL	22			17.62	5.68	
Fatigue	SIL	22	20.38	5.12	22.33	4.82	1.66 * p = 0.04
	PL	22			20.67	5.19	
Emotional function	SIL	22	34.14	10.38	37.33	9.32	2.62 * p = 0.06
	PL	22			34.71	10.91	

* Calculation based on available data

From the above data it may be concluded that after 6 weeks of treatment quality of life, with regard to dyspnea, fatigue and emotional function, is higher in the sildenafil group as compared to the placebo group by 4.33, 1.66 and 2.62 points, respectively. The difference in mean final values (calculated from data presented in the study) between the assessed therapeutic groups is 4.33 points for dyspnea, 1.66 points for fatigue and 2.62 points for emotional function. However, the result is statistically significant only for assessment of quality of life related to dyspnea and fatigue.

3.4.4.3. Increase of exercise capacity according to the NYHA/WHO classification (reclassification into a lower NYHA/WHO functional class)

Increase of exercise capacity according to the NYHA/WHO classification was assessed in three studies included in the analysis: *Bharani 2003*, *Singh 2006*, and SUPER-1. However, the studies differed as to methods of presentation of the results. The authors of the *Singh 2006* study presented mean value of the NYHA class after an observation period of 6 weeks, while in the studies of *Bharani 2003* and SUPER-1 the percentages of patients, in whom exercise capacity increased by at least one NYHA/WHO class after an observation period of 2 or 12 weeks, respectively, were reported.

Detailed results of the *Singh 2006* study are presented in the table below.

Table 89.
Mean exercise capacity according to the NYHA classification; SIL vs. PL

Study	Intervention	N	Baseline value		Final value		Difference in mean values between the groups (95% CI); SIL vs. PL
			Mean	SD	Mean	SD	
Singh 2006	SIL	20	2.65	0.59	1.55	0.51	-0.8 (-1.14 to -0.46) p = 0.0001
	PL	20			2.35	0.59	

The difference in mean values is -0.8 (95% CI: -1.14 to -0.46); p = 0.0001; exercise capacity is therefore higher by 0.8 NYHA class in the sildenafil group than in the placebo group and the result is statistically significant.

The table below presents the numbers and percentages of patients, whose exercise capacity increased by at least one NYHA/WHO functional class, reported by the authors of the *Bharani 2003* and SUPER-1 studies.

Table 90.
Numbers and percentages of patients, whose exercise capacity increased according to the NYHA/WHO classification; SIL vs. PL

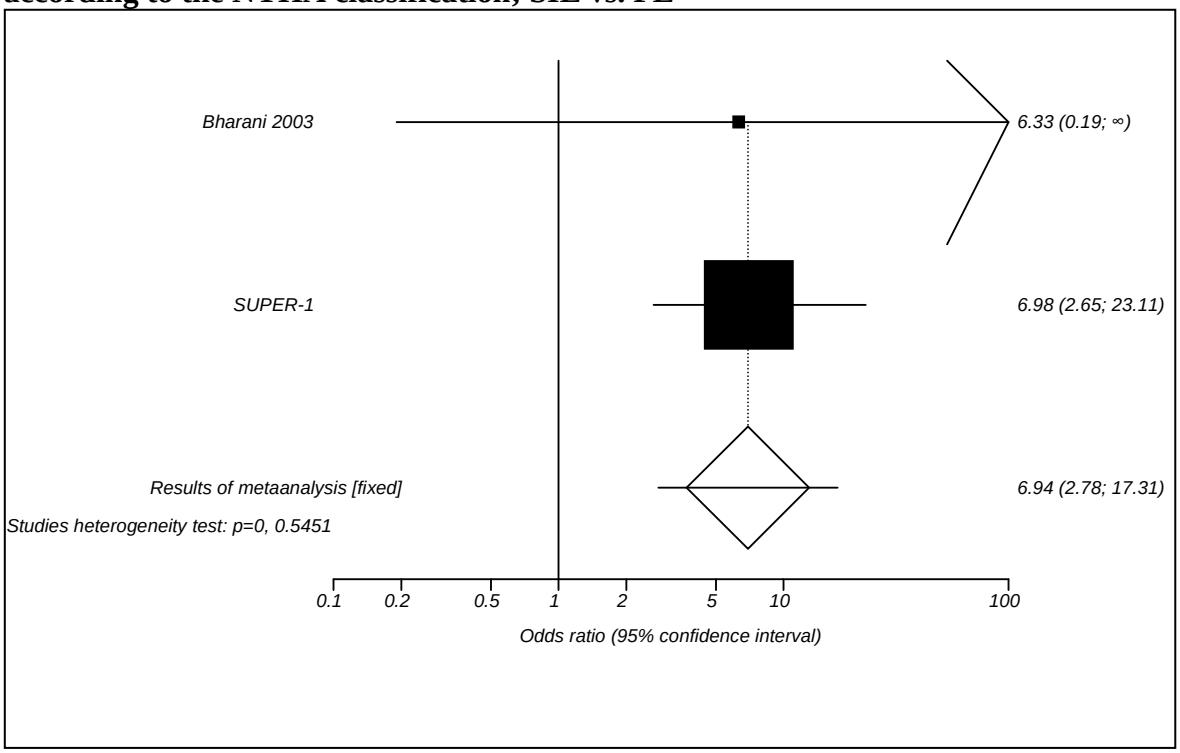
Study	SIL			PL			Statistical significance of differences between the groups; SIL vs. PL
	N	n	Percen-tage	N	n	Percen-tage	
Bharani 2003	9	2	22%*	9	0	0%	n.s.*
SUPER-1	204*†	72*	35%*	69	5*	7%	s.s.*

* Calculation based on available data
† The authors of the study presented data for 273 patients providing no information as to the numbers of patients in specific therapeutic groups; it was assumed that the patients who died were excluded from the analysis.

In the SUPER-1 study after an observation period of 12 weeks the percentage of patients, whose exercise capacity increased according to the WHO classification was significantly higher in the sildenafil group as compared to the placebo group. The authors of the *Bharani 2003* study reported increase of exercise capacity according to the NYHA classification in two patients in the sildenafil group.

A metaanalysis for the total number of patients, in whom this endpoint occurred during an observation period of 2-12 weeks, is presented in the figure below.

Figure 35.
Metaanalysis for the total number of patients with increase of exercise capacity according to the NYHA classification; SIL vs. PL



The odds ratio calculated in the metaanalysis is 6.94 (95% CI: 2.78 to 17.31). It means that the odds of reclassification into a lower NYHA/WHO functional class is nearly 7 times higher in the sildenafil group as compared to the placebo group. The result is statistically significant.

Additional EBM parameters were calculated for this endpoint: relative benefit (RB), relative benefit increase (RBI), absolute benefit increase (ABI) and the number of patients needed to treat in order to achieve one additional case of improved exercise capacity.

Table 91.
Increase of exercise capacity – additional EBM parameters; SIL vs. PL

RB (95% CI)	RBI (95% CI)	ABI (95% CI)	NNT (95% CI)
4.88 (2.13 to 11.18)	3.88 (1.13 to 10.18)	0.28 (0.19 to 0.36)	4 (3 to 6)

The relative benefit is 4.88 (95% CI: 2.13 to 11.18), which means that the probability of increase of exercise capacity by at least one NYHA/WHO functional class is 4.88 times higher in the sildenafil group than in the placebo group. The results are statistically significant. The relative benefit increase is 3.88 (95% CI: 1.13 to 10.18). The absolute benefit increase is 0.28 (95% CI: 0.19 to 0.36), which means that the probability of reclassification into a lower functional class is increased by 28 p.p. in the SIL group as compared to the PL group. In order to achieve one additional case of improvement in exercise capacity by at least one WHO functional class, sildenafil instead of placebo must be administered to 4 patients with PAH for a period of 2-12 weeks; NNT = 4 (95% CI: 3 to 6).

3.4.4.4. Results of the 6-minute walk test

Exercise capacity of the patients was assessed using the 6-minute walk test in the studies of *Bharani 2003*, *Singh 2006* and SUPER-1. The observation period varied between the studies and was 2 weeks in the *Bharani 2003* clinical trial, 6 weeks in the *Singh 2006* study and 12 weeks in the SUPER-1 study.

The table below presents mean baseline and final 6-minute walk distances reported by the authors of specific studies as well as change from baseline values in the sildenafil and placebo groups.

Table 92.
Results of the 6-minute walk test; SIL vs. PL

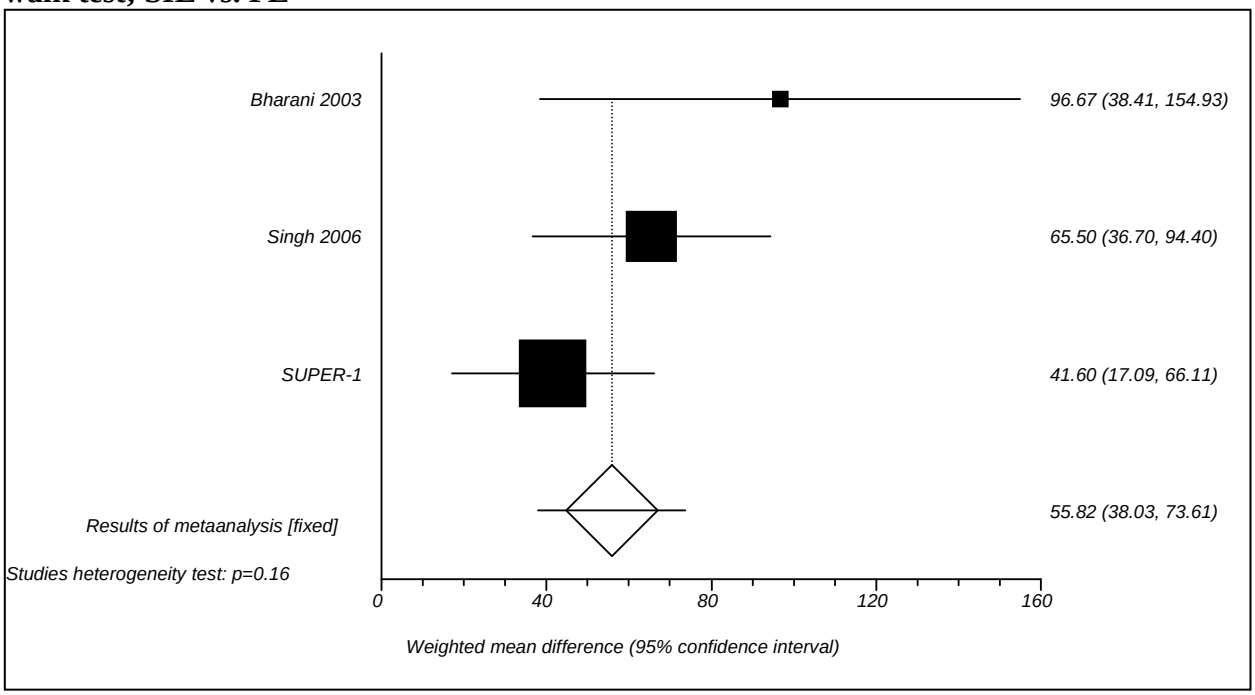
Study	Intervention	N	Baseline distance [m]		Final distance [m]		Change from baseline [m]		Mean difference in change between the groups (95% CI); SIL vs. PL
			Mean	SD	Mean	SD	Mean	SD	
Bharani 2003	SIL	9	163.89	110.73	266.67	131.45	102.78	31.11*	96.67 (38.41 to 154.93)* p < 0.005
	PL	9			170.0	105.0	6.11	20.01*	
Singh 2006	SIL	20	262	99	358.9	96.5	96.9	50.5	65.5 (36.7 to 94.4) p = 0.0001
	PL	20			293.4	89.4	31.4	41.1	
SUPER-1	SIL	207	344*	nd	nd	nd	nd	nd	41.6 (17.09 to 66.11)* p < 0.001
	PL	70	344	79	nd	nd	nd	nd	

* Calculation based on available data

In all clinical trials, in which this endpoint was assessed, increase of exercise capacity evaluated using the 6-minute walk test was statistically significantly higher in the sildenafil group as compared to the placebo group.

The figure below presents weighted mean difference in change of exercise capacity (evaluated using the 6-minute walk test) between the sildenafil and placebo groups in an observation period of 2-12 weeks.

Figure 36.
Weighted mean difference in change of exercise capacity evaluated using the 6-minute walk test; SIL vs. PL



Weighted mean difference in change of exercise capacity (evaluated using the 6-minute walk test) between the assessed groups was 55.82 m (95% CI: 38.03 to 73.61; $p < 0.0001$). It means that increase of exercise capacity is higher by 55.82 m in the sildenafil group as compared to the placebo group. The result is statistically significant.

3.4.4.5. Results of the treadmill test

In the studies of *Sastry 2004* and *Singh 2006* the time a patient was able to walk continuously on a treadmill was used as a measure of exercise capacity. The observation period in both clinical trials was 6 weeks.

Mean results of the treadmill test at baseline and after 6 weeks of treatment with sildenafil or placebo are presented below.

Table 93.
Results of the treadmill test; SIL vs. PL

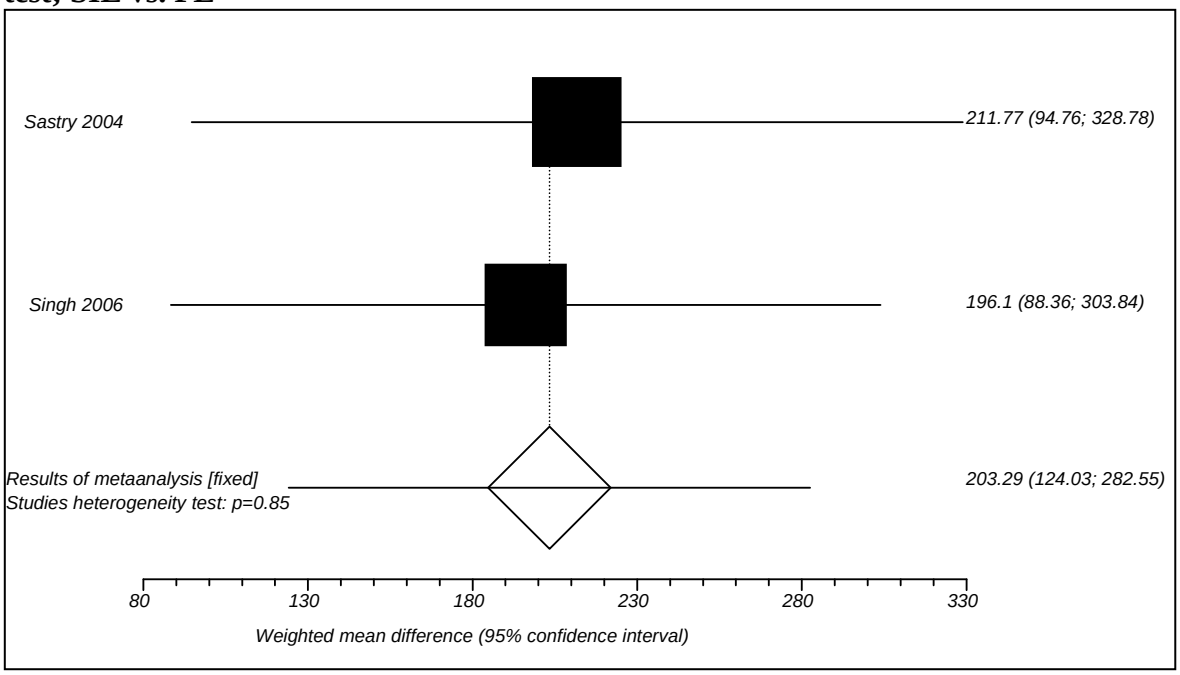
Study	Intervention	N	Baseline value [s]		Final value [s]		Mean difference between the groups (95% CI); SIL vs. PL
			Mean	SD	Mean	SD	
Sastry 2004	SIL	22	440.09	172.17	686.82	224.02	211.77* p < 0.0001
	PL	22			475.05	168.02	
Singh 2006	SIL	20	384.9	43.6	612.2	156.5*	196.1 p ≤ 0.001
	PL	20			416.1	189.6*	

* Calculation based on available data

In both studies after 6 weeks of treatment exercise capacity of the patients evaluated using the treadmill test was statistically significantly higher in the sildenafil group as compared to the placebo group.

The figure below presents weighted mean difference in change of exercise capacity (evaluated using the treadmill test) between the therapeutic groups in an observation period of 6 weeks.

Figure 37.
Weighted mean difference in change of exercise capacity evaluated using the treadmill test; SIL vs. PL



Weighted mean difference in final values of time of treadmill exercise between the sildenafil group an the placebo group is 203.29 s (95% CI: 124.03 to 282.55); $p < 0.0001$; exercise capacity after 6 weeks of treatment is therefore higher by 203.29 seconds in the sildenafil group than in the placebo group. The result is statistically significant.

3.4.4.6. Borg Dyspnea Score

In two clinical studies: *Bharani 2003* and SUPER-1 severity of dyspnea was assessed using the 11-point Borg Dyspnea Score, in which 0 represents no dyspnea and 10 – its highest severity. The observation period was 2 weeks in the *Bharani 2003* study and 12 weeks in the SUPER-1 trial.

Detailed results of both studies are presented in the table below.

Table 94.
Borg Dyspnea Score; SIL vs. PL

Study	Intervention	N	Baseline value		Final value		Change from baseline		Mean difference in change between the groups; SIL vs. PL
			Mean	SD	Mean	SD	Mean	SD	
Bharani 2003	SIL	9	5.22	1.64	3.56	1.01	-1.67	0.07*	-1.23* $p < 0.01$
	PL	9			5.11	1.45	-0.44	0.6*	
SUPER-1	SIL	207	nd	nd	nd	nd	nd	nd	-0.68* † n.s.
	PL	70	nd	nd	nd	nd	nd	nd	

* Calculation based on available data
† Difference in median values between the groups

In the *Bharani 2003* study mean difference in change between the groups was -1.23 points; reduction of severity of dyspnea assessed by the Borg Dyspnea Score was therefore higher by 1.23 points in the sildenafil group than in the placebo group and the result was statistically significant ($p < 0.01$).

The authors of the SUPER-1 study reported no statistically significant differences between the therapeutic groups with regard to this endpoint. Reduction of median Borg Dyspnea Score was higher in the sildenafil groups (20 mg and 80 mg) as compared to the placebo group and was -1 point (95% CI: -1 to 0) and -1 point (95% CI: -1.5 to 0), respectively. Reduction of the score in the sildenafil 40 mg group was the same as reduction in the placebo group: 0 points (95% CI: -1 to 0).

The difference in median values (calculated from the data reported in the SUPER-1 study) for the three sildenafil groups combined as compared to the placebo group is -0.68 points. It means that reduction of severity of dyspnea is higher by 0.68 points in the SIL group as compared to the placebo group. However, the result is not statistically significant.

3.4.4.7. Clinical worsening

This endpoint was assessed only in one clinical study included in the analysis: SUPER-1. Clinical worsening was defined as death, necessity of pulmonary transplantation, necessity of hospitalization due to pulmonary hypertension or introduction of additional treatment with intravenous epoprostenol or oral bosentan. The observation period in the SUPER-1 trial was 12 weeks.

The table below presents the numbers and percentages of patients, whose general condition worsened, and patients, for whom hospitalization or additional treatment with epoprostenol or bosentan was necessary.

Table 95.
Numbers and percentages of patients, whose general condition worsened; SIL vs. PL

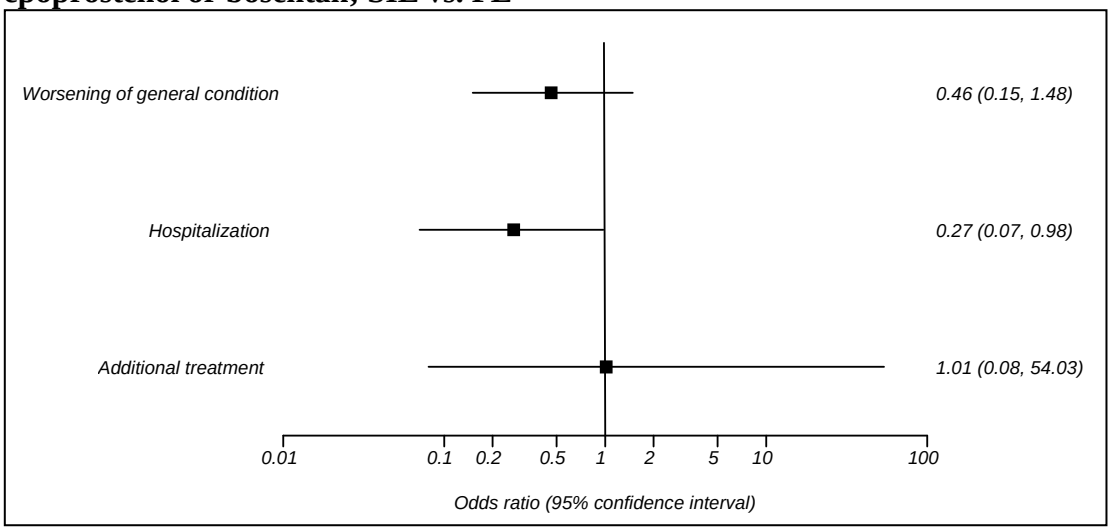
Parameter	SIL			PL			Statistical significance of differences between the groups; SIL vs. PL
	N	n	Percen-tage	N	n	Percen-tage	
Clinical worsening	207*	10*	5%*	70	7	10%	n.s.
Hospitalization	207*	6*	3%*	70	7	10%	p = 0.02
Additional treatment with epoprostenol or bosentan	207*	3*	1.5%*	70	1	1.4%*	n.s.

* Calculation based on available data

In the SUPER-1 study the percentage of patients hospitalized during an observation period of 12 weeks was significantly lower in the sildenafil group as compared to the placebo group, while no statistically significant differences between the groups were observed with regard to frequency of clinical worsening or necessity of additional treatment with epoprostenol or bosentan.

The odds ratios (calculated from data reported in the SUPER-1 study) for clinical worsening, necessity of hospitalization or introduction of additional treatment with epoprostenol or bosentan in an observation period of 12 weeks are presented below.

Figure 38.
Odds ratios for clinical worsening, hospitalization and additional treatment with epoprostenol or bosentan; SIL vs. PL



The odds ratio for clinical worsening is 0.46 (95% CI: 0.15 to 1.48), which means that the odds of occurrence of this endpoint is lower in the sildenafil group and is 46% of this odds in the placebo group. The result is not statistically significant.

The odds of necessity of additional treatment with epoprostenol or bosentan in the SIL group is 101% of this odds in the placebo group. The odds ratio is 1.01 (95% CI: 0.08 to 54.03) and the result is not statistically significant.

The odds ratio for necessity of hospitalization is 0.27 (95% CI: 0.07 to 0.98); the odds of occurrence of this endpoint is therefore lower in the sildenafil group and is 27% of this odds in the placebo group. The result reached statistical significance.

Additional EBM parameters calculated for necessity of hospitalization are presented below: relative risk (RR), relative risk reduction (RRR), absolute risk reduction (ARR) and the NNT.

Table 96.
Necessity of hospitalization – additional EBM parameters; SIL vs. PL

RR (95% CI)	RRR (95% CI)	ARR (95% CI)	NNT (95% CI)
0.29 (0.11 to 0.80)	0.71 (0.20 to 0.89)	0.07 (0.01 to 0.17)	15 (7 to 86)

The relative risk is 0.29 (95% CI: 0.11 to 0.80), which means that the risk of necessity of hospitalization is lower in the sildenafil group and is 29% of this risk in the placebo group; the result is statistically significant. The relative risk reduction is 0.71 (95% CI: 0.20 to 0.89). The absolute risk reduction is 0.07 (95% CI: 0.01 to 0.17), which means that the risk of occurrence of this endpoint in the SIL group as compared to the PL group is lower by 7 percentage points. Sildenafil instead of placebo must be administered to 15 patients for 12 weeks in order to avoid one additional hospitalization due to pulmonary arterial hypertension; NNT = 15 (95% CI: 7 to 86).

3.4.4.8. Hemodynamic parameters

3.4.4.8.1. Mean pulmonary artery pressure

Mean pulmonary artery pressure was assessed in all studies included in the analysis. The observation period varied between the clinical trials and was 2 weeks in the *Bharani 2003* study, 6 weeks in the trials of *Sastry 2004* and *Singh 2006* and 12 weeks in the SUPER-1 study.

Detailed results of specific studies are presented in the table below.

Table 97.
Mean pulmonary artery pressure; SIL vs. PL

Study	Intervention	N	Baseline value [mmHg]		Final value [mmHg]		Change from baseline [mmHg]		Mean difference in change between the groups (95% CI); SIL vs. PL
			Mean	SD	Mean	SD	Mean	SD	
Bharani 2003	SIL	9	80.78	21.30	55.33	16.52	-25.44	23.16*	-20.00* (nd) p < 0.005
	PL	9			75.33	19.75	-5.44	3.93*	
Sastry 2004	SIL	22	107.36	24.98	98.50	24.38	-8.86*	16.61*	-6.73* (nd) p = 0.09
	PL	22			105.23	17.82	-2.13*	11.59*	
Singh 2006	SIL	20	98.8	20.5	78.3	15.3	-20.6	13.0*	-16.6 (-22.4 to -10.9) p = 0.0001
	PL	20			94.8	16.5	-3.9	8.9*	
SUPER-1	SIL	193*	51.7*	nd	nd	nd	-3.14*	8.03*	-3.74* (nd) p < 0,05
	PL	65	56	16	nd	nd	0.6	5.76*	

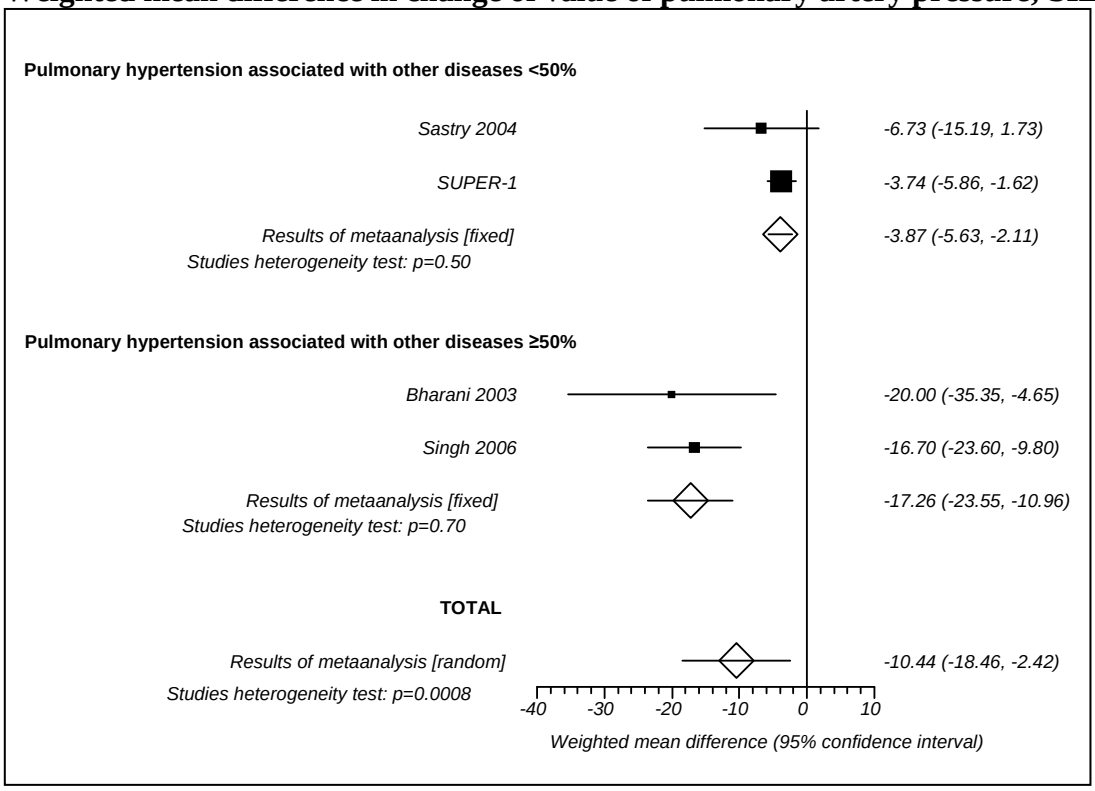
* Calculation based on available data

From the above data it may be concluded that in all clinical trials reduction of mean pulmonary artery pressure was higher in the sildenafil group as compared to the placebo group. In three studies *(Bharani 2003, Singh 2006, SUPER-1)* the result was statistically significant. The exception was the *Sastry 2004* study, in which the result did not reach statistical significance (p = 0.09).

In the studies of *Sastry 2004* and SUPER-1, in which most patients (≥ 50%) suffered from primary PAH, mean differences in change of pulmonary artery pressure were slightly lower than the respective mean values reported in those clinical trials *(Bharani 2003, Singh 2006),* in which patients with PAH associated with other diseases constituted the majority.

As a part of sensitivity analysis the results were metaanalyzed separately for subgroups created with respect to the percentage of patients with primary PAH or PAH associated with other diseases as well as for all studies, regardless of the type of PAH. The results of those metaanalyses are presented in the figure below.

Figure 39.
Weighted mean difference in change of value of pulmonary artery pressure; SIL vs. PL



Weighted mean difference calculated from the results of studies, in which patients with primary PAH constituted the majority, is -3.87 mmHg (95% CI: -5.63 to -2.11); $p < 0.0001$. It means that reduction of mean pulmonary artery pressure is higher by 3.87 mmHg in the sildenafil group as compared to the placebo group. The result is statistically significant.

Weighted mean difference calculated for the population, in which most patients were those with PAH associated with other diseases, is -17.26 mmHg (95% CI: -23.55 to -10.96) in favor of the sildenafil group; $p < 0.0001$. The results of above post-hoc subgroup analysis need to be interpreted cautiously.

Due to positive result of the studies' heterogeneity test ($p = 0.0008$) the metaanalysis for the whole population of patients was performed using a random effect model. Weighted mean difference in change of this parameter between the therapeutic groups is -10.44 mmHg (95% CI: -18.46 to -2.42); reduction of mean pulmonary artery pressure is therefore higher by 10.44 mmHg in the sildenafil group as compared to the placebo group. The result is statistically significant.

3.4.4.8.2. Pulmonary vascular resistance

Pulmonary vascular resistance was assessed only in one study included in the analysis: SUPER-1. The observation period in this trial was 12 weeks.

Mean baseline values and mean values of change from baseline after 12 weeks of observation for patients in the sildenafil and placebo groups are presented in the table below.

Table 98.
Mean pulmonary vascular resistance; SIL vs. PL

Study	Intervention	N	Baseline value [dyn x s/cm^5]		Change from baseline [dyn x s/cm^5]		Mean difference in change between the groups (95% CI);
			Mean	SD	Mean	SD	
SUPER-1	SIL	193*	925.14*	nd	-175.67*	377.86*	-224.67 (-334.4 to -114.94)*
	PL	65	1051	512	49	425.74*	

* Calculation based on available data

Mean difference in change of pulmonary vascular resistance between the therapeutic groups as calculated from the results presented by the authors of the SUPER-1 study is -224.67 dyn x s/cm^5 (95% CI: -334.4 to -114.94); reduction of this parameter is therefore higher by 224.67 dyn x s/cm^5 in the sildenafil group (doses of 20, 40 and 80 mg combined) as compared to the placebo group. The result is statistically significant.

3.4.4.8.3. Cardiac index

This parameter was evaluated in two clinical studies: *Sastry 2004* and SUPER-1. The observation period was 6-12 weeks.

Detailed results of both studies are presented in the table below.

Table 99.
Mean values of cardiac index; SIL vs. PL

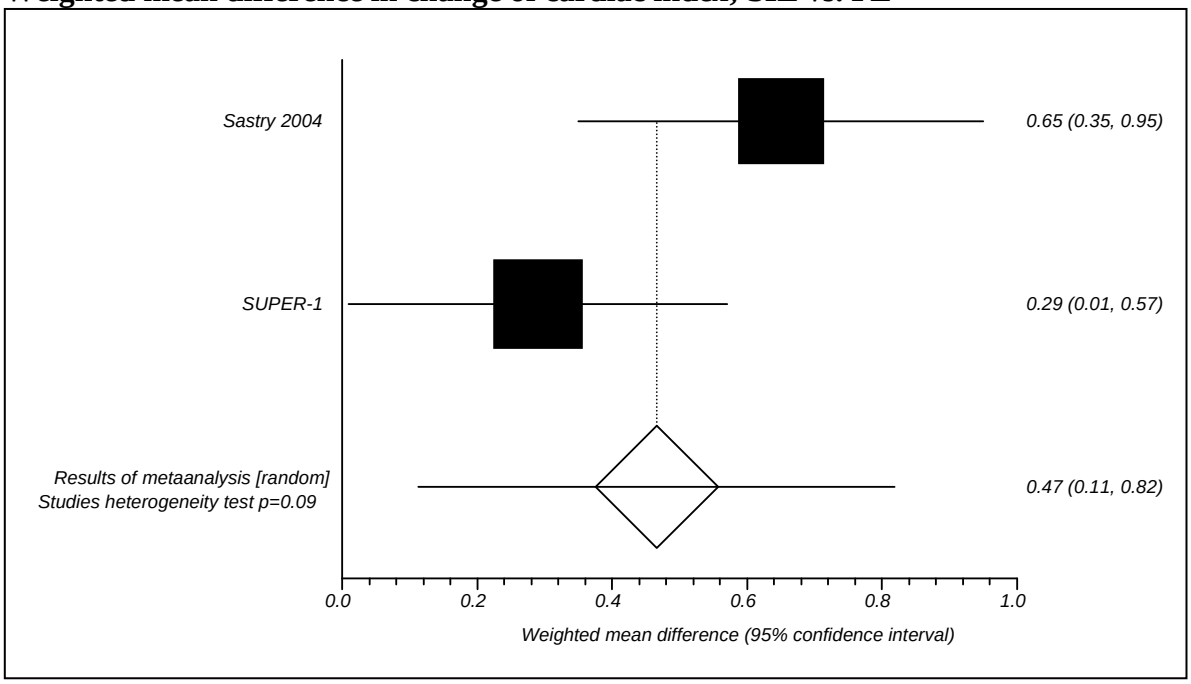
Study	Intervention	N	Baseline value [l/min/m^2]		Final value [l/min/m^2]		Change from baseline [l/min/m^2]		Mean difference in change between the groups (95% CI); SIL vs. PL
			Mean	SD	Mean	SD	Mean	SD	
Sastry 2004	SIL	22	2.83	1.06	3.45	1.16	0.62	nd	0.65 (0.35 to 0.95)* p < 0.0001
	PL	22			2.80	0.90	-0.03	nd	
SUPER-1	SIL	193*	2.4*	nd	nd	nd	0.27*	1.09*	0.29 (0.01 to 0.57)*
	PL	65	2.2	0.6	nd	nd	-0.02	0.62*	

* Calculation based on available data

In both assessed clinical studies increase of cardiac index was statistically significantly higher in the sildenafil group as compared to the placebo group.

Weighted mean difference in change of this parameter for an observation period of 6-12 weeks is presented below.

Figure 40.
Weighted mean difference in change of cardiac index; SIL vs. PL



Weighted mean difference in change of cardiac index value between the groups is 0.47 l/min/m^2 (95% CI: 0.11 to 0.82), p = 0.0096; increase of this parameter is therefore higher by 0.47 l/min/m^2 in the sildenafil group as compared to the placebo group; the result is statistically significant.

3.4.5. Assessment of safety

3.4.5.1. Adverse events

Incidence of adverse events was assessed in all clinical trials included in the analysis; however, detailed numbers or percentages of patients, in whom specific adverse events were observed, were presented only in the studies of *Sastry 2004* and SUPER-1.

The authors of the *Bharani 2003* and *Singh 2006* studies stated only that in an observation period of 2 and 6 weeks, respectively, sildenafil was well tolerated and neither serious adverse events nor effects of the drug on sexual function or libido in male participants were observed.

Numbers and percentages of patients participating in the *Sastry 2004* and SUPER-1 studies, in whom specific adverse events were observed, are presented in the table below.

Table 100.
Numbers and percentages of patients, in whom specific adverse events were observed; SIL vs. PL

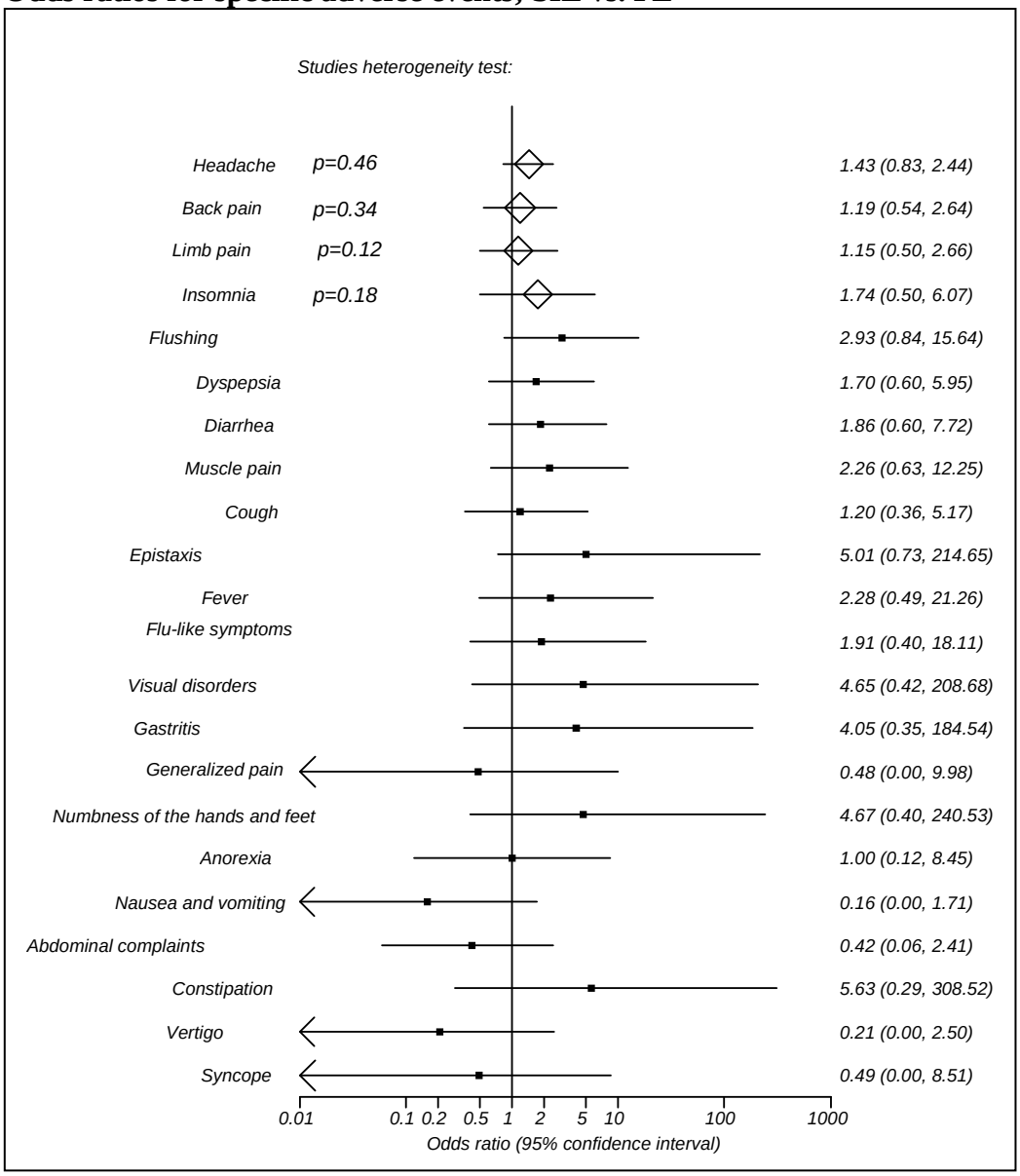
Adverse event	Study	SIL			PL			Statistical significance of differences between the groups; SIL vs. PL
		N	n	Percen-tage	N	n	Percen-tage	
Headache	***Sastry 2004***	22	3	14%*	22	1	5%*	n.s.*
	SUPER-1	207*	95*	46%*	70	27	39%	n.s.*
Back pain	***Sastry 2004***	22	3	14%*	22	1	5%*	n.s.*
	SUPER-1	207*	24*	12%*	70	8	11%	n.s.*
Limb pain	***Sastry 2004***	22	3	14%*	22	6	27%*	n.s.*
	SUPER-1	207*	21*	10%*	70	4	6%	n.s.*
Insomnia	***Sastry 2004***	22	2	9%*	22	3	14%*	n.s.*
	SUPER-1	207*	11*	5%*	70	1	1%	n.s.*
Flushing	**SUPER-1**	207*	24*	12%*	70	3	4%*	n.s.*
Dyspepsia	**SUPER-1**	207*	24*	12%*	70	5	7%	n.s.*
Diarrhea	**SUPER-1**	207*	21*	10%*	70	4	6%	n.s.*
Muscle pain	**SUPER-1**	207*	19*	9%*	70	3	4%	n.s.*
Cough	**SUPER-1**	207*	14*	7%*	70	4	6%	n.s.*
Epistaxis	**SUPER-1**	207*	14*	7%*	70	1	1%	n.s.*
Fever	**SUPER-1**	207*	13*	6%*	70	2	3%	n.s.*
Flu-like symptoms	**SUPER-1**	207*	11*	5%*	70	2	3%	n.s.*
Visual disorders	**SUPER-1**	207*	8*	4%*	70	0	0%	n.s.*
Gastritis	**SUPER-1**	207*	7*	3%*	70	0	0%	n.s.*
Generalized pain	**Sastry 2004**	22	1	5%*	22	2	9%*	n.s.*
Numbness of the hands and feet	**Sastry 2004**	22	4	18%*	22	1	5%*	n.s.*
Anorexia	**Sastry 2004**	22	3	14%*	22	3	14%*	n.s.*
Nausea and vomiting	**Sastry 2004**	22	1	5%*	22	5	23%*	n.s.*
Abdominal complaints	**Sastry 2004**	22	3	14%*	22	6	27%*	n.s.*
Constipation	**Sastry 2004**	22	3	14%*	22	0	0%	n.s.*
Vertigo	**Sastry 2004**	22	1	5%*	22	4	18%*	n.s.*
Syncope	**Sastry 2004**	22	0	0%	22	1	5%*	n.s.*

* Calculation based on available data

No statistically significant differences between the sildenafil group and the placebo group with regard to incidence of any of the assessed adverse events were found in any of the studies.

The figure below presents the odds ratios for specific adverse events. This parameter was calculated in a metaanalysis for the total number of patients in the *Sastry 2004* and SUPER-1 studies for the following adverse events: headache, back pain, limb pain and insomnia. For the remaining adverse events the odds ratios calculated from the results of single clinical trials are presented.

Figure 41.
Odds ratios for specific adverse events; SIL vs. PL



The odds ratios for occurrence of headache, back pain, limb pain and insomnia as calculated in the metaanalyses are: 1.43 (95% CI: 0.83 to 2.44), p = 0.25; 1.19 (95% CI: 0.54 to 2.64), p = 0.82; 1.15 (95% CI: 0.50 to 2.66), p = 0.90 and 1.74 (95% CI: 0.50 to 6.07), p = 0.57, respectively. It means that the odds of occurrence of these adverse events in the sildenafil group is 143%, 119%, 115% and 174% of the respective odds in the placebo group. However, none of the results reached statistical significance.

For generalized pain, nausea and vomiting, abdominal complaints, vertigo and syncope the odds of occurrence of these adverse events was lower in the sildenafil group as compared with the placebo group. The oddss of occurrence for the remaining adverse events (flushing,

dyspepsia, diarrhea, muscle pain, cough, epistaxis, fever, flu-like symptoms, visual disorders, gastritis, numbness of hands and feet and constipation) were higher in the sildenafil group than the respective oddss in the placebo group. However, the differences between the groups are not statistically significant.

3.4.5.2. Withdrawal from the study

This endpoint was evaluated only in two clinical studies included in the analysis: *Sastry 2004* with an observation period of 6 weeks and SUPER-1 with an observation period of 12 weeks.

In the *Sastry 2004* study it was reported that none of the patients discontinued treatment due to adverse events, while from the SUPER-1 trial eight patients were withdrawn: 2 patients due to violation of the study protocol, 2 patients due to withdrawal of the consent for participation in the trial and 4 patients due to adverse events (renal dysfunction, leg edema, cardiac arrhythmia and headache). However, the authors did not present the percentages of patients, in whom these adverse events were observed, with regard to the compared therapeutic groups.

3.5. Sildenafil vs. placebo – children

3.5.1. Results of search for the studies

Two primary randomized, double-blind clinical studies, in which sildenafil was compared to placebo in newborns and children with pulmonary arterial hypertension, were identified during the search of medical databases: *Baquero 2006* and *Namachivayam 2006*. Both clinical trials were performed in single treatment centers.

Publications related to the studies included in the analysis, duration of the observation period and the *Jadad* scores for specific studies are presented in the table below.

Table 101.
Characteristics of the clinical trials included in the analysis; SIL vs. PL

Study	Publications	Observation period	*Jadad* score
Baquero 2006	*Baquero 2006*	42 hours	5
Namachivayam 2006	*Namachivayam 2006*	4 hours	4

The observation period was 4 hours in the *Namachivayam 2006* study and 42 hours in the *Baquero 2006* trial.

In the 5-point *Jadad* scale the study of *Baquero 2006* scored 5 points and the *Namachivayam 2006* trial – 4 points.

3.5.2. Population

In both clinical studies patients with pulmonary hypertension were enrolled. The *Baquero 2006* study concerned newborns aged less than 3 days and fetuses with persistent pulmonary

hypertension, above 35.5 weeks of gestation. The inclusion criteria included severe, refractory hypoxemia and pulmonary hypertension as evaluated by echocardiography, necessity of mechanical ventilation and oxygen index ≥ 40, high risk of death, left-to-right shunt confirmed by echocardiography and pulmonary artery pressure at least 40 mmHg. The patients with congenital heart diseases, such as: pulmonary artery stenosis, atrial or ventricular septal defect or anomalous pulmonary venous drainage, were excluded from the study.

In the study of *Namachivayam 2006* newborns or children with pulmonary hypertension participated, to whom inhaled nitrogen oxide was administered at a dose of at least 10 ppm for at least 12 hours and in whom mechanical ventilation was necessary. Among the exclusion criteria the authors listed previous unsuccessful attempt to discontinue treatment with nitrogen oxide, use of intravenous vasodilators (nitrates), hepatocellular damage, oxygen fraction in the inhaled air above 0.6, congenital heart diseases with anomalous pulmonary or systemic venous drainage and impossibility of measurement of pulmonary artery pressure or the right ventricle.

Table 102.
Baseline characteristics of the patients enrolled in particular studies; SIL vs. PL

Study	Number of patients		Mean age (SD) [weeks]		Mean body mass (SD) [kg]		Percentage of the newborns with congenital heart diseases	
	SIL	PL	SIL	PL	SIL	PL	SIL	PL
Baquero 2006	7	6	38.4 (2.6) ‡‡	37.2 (1.9) ‡‡	2.8 (0.6)	2.7 (0.6)	0%	0%
Namachivayam 2006	15	14	24.4 * ‡	14.6 * ‡	4.6‡	4.0‡	86.7%*	71.4%*
Total	**22**	**20**						

* calculation based on available data
‡ median (interquartile range)
‡‡ pertains to gestational age

The analysis included 42 fetuses or newborns; 22 patients were assigned to the sildenafil group and 20 – to the placebo group. Characteristics of patients enrolled in the studies differed with regard to mean age and body mass. In the study of *Baquero 2006* mean age of the fetuses or newborns was 38 and 37 weeks, while for the *Namachivayam 2006* trial children aged 24 and 15 weeks were qualified, in the SIL and PL groups, respectively. In the *Baquero 2006* trial mean body mass in the sildenafil and placebo groups was 2.8 and 2.7 kg, respectively, while median body mass in the *Namachivayam 2006* study was 4.6 and 4.0 kg, respectively. In most newborns enrolled in the *Namachivayam 2006* study a congenital heart disease was diagnosed, while children with pulmonary hypertension associated with a disease of that type were excluded from the *Baquero 2006* trial

3.5.3. Intervention

Patients enrolled in the *Baquero 2006* and *Namachivayam 2006* clinical trials were randomly assigned to the sildenafil (SIL) group or the placebo (PL) group.

Detailed dosage is presented in the table below.

Table 103.
Description of the interventions; SIL vs. PL

Study	SIL	PL
Baquero 2006	Sildenafil at an initial dose of 1 mg/kg (0.5 ml/kg), administered not later than 30 minutes after randomization, and then every 6 hours. The dose was doubled (2.0 mg/kg or 1/0 ml/kg) if oxygen index did not improve and arterial blood pressure remained stable after administration of the previous dose.	Placebo – solvent 0.5-1 ml/kg.
Namachivayam 2006	Sildenafil at a dose of 0.4 mg/kg (range: 0.3-0.5 mg/kg) administered an hour before discontinuation of NO.	Placebo administered an hour before discontinuation of NO.

Sildenafil was administered at a dose of 1 mg/kg in the *Baquero 2006* study and 0.4 mg/kg in the trial of *Namachivayam 2006*. In the study of *Baquero 2006* the drug at a concentration of 2 mg/ml was prepared by dissolution of a 50 mg tablet in 25 ml of the Orabase solvent and administered by an oropharyngeal tube. If oxygen index did not improve and arterial blood pressure remained stable after administration of the previous dose, the dose of sildenafil was increased to 2 mg/kg. In the *Namachivayam 2006* trial the drugs were administered by a nasogastric tube.

In the clinical trial of *Baquero 2006* the treatment was discontinued if oxygen index decreased below 20 or after eight doses of sildenafil or placebo were administered.

In the *Namachivayam 2006* study all patients were treated with NO at a dose of at least 20 ppm for at least 12 hours prior to enrollment. The dose of NO was reduced by 1 ppm every 30 min. Treatment with sildenafil or placebo was introduced when the dose of NO was reduced to 2 ppm, i.e. one hour before discontinuation.

3.5.4. Analysis of efficacy

3.5.4.1. Mortality

In both clinical studies included in the analysis mortality in newborns and children was evaluated. The observation period was 4 hours in the *Namachivayam 2006* study and 42 hours in the *Baquero 2006* trial.

The numbers and percentages of patients, in whom this endpoint occurred, are presented in the table below.

Table 104.
Numbers and percentages of patients who died; SIL vs. PL

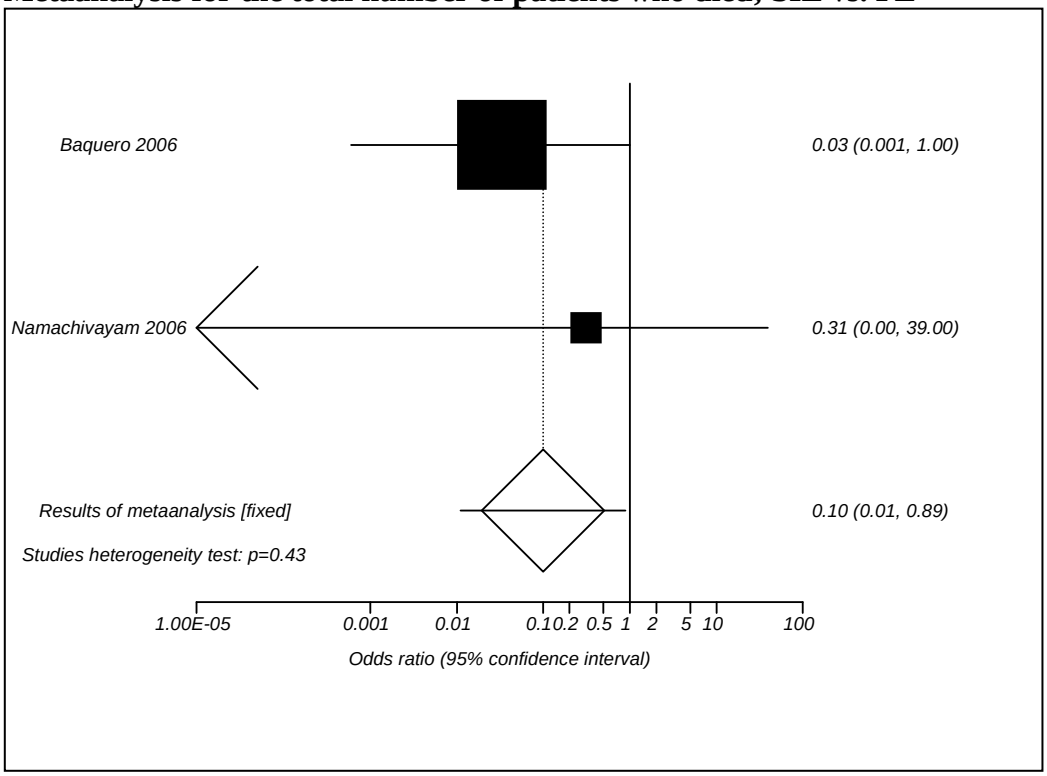
Study	SIL			PL			Statistical significance of differences between the groups; SIL vs. PL
	N	n	Percen-tage	N	n	Percen-tage	
Baquero 2006	7	1	14.3%*	6	5	83.3%*	p < 0.02
Namachivayam 2006	15	0	0%	15	1	6.7%*	n.s.

* Calculation based on available data

In the study of *Baquero 2006* the percentage of children who died during an observation period of 42 hours was statistically significantly lower in the sildenafil group than in the placebo group. In the *Namachivayam 2006* trial one patient assigned to the placebo group died during an observation period of 4 hours. The authors of the study stated that death occurred before nitric oxide was discontinued and the intervention introduced.

A metaanalysis for the total number of patients who died during an observation period of 4-42 hours is presented in the figure below.

Figure 42.
Metaanalysis for the total number of patients who died; SIL vs. PL



The odds ratio is 0.10 (95% CI: 0.01 to 0.89); p = 0.055; the odds of death is therefore lower in the sildenafil group and is 10% of this odds in the placebo group. The result is statistically significant.

Additional EBM parameters were calculated for this endpoint: relative risk (RR), relative risk reduction (RRR), absolute risk reduction (ARR) and the NNT.

Table 105.
Mortality – additional EBM parameters; SIL vs. PL

RR (95% CI)	RRR (95% CI)	ARR (95% CI)	NNT (95% CI)
0.21 (0.04 to 1.01)	0.79 (-0.01 to 0.96)	0.25 (0.08 to 0.43)	4 (3 to 13)

The relative risk is 0.21 (95% CI: 0.04 to 1.01), which means that the risk of death is lower in the sildenafil group and is 21% of this risk in the placebo group; the result is on the verge of statistical significance. The relative risk reduction is 0.79 (95% CI: -0.01 to 0.96). The absolute risk reduction is 0.25 (95% CI: 0.08 to 0.43), which means that the risk of occurrence of this endpoint in the SIL group as compared to the PL group is lower by 25 percentage points. Sildenafil instead of placebo must be administered to 4 patients for 4-42 hours in order to avoid one additional death due to pulmonary arterial hypertension; NNT = 4 (95% CI: 3 to 13).

3.5.4.2. Exacerbation of symptoms of PAH after discontinuation of treatment with nitric oxide

This endpoint was assessed only in the clinical trial of *Namachivayam 2006*, in which all patients were treated with NO at a dose of at least 20 ppm for at least 12 hours. The dose of NO was reduced by 1 ppm every 30 min. The observation period was 4 hours.

Numbers and percentages of patients, in whom exacerbation of symptoms of the disease was observed after discontinuation of treatment with NO, are presented in the table below.

Table 106.
Numbers and percentages of patients, in whom exacerbation of symptoms of the disease was observed after discontinuation of NO; SIL vs. PL

Study	SIL			PL			Statistical significance of differences between the groups; SIL vs. PL
	N	n	Percen-tage	N	n	Percen-tage	
Namachivayam 2006	15	0	0%	14	10	71.4%*	p < 0.001

* Calculation based on available data

In the study of *Namachivayam 2006* incidence of exacerbation of symptoms of PAH was statistically significantly lower in the sildenafil group as compared to the placebo group. The odds ratio calculated from the above data is 0.01 (95% CI: 0.00 to 0.15). It means that the odds of occurrence of this endpoint in the sildenafil group is 1% of this odds in the placebo group and the result is statistically significant.

Additional EBM parameters calculated for this endpoint are presented in the table below.

Table 107.
Exacerbation of symptoms of the disease after discontinuation of NO – additional EBM parameters; SIL vs. PL

RR (95% CI)	RRR (95% CI)	ARR (95% CI)	NNT (95% CI)
0.04 (0.01 to 0.35)	0.96 (0.65 to 0.99)	0.72 (0.45 to 0.88)	2 (2 to 3)

The relative risk is 0.04 (95% CI: 0.01 to 0.35), which means that the risk of exacerbation of symptoms of PAH in the sildenafil group is 4% of this risk in the placebo group and the result is statistically significant. The relative risk reduction is 0.96 (95% CI: 0.65 to 0.99). The absolute risk reduction is 0.72 (95% CI: 0.45 to 0.88), which means that the risk of occurrence of this endpoint in the SIL group as compared to the PL group decreased by 72 percentage points. Sildenafil instead of placebo must be administered to 2 patients for 4 hours in order to avoid one additional exacerbation of symptoms of the disease after discontinuation of NO; NNT = 2 (95% CI: 2 to 3).

3.5.4.3. Reintroduction of treatment with nitric oxide

In the study of *Namachivayam 2006*, in which all patients were treated with nitric oxide prior to enrollment, the possibility of complete discontinuation of such treatment after an observation period of 4 hours was evaluated. The indications for reintroduction of treatment with NO were: exacerbation of symptoms of pulmonary hypertension with values of pulmonary pressure reaching or exceeding those of systemic pressure, drastic desaturation or exacerbation of symptoms of pulmonary hypertension with arterial hypotension.

Numbers and percentages of patients, in whom treatment with nitric oxide was reintroduced in an observation period of 4 hours, are presented in the table below.

Table 108.
Numbers and percentages of patients, in whom treatment with NO was reintroduced; SIL vs. PL

Study	SIL			PL			Statistical significance of differences between the groups; SIL vs. PL
	N	n	Percen-tage	N	n	Percen-tage	
Namachivayam 2006	15	0	0%	14	4	26.7%*	p = 0.042

* Calculation based on available data

Attempts to discontinue treatment with NO were successful in all patients in the sildenafil group. This treatment could not be discontinued in 4 patients in the placebo group. In one patient exacerbation of symptoms was observed as soon as the NO dose was reduced to 1 ppm, in two patients after 10 minutes and in 2 patients treatment with NO was reintroduced within 2 hours from discontinuation.

The odds ratio calculated from the above data is 0.07 (95% CI: 0 to 0.85), which means that the odds of reintroduction of treatment with NO is lower in the sildenafil group and is 7% of this odds in the placebo group; the result is statistically significant.

Additional EBM parameters calculated for this endpoint are presented below.

Table 109.
Reintroduction of treatment with NO – additional EBM parameters; SIL vs. PL

RR (95% CI)	RRR (95% CI)	ARR (95% CI)	NNT (95% CI)
0.1 (0.01 to 0.93)	0.90 (0.07 to 0.99)	0.29 (0.05 to 0.55)	4 (2 to 22)

The relative risk is 0.1 (95% CI: 0.01 to 0.93), which means that the risk of necessity of reintroduction of treatment with NO in the sildenafil group is 1% of this risk in the placebo group and the result is statistically significant; NNT = 4 (95% CI: 2 to 22).

3.5.4.4. Mean pulmonary artery pressure

Mean pulmonary artery pressure was assessed only in one study included in the analysis: *Namachivayam 2006*. This hemodynamic parameter was assessed after 1 hour and again after

4 hours of observation of the newborns and children. Detailed results of specific studies are presented in the table below.

Table 110.
Mean pulmonary artery pressure; SIL vs. PL

Study	Observation period [h]**	Intervention	N	Baseline value [mmHg]		Final value [mmHg]		Change from baseline [mmHg]		Mean difference in change between the groups (95% CI); SIL vs. PL
				Mean	SD	Mean	SD	Mean	95% CI	
Namachivayam 2006	1	SIL	15	35.1	13.3	35.8	14.8	1.3	-9.1 to 5.3	-23.7* p < 0.001
		PL	14	31.0	9.0	45.2	20.4	25.0	14.2 to 66.7	
	4	SIL	15	35.1	13.3	33.8	11.8	-1.3*	nd	-6.9*
		PL	14	31.0	9.0	36.6	9.9	5.6*	nd	

* Calculation based on available data
** Time after discontinuation of treatment with NO

From the above data it may be concluded that increase of mean pulmonary artery pressure one hour after discontinuation of treatment with nitric oxide was lower by 23.7 mmHg in the sildenafil group as compared to the placebo group. The result was statistically significant.

Mean difference in change of this parameter after 4 hours of observation was -6.9 mmHg; the reduction was therefore higher by 6.9 mmHg in the sildenafil group as compared to the placebo group. The authors of the study provided no information concerning statistical significance of differences between the groups for that observation period.

3.5.4.5. Oxygen index

Reduction of value of oxygen index is related to improved oxygenation of arterial blood. In the study of *Baquero 2006* the assigned treatment was discontinued if oxygenation as evaluated by oxygen index improved.
Numbers and percentages of patients, in whom oxygen index was < 20 after administration of 6 or 7 doses of sildenafil or placebo, are presented in the table below.

Table 111.
Numbers and percentages of patients, in whom oxygen index decreased < 20; SIL vs. PL

Study	Number of doses	SIL			PL			Statistical significance of differences between the groups; SIL vs. PL
		N	n	Percentage	N	n	Percentage	
Baquero 2006	**6**	7	2	28.6%*	6	0	0%	n.s.*
	7	7	5	71.4%*	6	0	0%	s.s.*

* Calculation based on available data

The odds ratio for decrease of oxygen index below 20 after administration of 6 and 7 doses of the assigned drug as calculated from data presented in the *Baquero 2006* study is 6.11 (95% CI: 0.07 to 141.23) and 40.33 (95% CI: 2.1 to infinity), respectively; the odds of improved oxygenation in the sildenafil group as compared with the placebo group is therefore 6.11 and 40.33 times higher, respectively. The result is statistically significant only for 7 doses of the drug; NNT = 2 (95% CI: 2 to 3).

3.6. Treprostinil vs. placebo

3.6.1. Results of search for the studies

In searched medical databases two primary randomized clinical studies fulfilling the inclusion criteria were identified, in which treprostinil (TRE) used in combination with conventional treatment was compared to placebo (PL) with conventional treatment (CT): *Simonneau 2002* and *McLaughlin 2003*. It should be noted that the authors of the *McLaughlin 2003* study did not clearly specify whether conventional treatment was continued after enrollment. Both studies were double-blind.

In the study of *McLauglin 2003* 3 primary studies were presented; however, in this analysis only the results of the trial, in which treprostinil was compared to placebo, were taken into account.

Detailed characteristics of specific studies are presented in the table below.

Table 112.
Characteristics of the studies included in the analysis; TRE vs. PL

Study	Publications	Observation period	*Jadad* score
Simonneau 2002	*Simonneau 2002* *Oudiz 2004*	12 weeks	4
McLaughlin 2003	*McLaughlin 2003*	8 weeks	3

The observation period was 8 weeks in the *McLaughlin 2003* study and 12 weeks in the *Simonneau 2002* study. The studies included in the analysis scored 3 points *(McLaughlin 2003)* and 4 points *(Simonneau 2002)* in the *Jadad* scale, respectively.

3.6.2. Description of the population

In both analyzed studies patients with pulmonary arterial hypertension participated. In the study of *McLaughlin 2003* patients with primary PAH diagnosed according to the *National Institutes of Health* (NIH) criteria were enrolled. In the *Simonneau 2002* study patients with primary PAH, PAH associated with connective tissue diseases or PAH associated with congenital left-to-right shunt participated.

Patients qualified for the *McLaughlin 2003* study were in NYHA *(New York Heart Association)* functional class III-IV despite conventional treatment, while those participating in the *Simonneau 2002* trial – in NYHA functional class II, III or IV.

Moreover, the following parameters were listed among the inclusion criteria for both studies:

- 6-minute walk distance between 50 and 450 m;
- mean pulmonary artery pressure (mPAP) at least 25 mmHg;
- mean pulmonary capillary wedge pressure or end-systolic left ventricular pressure ≤ 15 mmHg;
- pulmonary vascular resistance > 3 Wood units (in the *McLaughlin 2003* study) or > 3 mmHg/l/min (in the *Simonneau 2002* study).

From the *Simonneau 2002* study those patients were excluded, in whom one of the following was documented:

- signs of thromboembolic disease as diagnosed by means of ventilation-perfusion scintigraphy or pulmonary angiography;
- severe interstitial lung disease diagnosed by means of functional tests and high resolution computed tomography;
- portopulmonary hypertension or pulmonary hypertension associated with HIV infection;
- uncontrolled sleep-apnea syndrome;
- history of a disease of the left heart;
- other diseases associated with pulmonary hypertension (e.g. sickle cell anemia);
- introduction of a new long-term treatment for pulmonary hypertension within the previous month;
- discontinuation of any treatment for pulmonary hypertension (excepting anticoagulants) in the previous week;
- use of prostaglandin derivatives within the previous 30 days.

Detailed baseline characteristics of the patients enrolled in specific clinical trials are presented in the table below.

Table 113.
Baseline characteristics of the patients enrolled in specific studies

Study	Number of patients		Mean age (SD) [years]		Percentage of men		Percentage of patients with primary/secondary PAH		Percentage of patients in NYHA functional class II/III/IV		Percentage of patients treated with oral vasodilators		Mean time from diagnosis (SD) [years]		Mean 6-minute walk distance (SD) [m]	
	TRE	PL	TRE	PL	TRE	PL	TRE	PL	TRE	PL	TRE	PL	TRE	PL	TRE	PL
Simonneau 2002	233	236	44.6 (16.3)*	44.4 (13.8)*	16%	22%	58%/42%	58%/42%	11%/82%/8%	12%/81%/7%	100%	100%	4.3 (7.65)*	3.3 (7.7)*	326 (7.6)*	327 (92)*
McLaughlin 2003	17	9	37 (17)		19%		100%/0%	100%/0%	0%/96%/4%		nd		nd		373 (25)	384 (27)
Total**	250	245	43.8	43.7	16.3%	21.7%	60.8%/ 39.2%	60.8%/ 39.2%	10%/83%/7%	11%/82%/7%	-		-		329.2**	329.1**

* calculation based on available data
** weighted mean value (excepting data concerning the number of patients)

The total number of patients enrolled in both evaluated studies is 495, of whom 250 were assigned to the TRE group and 245 to the PL group.

Mean age was: 43.8 years in the TRE group and 43.7 years in the PL group and the percentage of men was 16.3% and 21.7%, respectively. The percentage of patients with primary PAH was 60.8% in both groups.

The percentages of patients in specific NYHA functional classes: II, III and IV were as follows: 10%, 83% and 7% in the TRE group and 11%, 82% and 7% in the PL group.

In the *Simonneau 2002* study mean duration of the disease before introduction of the treatment was 4.3 years in the treprostinil group and 3.3 years in the placebo group. In the study of *McLaughlin 2003* no information concerning time from diagnosis was provided.

Mean 6-minute walk distance was similar in both groups and was 329.2 m in the TRE group and 329.1 m in the PL group.

In none of the studies any statistically significant differences in baseline characteristics of the patients were found.

From the above data it may be concluded that baseline characteristics of the patients in both studies are similar with regard to mean age and the percentage of men as well as the percentage of patients in NYHA functional class III and IV and the 6-minute walk distance. However, they are different as to the percentage of patients with primary PAH and PAH associated with other diseases.

3.6.3. Description of the interventions

In both clinical trials included in the analysis the patients were randomly assigned to the treprostinil group or the placebo group. All patients received additional conventional treatment.

Details of dosage and the route of administration of treprostinil as well as drugs used in conventional treatment are presented in the table below.

Table 114.
Description of the interventions; TRE vs. PL

Study	TRE		PL	Additional treatment
	Dose	Route of administration		
Simonneau 2002	The initial dose of treprostinil was 1.25 ng/kg/min and was increased during the study; the maximum dose after 12 weeks was 22.5 ng/kg/min.	Continuous subcutaneous infusion by means of a microinfusion pump (MiniMed, Symar, CA).	Placebo in continuous infusion	CT: oral vasodilators, anticoagulants, diuretics, digitalis glycosides
McLaughlin 2003	The initial dose of treprostinil was 2.5 to 5.0 ng/kg/min and was increased every 24h by 2.5-5.0 ng/kg/min up to a maximum dose of 20 ng/kg/min.	Continuous subcutaneous infusion	Placebo	nd

In the *Simonneau 2002* study a period of initial conventional treatment (at least 1 month) was adopted before randomization of patients into the two therapeutic groups. Conventional treatment included: oral vasodilators, anticoagulants, diuretics, digitalis glycosides (admissible). Treprostinil or placebo was administered in subcutaneous infusion (into abdominal subcutaneous tissue) by means of a MiniMed microinfusion pump. Treprostinil was administered at the initial dose of 1.25 ng/kg/min, which was then increased up to 22.5 ng/kg/min (the maximum tolerated dose) according to symptoms and the type and severity of adverse events. All patients, both in the TRE group and in the PL group, received conventional treatment.

In the study of *McLaughlin 2003* after initial assessment of general condition and hemodynamic parameters the patients were randomly assigned to the TRE or PL groups. Both treprostinil and placebo were administered in continuous subcutaneous infusion. Treprostinil was initially administered at a dose of 2.5 to 5.0 ng/kg/min, which was then increased by 2.5-5.0 ng/kg/min every 24h, according to response to treatment and the adverse events encountered. The maximum dose administered was 20 ng/kg/min. The drug was initially administered in hospital settings; after a period of observation and appropriate training of the patient the treatment was continued in ambulatory settings.

3.6.4. Analysis of efficacy

3.6.4.1. Mortality

Mortality was assessed in the study of *Simonneau 2002* only. The observation period was 12 weeks.

Numbers and percentages of patients who died are presented below.

Table 115.
Numbers and percentages of patients who died; TRE vs. PL

Study	Population	TRE			Placebo			Statistical significance of differences between the groups; TRE vs. PL
		N	n	Percentage	N	n	Percentage	
Simonneau 2002	PAH associated with connective tissue diseases	41	1	2.44%*	49	3	6.12%*	n.s.
	Total	233	9	3.86%*	236	10	4.24%*	n.s.

* Calculation based on available data

From the data presented in the study it may be concluded that the odds of death is lower in the TRE group and is 91% of this odds in the conventional treatment group; OR = 0.91 (95% CI: 0.32 to 2.54). The difference in mortality between both groups is not statistically significant. The odds of death in the population of patients with PAH associated with connective tissue diseases is lower in the TRE group and is 38% of this odds in the conventional treatment

group; OR = 0.38 (95% CI: 0.01 to 5.04). The difference in mortality between the assessed groups is not statistically significant.

3.6.4.2. Quality of life

Quality of life was assessed in the *Simonneau 2002* study using the *"Minnesota Living with Heart Failure Questionnaire"*. This questionnaire evaluates the symptoms of heart failure and the results of treatment with regard to four aspects: physical and psychical condition as well as emotional and social function.

After 12 weeks of observation the patients treated with TRE as compared to the control group demonstrated statistically significantly higher improvement with regard to physical condition (p = 0.0064). No statistically significant difference between the groups was observed with regard to results of the whole questionnaire (p = 0.17).

3.6.4.3. Exercise capacity – results of the 6-minute walk test

In both studies exercise capacity was evaluated using the 6-minute walk test (6MWT) and observing changes in walk distance in the therapeutic groups. The observation period in the studies of *Simonneau 2002* and *McLaughlin 2003* was 12 and 8 weeks, respectively.

Detailed results of specific studies are presented below.

Table 116.
Results of the 6-minute walk test; TRE vs. PL

Study	Population	Intervention	N	Baseline distance [m]		Final distance [m]		Change from baseline [m]		Mean difference in change between the groups (95% CI); TRE vs. PL
				Mean	SD	Mean	SD	Mean	SD	
Simonneau 2002	PAH (connective tissue diseases)	TRE	41	280	83.2*	305	76.8*	24	76.8*	21 (-6.49 to 48.49)*
		PL	49	296	91*	303	98*	3	56*	
	Total	TRE	233	326	76*	nd	nd	10**	nd	16 (4.4 to 27.6)**. p = 0.006
		PL	236	327	92*	nd	nd	0**	nd	
McLaughlin 2003	Primary PAH	TRE	15	373	103*	411	nd	37	65.84*	43 (-17.3 to 103.3)*
		PL	9	384	81*	379	nd	-6	84.00*	

* Calculation based on available data
** Median value

In the *Simonneau 2002* study increase of exercise capacity from baseline value was observed in the TRE group: median change from baseline was 10 m (the range between the 25. and 75. percentile was -24 to 47), while in the PL group no change was observed: median change from baseline in this group was 0 m (the range between the 25. and 75. percentile was -

44 to 32). The difference in median change between the two groups, as calculated using the *Hodges-Lehmann* method, was statistically significant and was 16 m (95% CI: 4.4 to 27.6), p = 0.006, in favor of the TRE group. The authors of the study noted that increase of exercise capacity was higher in more severely ill patients and independent of the etiology of the disease.

In the population of patients with PAH associated with connective tissue diseases mean difference in change of exercise capacity between the groups as evaluated using the 6-minute walk test was 21 m (95% CI: -6.49 to 48.49) in favor of the TRE group. The result is not statistically significant.

In the *McLaughlin 2003* study, in which patients with primary PAH participated, improvement in exercise capacity was observed in the TRE group only; however, this improvement was not statistically significant. The mean change of this parameter from baseline value was: +37 m in the TRE group and -6 m in the PL group, respectively. Mean difference in change of exercise capacity calculated from the above data is 43 m (95% CI: -17.3 to 103.3); increase of this parameter is therefore higher by 43 m in the TRE group as compared to the placebo group. The result is not statistically significant.

3.6.4.4. Assessment of dyspnea

3.6.4.4.1. Borg Dyspnea Score

Severity of dyspnea was assessed using the *Borg Dyspnea Score* in both studies. In this scale lower score reflects less severe dyspnea.

Values of change from baseline scores in both therapeutic groups are presented in the table below.

Table 117.
Borg Dyspnea Score; TRE vs. PL

Study	Popula-tion	TRE			PL			Mean difference in change between the groups (95% CI); TRE vs. PL
		N	Change from baseline	SD	N	Change from baseline	SD	
Simonneau 2002	PAH (connective tissue diseases)	41	-0.6	3.2*	49	0.2	3.5*	-0.8 (-2.2 to 0.6)*
	Total	233	-1.1*	nd	236	-0.2*	nd	-0.9 (-1.35 to -0.45)*
McLaughlin 2003	Primary PAH	15	0	1.55*	9	1.0	2.4*	-1.0 (-2.57 to 0.57)*

* Calculation based on available data

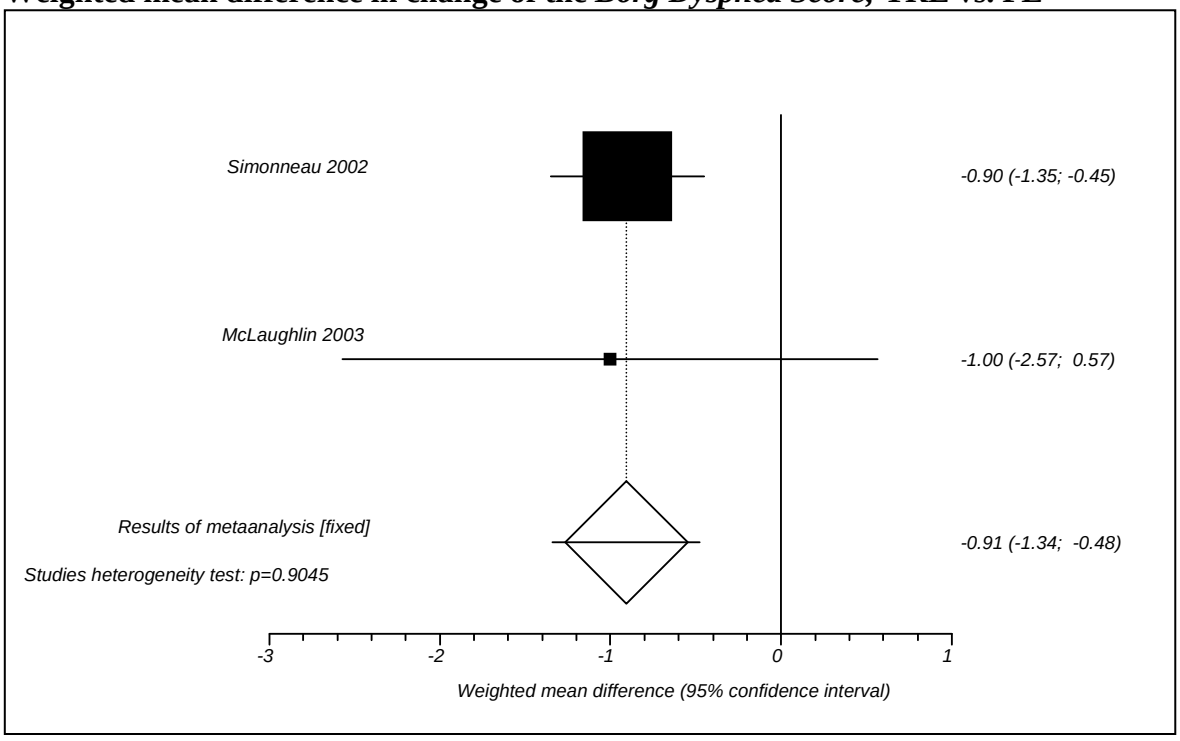
In the *Simonneau 2002* study reduction of the *Borg Dyspnea Score* from baseline values by 1.1 points in the TRE group and 0.2 points in the PL group was observed. Mean difference in change between the two groups was statistically significant and was -0.9 points (95% CI: -1.35 to -0.45) in favor of the TRE group.

In the *Simonneau 2002* substudy concerning the population of patients with PAH associated with connective tissue diseases the authors observed no statistically significant difference in the *Borg Dyspnea Score* between the TRE and PL groups. Mean difference in reduction of dyspnea from baseline values was 0.8 (95% CI: -2.2 to 0.6), p = 0.168, in favor of the TRE group.

In the study of *McLaughlin 2003* no change in severity of dyspnea from baseline values was observed in the TRE group, while in the PL group increase of severity of dyspnea by 1 point was noted. Mean difference in change between the groups is not statistically significant and is -1.0 points (95% CI: -2.57 to 0.57); reduction of dyspnea is therefore higher by 1 point in the *Borg Dyspnea Score* in the TRE group as compared to the PL group.

The figure below presents weighted mean difference in change of the *Borg Dyspnea Score* between the TRE and PL group in an observation period of 8-12 weeks.

Figure 43
Weighted mean difference in change of the *Borg Dyspnea Score;* TRE vs. PL



Weighted mean difference in change of the *Borg Dyspnea Score* between the groups is -0.91 (95% CI: -1.34 to -0.48); p < 0.0001; reduction of severity of dyspnea is therefore higher by 0.91 points in the TRE group as compared to the PL group. The result is statistically significant.

3.6.4.4.2. Dyspnea – Fatigue Rating

In both studies the *Dyspnea – Fatigue Rating* scale was used for assessment of severity of dyspnea and fatigue. This scale consists of 3 components, each rated from 0 to 4. Lower score reflects higher severity of the symptoms.

Assessment in this scale was presented in both studies.

Values of change from baseline scores in both therapeutic groups are presented in the table below.

Table 118.
Changes in *Dyspnea – Fatigue Rating;* TRE vs. PL

Study	Population	TRE			PL			Mean difference in change between the groups (95% CI); TRE vs. PL
		N	Change from baseline	SD	N	Change from baseline	SD	
Simonneau 2002	PAH (connective tissue diseases)	41	0.9	1.3*	49	0	2.1*	0.9 (0.16 to 1.64)*
	Total	233	1.2*	nd	236	-0.1*	nd	1.3* (p = 0.0001)
McLaughlin 2003	Primary PAH	15	0.8	nd	9	-0.7	nd	1.5* (NS)

* Calculation based on available data

Both in the *Simonneau 2002* and the *McLaughlin 2003* study decrease of severity of dyspnea and fatigue was observed in the TRE group along with worsening in the PL group. In the study of *McLaughlin 2003* the difference in change of the rating between the groups was not statistically significant, while in the *Simonneau 2002* trial it reached statistical significance (p = 0.0001).

In the subgroup of patients with PAH associated with connective tissue diseases (the study of *Simonneau 2002)* decrease of severity of dyspnea and fatigue by 0.9 points as related to baseline values was observed in the TRE group, while no change of this parameter was noted in the PL group. The result is statistically significant.

3.6.4.5. Pulmonary transplantation

A case of pulmonary transplantation was reported in the study of *Simonneau 2002*. It was performed in a patient qualified to the PL group; after a study period of 12 weeks the patient was still alive.

Table 119.
Numbers and percentages of patients, in whom pulmonary transplantation was performed; TRE vs. PL

Study	TRE			Placebo			Statistical significance of differences between the groups; TRE vs. PL
	N	n	Percen-tage	N	n	Percen-tage	
Simonneau 2002	233	0	0	236	1	0.4%*	n.s.*

* Calculation based on available data

From the data presented in the study it may be concluded that the odds of pulmonary transplantation is lower in the TRE group and is 13% of this odds in the PL group. The odds ratio calculated using the *Peto* method is 0.13 (95% CI: 0.002 to 6.91). The difference between both groups with regard to this endpoint is not statistically significant.

3.6.4.6. Withdrawal from the study due to clinical worsening

Clinical worsening of the disease being the cause of the patient's withdrawal from the study was reported in the study of *Simonneau 2002*. In each group 6 patients did not complete the study for this reason.

Table 120.
Numbers and percentages of patients, in whom clinical worsening was the cause of withdrawal from the study; TRE vs. PL

Study	TRE			Placebo			Statistical significance of differences between the groups; TRE vs. PL
	N	n	Percen-tage	N	n	Percen-tage	
Simonneau 2002	233	6	2.6%*	236	6	2.5%*	n.s.*

* Calculation based on available data

From the data presented in the study it may be concluded that the odds of the patient's withdrawal from the study due to exacerbation of symptoms of the disease is nearly equal in both groups; OR = 1.01 (95% CI: 0.27 to 3.85). The result is not statistically significant.

3.6.4.7. Death, pulmonary transplantation or withdrawal from the study due to clinical worsening

This composite endpoint was evaluated in the *Simonneau 2002* study.

Table 121.
Numbers and percentages of patients, in whom death, pulmonary transplantation or withdrawal from the study due to clinical worsening (a composite endpoint) occurred

Study	TRE			Placebo			Statistical significance of differences between the groups; TRE vs. PL
	N	n	Percen-tage	N	n	Percen-tage	
Simonneau 2002	233	13	5.6%*	236	16	6.8%*	n.s.*

* Calculation based on available data

From the data presented in the study it may be concluded that the odds of death, pulmonary transplantation or withdrawal from the study due to clinical worsening is lower in the TRE group and is 81% of this odds in the PL group; OR = 0.81 (95% CI: 0.35 to 1.85). The difference between both groups with regard to this endpoint is not statistically significant.

3.6.4.8. Hemodynamic parameters

3.6.4.8.1. Mean pulmonary artery pressure (mPAP)

Mean pulmonary artery pressure was assessed both clinical trials included in the analysis. The observation period in this regard was 8 weeks in the *McLaughlin 2003* study and 12 weeks in the trial of *Simonneau 2002*.

Detailed results of specific studies are presented below.

Table 122.
Mean pulmonary artery pressure; TRE vs. PL

Study	Population	Interven-tion	N	Baseline value [mmHg]		Change from baseline [mmHg]		Mean difference in change between the groups (95% CI); TRE vs. PL
				Mean	SD	Mean	SD	
Simonneau 2002	PAH (connective) tissue	TRE	41	52	12.8*	-3	6.4*	-2 (-4.79 to 0.79)*
		PL	49	55	14*	-1	7*	
	Total	TRE	233	62	15*	-2.3	7.6*	-3.00 (-4.53 to -1.47)*
		PL	236	60	15*	0.7	9.2*	
McLaughlin 2003	Primary PAH	TRE	15	59**	16.5*	0	11.6*	2.00 (-5.79 to 9.79)*
		PL	9	64	18*	-2	3*	

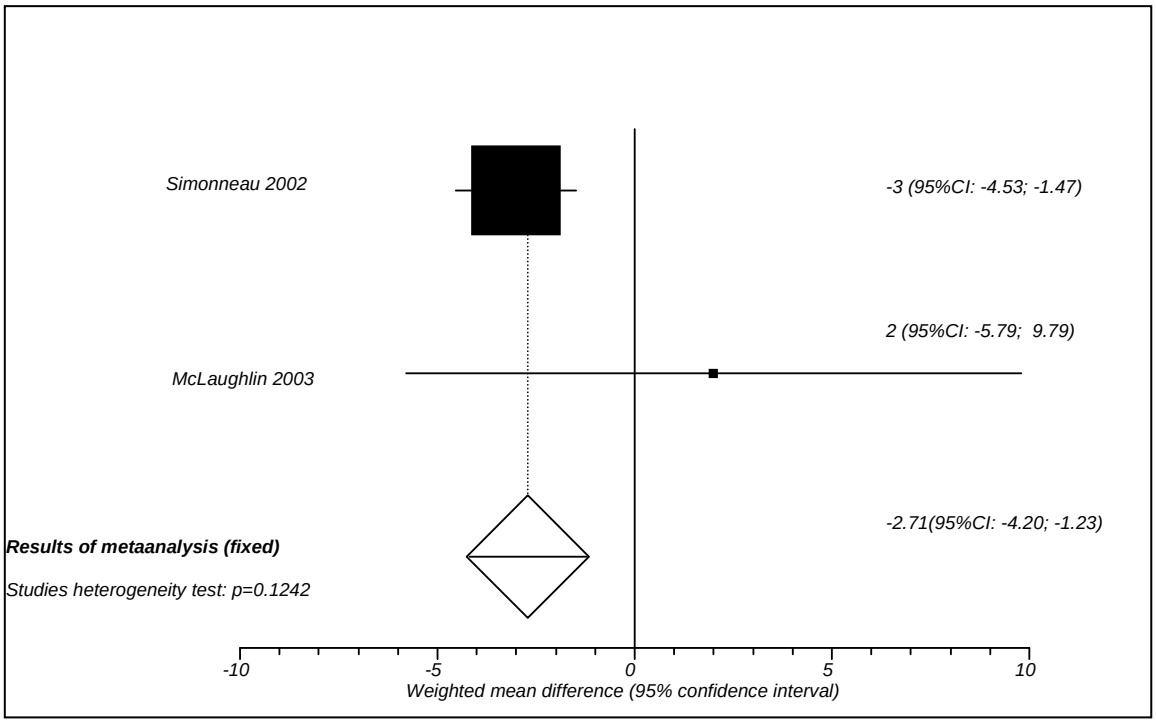
* Calculation based on available data
** Calculated for 17 patients in the TRE group

In the study of *Simonneau 2002* reduction of mean pulmonary artery pressure was statistically significantly higher in the TRE group for the whole population of patients. For the population of patients with PAH associated with connective tissue diseases reduction of this parameter as related to baseline values was higher in the TRE group as compared to the PL group; however, the result was not statistically significant.

In the *McLaughlin 2003* study reduction of mean pulmonary artery pressure was higher in the placebo group as compared to the TRE group; however, the result was statistically insignificant.

The figure below presents a metaanalysis for the difference in change of mean pulmonary artery pressure between the TRE and PL group.

Figure 44.
Weighted mean difference in change of mean pulmonary artery pressure (mPAP); TRE vs. PL



From this metaanalysis it may be concluded that after an observation period of 8-12 weeks reduction of mean pulmonary artery pressure is higher by 2.71 mmHg in the TRE group as compared to the PL group. Weighted mean difference in change of this parameter between the therapeutic groups is -2.71 mmHg (95% CI: -4.20 to -1.23), p = 0.0003. The result is statistically significant.

3.6.4.8.2. Pulmonary vascular resistance index (PVRI)

Pulmonary vascular resistance was assessed in both studies. The observation period in this regard was 8 weeks in the *McLaughlin 2003* study and 12 weeks in the trial of *Simonneau 2002*.

Detailed results of specific studies are presented below.

Table 123.
Pulmonary vascular resistance index; TRE vs. PL

Study	Population	Interven-tion	N	Baseline value [unit/m^2]		Change from baseline [unit/m^2]		Mean difference in change between the groups (95% CI); TRE vs. PL
				Mean	SD	Mean	SD	
Simonneau 2002	PAH (connective tissue	TRE	41	25	19.2*	-4	14*	-5 (-9.46 to -0.54)*
		PL	49	24	6.4*	1	7*	
	Total	TRE	233	26	15*	-3.5	9.2*	-4.70 (-6.37 to -3.03)*
		PL	236	25	15	1.2	9.2*	
McLaughlin 2003	Primary PAH	TRE	15	24.8**	10.7*	-4.8	5.4*	-5.00 (-9.55 to -0.45)*
		PL	9	24.7	9.0*	0.2	5.7*	

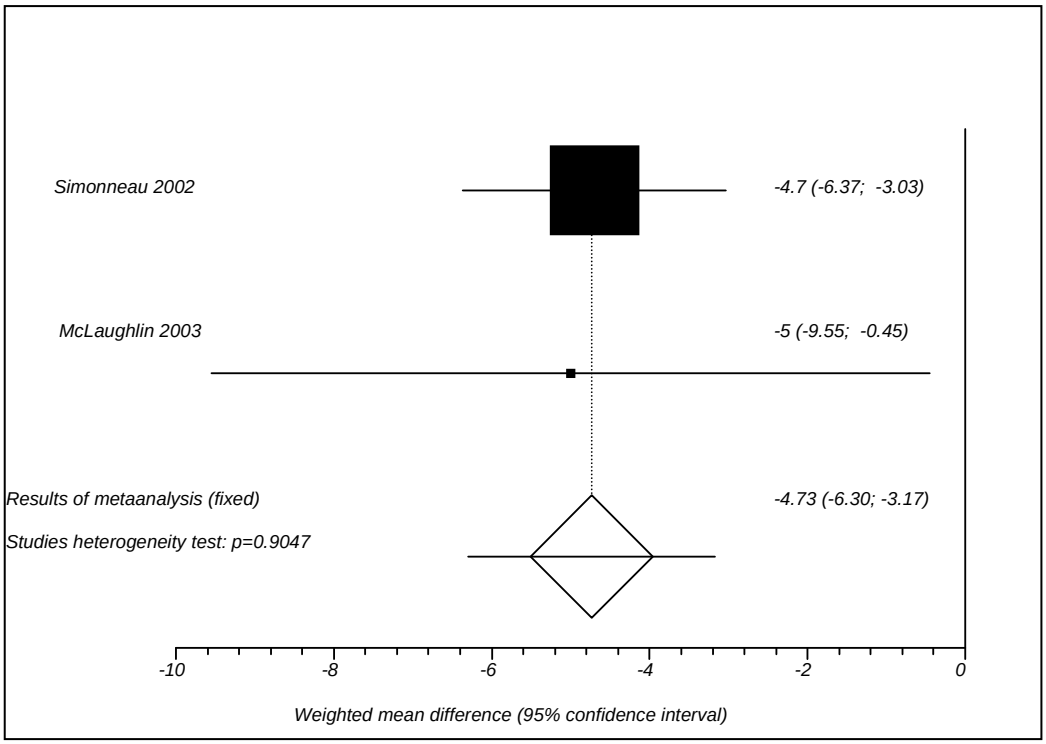
* Calculation based on available data
** Calculated for 17 patients

In the study of *Simonneau 2002* reduction of pulmonary vascular resistance was statistically significantly higher in the TRE group as compared to the control group, both with regard to the whole population and the population of patients with PAH associated with connective tissue diseases. Mean difference in change of PVRI calculated from the above data is: -4.70 (95%CI: -6.37 to -3.03) for the whole population and -5 (95% CI: -9.46 to -0.54) for the population of patients with PAH associated with connective tissue diseases; both results are statistically significant.

According to data presented by the authors of the *McLaughlin 2003* study reduction of PVRI by 20% was achieved in the TRE group; however, differences between the assessed groups are not statistically significant (p = 0.065). Mean difference in change of PVRI calculated from the above data is -5.00 (95% CI: -9.55 to -0.45) and the result is statistically significant.

The figure below presents weighted mean difference in change of pulmonary vascular resistance index.

Figure 45.
Weighted mean difference in change of pulmonary vascular resistance index (PVRI); TRE vs. PL



In the metaanalysis of the results of two studies statistically significantly higher reduction of pulmonary vascular resistance index in the TRE group as compared to the placebo group was found. Weighted mean difference in change of this parameter between the groups in an observation period of 8-12 weeks is 4.73 units/m^2 (95% CI: -6.30 to -3.17), $p < 0.0001$. The result is statistically significant.

3.6.4.8.3. Cardiac index (CI)

Cardiac index is a parameter expressing the relation between cardiac output and the body surface area (cardiac output at rest is divided by the body surface area in square meters). Cardiac index was assessed in both studies included in the analysis.

Detailed results of specific studies are presented below.

Table 124.
Cardiac index; TRE vs. PL

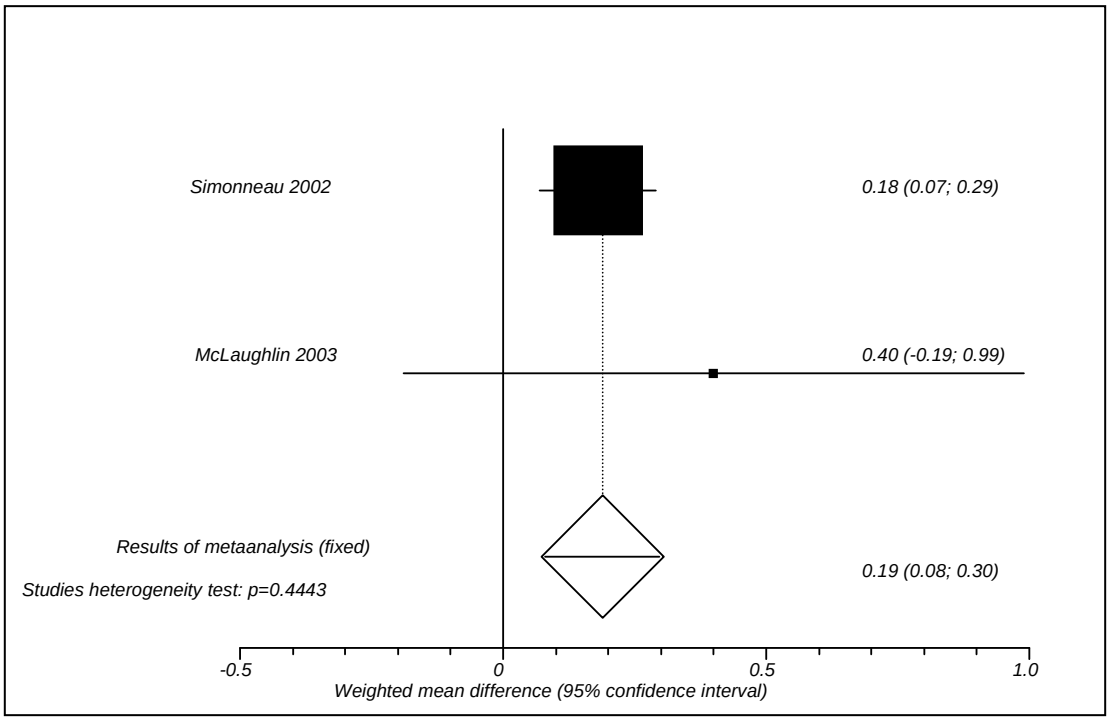
Study	Population	Interven-tion	N	Baseline value [l/min/m^2]		Change from baseline [l/min/m^2]		Mean difference in change between the groups (95% CI); TRE vs. PL
				Mean	SD	Mean	SD	
Simonneau 2002	PAH (connective tissue diseases)	TRE	41	2.1	0.64*	0.2	0.64*	0.3 (0.02 to 0.58)*
		PL	49	2.1	0.7*	-0.1	0.7*	
	Total	TRE	233	2.4	1.53*	0.12	0.61*	0.18 (0.07; 0.29)*
		PL	236	2.3	1.54*	-0.06	0.61*	
McLaughlin 2003	Primary PAH	TRE	15	2.3	0.8*	0.4	0.77*	0.4 (-0.19 to 0.99)*
		PL	9	2.4	0.6*	0	0.6*	

* Calculation based on available data

In both studies increase of cardiac index was higher in the TRE group as compared to the PL group, both with regard to the whole population and the population of patients with PAH associated with connective tissue diseases. However, the difference between the groups was significant only in the trial of *Simonneau 2002*.

The figure below presents a metaanalysis for difference in change of cardiac index in an observation period of 8-12 weeks.

Figure 46.
Weighted mean difference in change of cardiac index (CI); TRE vs. PL



Weighted mean difference in changes of cardiac index is 0.19 l/min/m^2 (95% CI: 0.08 to 0.30); increase of cardiac index is therefore higher by 0.19 l/min/m^2 in the TRE group as compared to the PL group. The result is statistically significant.

3.6.4.8.4. Mixed venous blood oxygen saturation

Mixed venous blood oxygen saturation was assessed in both studies: *Simonneau 2002* and *McLaughlin 2003*.

Detailed results of specific studies are presented below.

Table 125.
Mixed venous blood oxygen saturation; TRE vs. PL

Study	Population	Intervention	N	Baseline value [%]		Change from baseline [%]		Mean difference in change between the groups (95% CI); TRE vs. PL
				Mean	SD	Mean	SD	
Simonneau 2002	PAH (connective tissue diseases)	TRE	41	61	12.8*	0	12.8*	3.00 (-2.59 to 8.89)*
		PL	49	61	14*	-3	14*	
	Total	TRE	233	62	15*	2.0	12.2*	3.4 (1.32 to 5.48)*
		PL	236	60	15*	-1.4	10.8*	
McLaughlin 2003	Primary PAH	TRE	15	62.1**	12.37*	-2.0	7.75*	0 (-5.32 to 5.32)*
		PL	9	61.7	8.4*	-2.0	3*	

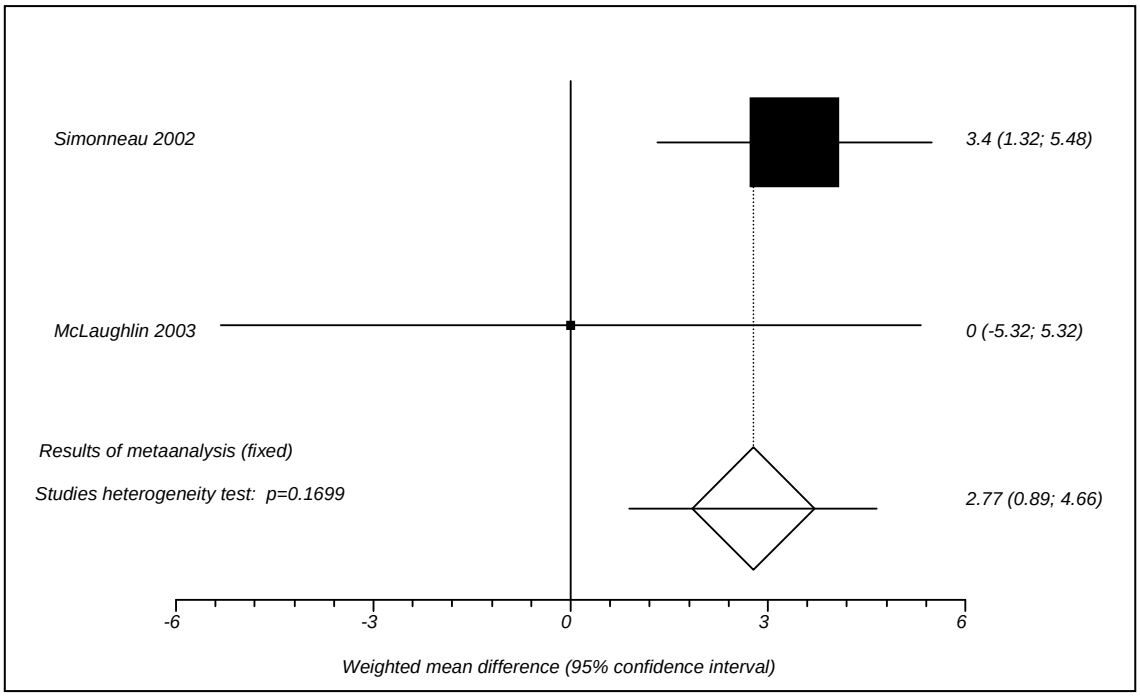
* Calculation based on available data
** Calculated for 17 patients in the TRE group

In the study of *Simonneau 2002* statistically significantly higher increase of mixed venous blood oxygen saturation was observed in the TRE group as compared with the PL group. Mean difference in change of this parameter calculated from the above data is: 3.4% (95%CI: 1.32 to 5.48) for the whole population and 3% (95% CI: -2.59 to 8.89) for the population of patients with PAH associated with connective tissue diseases. The result is statistically significant for the whole population only.

In the *McLaughlin 2003* study no differences in change of this parameter were observed between the assessed groups.

The figure below presents a metaanalysis for difference in change of mixed venous blood oxygen saturation.

Figure 47.
Weighted mean difference in change of mixed venous blood oxygen saturation; TRE vs. PL



Weighted mean difference in change of mixed venous blood oxygen saturation is 2.77 p.p. (95%CI: 0.89 to 4.66). It means that increase of mixed venous blood oxygen saturation is higher by 2.77 p.p. in the TRE group as compared to the PL group. The result is statistically significant.

Neither in the *Simonneau 2002* study nor in the *McLaughlin 2003* trial were the following endpoints taken into account:

- change of the NYHA functional class
- number of hospitalizations

It should be noted that mortality and necessity of pulmonary transplantation was assessed only in the subgroup of patients with PAH associated with connective tissue diseases in the study of *Simonneau 2002*.

3.6.5. Assessment of safety

Safety of the compared treatment options was assessed in both studies included in the analysis. The observation period in this regard was 8 weeks in the *McLaughlin 2003* study and 12 weeks in the trial of *Simonneau 2002*.

The table below presents numbers and percentages of patients participating in the studies of *Simonneau 2002* and *McLaughlin 2003*, in whom specific adverse events were observed.

Table 126.
Numbers and percentages of patients in the *Simonneau 2002* and *McLaughlin 2003* studies, in whom specific adverse events were observed; TRE vs. PL

Adverse event	Study	TRE			PL			Statistical significance of differences between the groups; TRE vs. PL
		N	n	Percen-tage	N	n	Percen-tage	
Pain at the injection site	*Simonneau 2002*	233	200	85%	236	62	27%	p < 0.0001
	McLaughlin 2003	16	15	88%	9	2	22%	p = 0.0016
Vomiting	*Simonneau 2002*	233	12	5%	236	14	6%	n.s.
	McLaughlin 2003	17	4	24%	9	0	0%	n.s.
Reaction at the injection site	*Simonneau 2002*	233	196	83%	236	62	27%	p < 0.0001
Bleeding or lividity at the injection site	*Simonneau 2002*	233	79	34%	236	102	44%	n.s.
Headache	*Simonneau 2002*	233	64	27%	236	54	23%	n.s.
Diarrhea	*Simonneau 2002*	233	58	25%	236	36	16%	p < 0.009
Nausea	*Simonneau 2002*	233	52	22%	236	41	18%	n.s.
Skin rash	*Simonneau 2002*	233	32	14%	236	26	11%	n.s.
Jaw pain	*Simonneau 2002*	233	31	13%	236	11	5%	p < 0.001
Sudden vasodilation	*Simonneau 2002*	233	25	11%	236	11	5%	p < 0.01
Vertigo	*Simonneau 2002*	233	21	9%	236	19	8%	n.s.
Edema	*Simonneau 2002*	233	21	9%	236	6	3%	p < 0.002
Gastrointestinal bleeding	*Simonneau 2002*	233	3	1.3%	236	0	0%	nd
Blood transfusion	*Simonneau 2002*	233	2	0.9%	236	0	0%	nd
Hypotension	*McLaughlin 2003*	16	4	24%	9	0	0%	n.s.
Bradycardia	*McLaughlin 2003*	17	2	12%	9	0	0%	n.s.
Vasovagal symptoms	*McLaughlin 2003*	17	0	0%	9	2	22%	n.s.
Syncope	*McLaughlin 2003*	17	1	6%	9	3	33%	n.s.
Insomnia	*McLaughlin 2003*	17	1	6%	9	3	33%	n.s.
Hematoma/ induration of the injection site	*McLaughlin 2003*	17	16	94%	9	2	22%	p = 0.0004

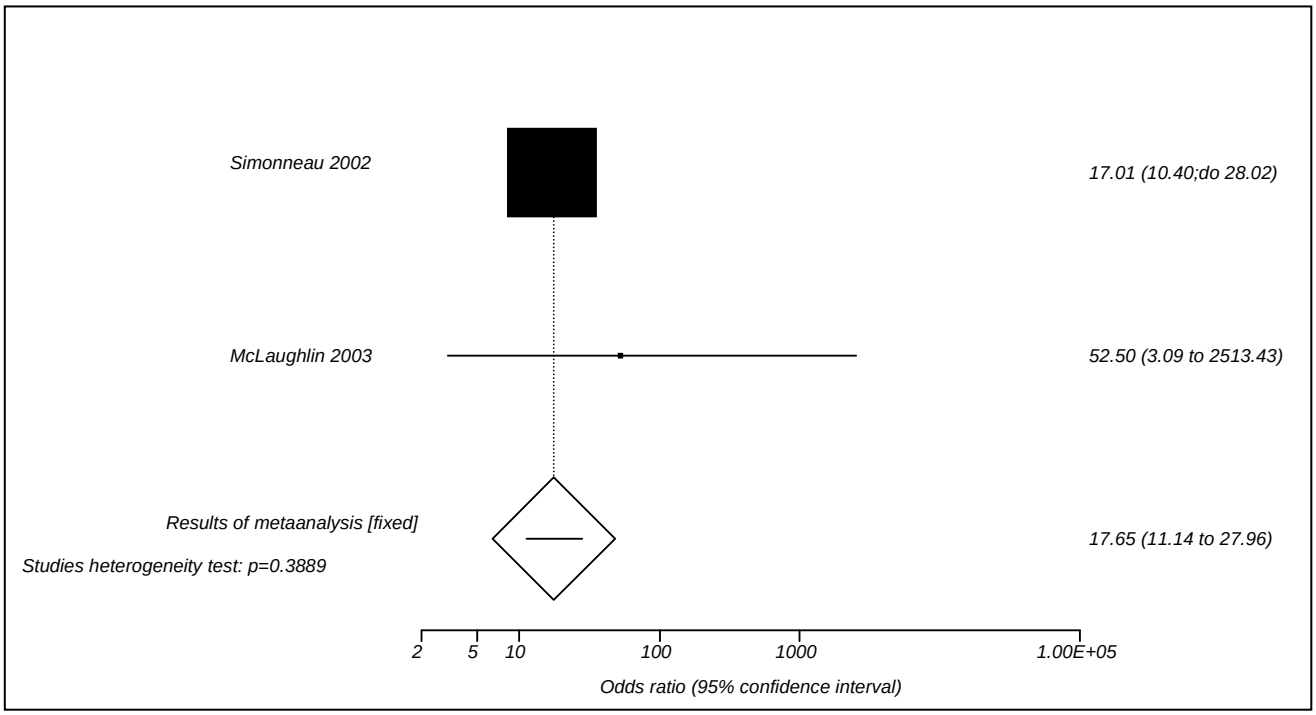
In the study of *Simonneau 2002* no significant abnormalities in hematological or biochemical laboratory tests were found in either of the groups. In both groups the most common adverse reaction was pain at the injection site (observed more often in the treprostinil group). In 18 patients in the TRE group and 1 in the PL group the treatment was discontinued due to unacceptable pain at the injection site in the abdominal wall. Other adverse events related to prostacyclin, such as diarrhea, jaw pain, flushing or edema of the lower extremities, were observed more often in the TRE group. Most of the remaining adverse events listed in the table were also observed more frequently in the TRE group; however, difference between the groups was significant with regard to 6 types of adverse events: pain at the injection site, reaction at the injection site, diarrhea, jaw pain, sudden vasodilation and edema.

Infection of the injection site was not observed in any of the patients. Moreover, in 3 patients in the TRE group gastrointestinal bleeding was observed (one of the patients received naproxen), which resolved spontaneously without any clinical sequelae.

In the study of *McLaughlin 2003* the most commonly observed adverse events in the TRE group were: hematoma or induration and pain at the injection site – differences between the groups were statistically significant. Frequency of three other adverse events (vomiting, hypotension and bradycardia) was also higher in the TRE group, but no statistical significance was found. On the other hand in the control group vasovagal symptoms, syncope and insomnia occurred more often (however, no statistically significant differences were found between the groups).

Pain at the injection site and vomiting were the two adverse events taken into account in both studies *(Simonneau 2002* and *McLaughlin 2003).* Odds ratios calculated for these reactions in a metaanalysis of the results of both studies are presented below.

Figure 48.
Metaanalysis for the total number of patients who reported pain at the injection site; TRE vs. PL



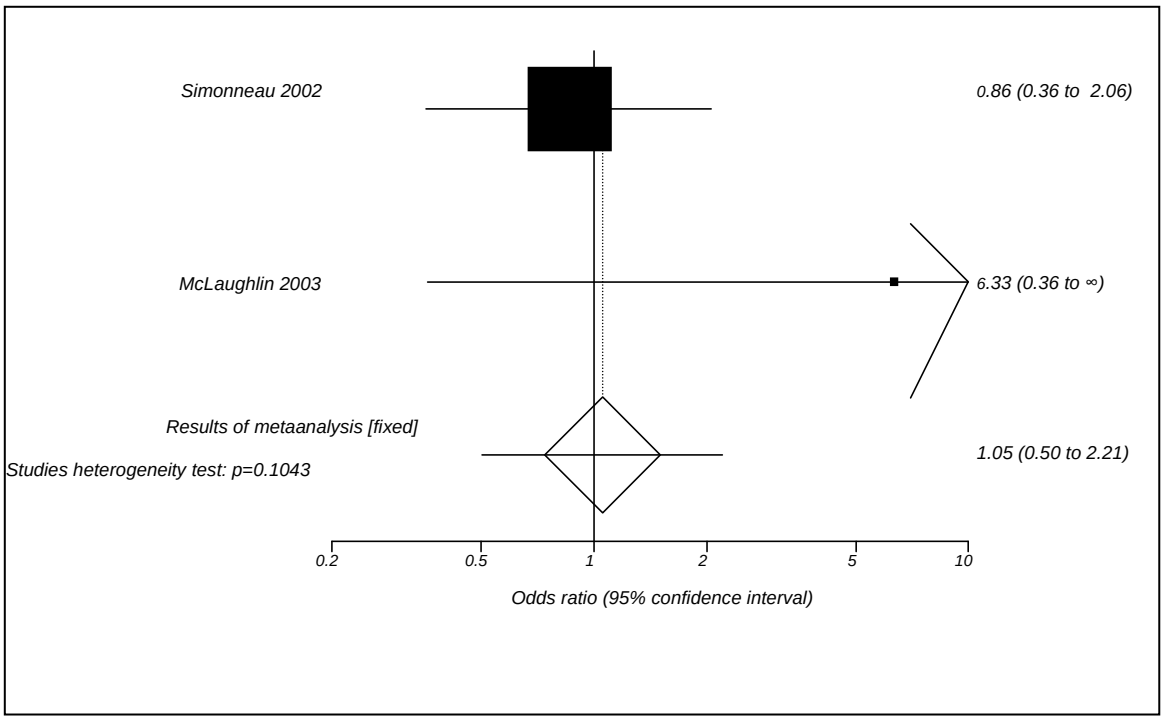
The odds ratio calculated in the metaanalysis for pain at the injection site is 17.65 (95% CI: 11.14 to 27.96), $p < 0.0001$. It means that the odds of occurrence of this adverse event is more

than 17 times higher in the TRE group as compared to the PL group. The result is statistically significant.

The NNH is 2 (95% CI: 2 to 2). It means that administration of treprostinil instead of placebo to 2 patients for a period of 8-12 weeks is associated with one additional case of pain at the injection site.

A metaanalysis for the total number of patients, in whom vomiting was observed during 8-12 weeks of treatment with treprostinil or placebo, is presented below.

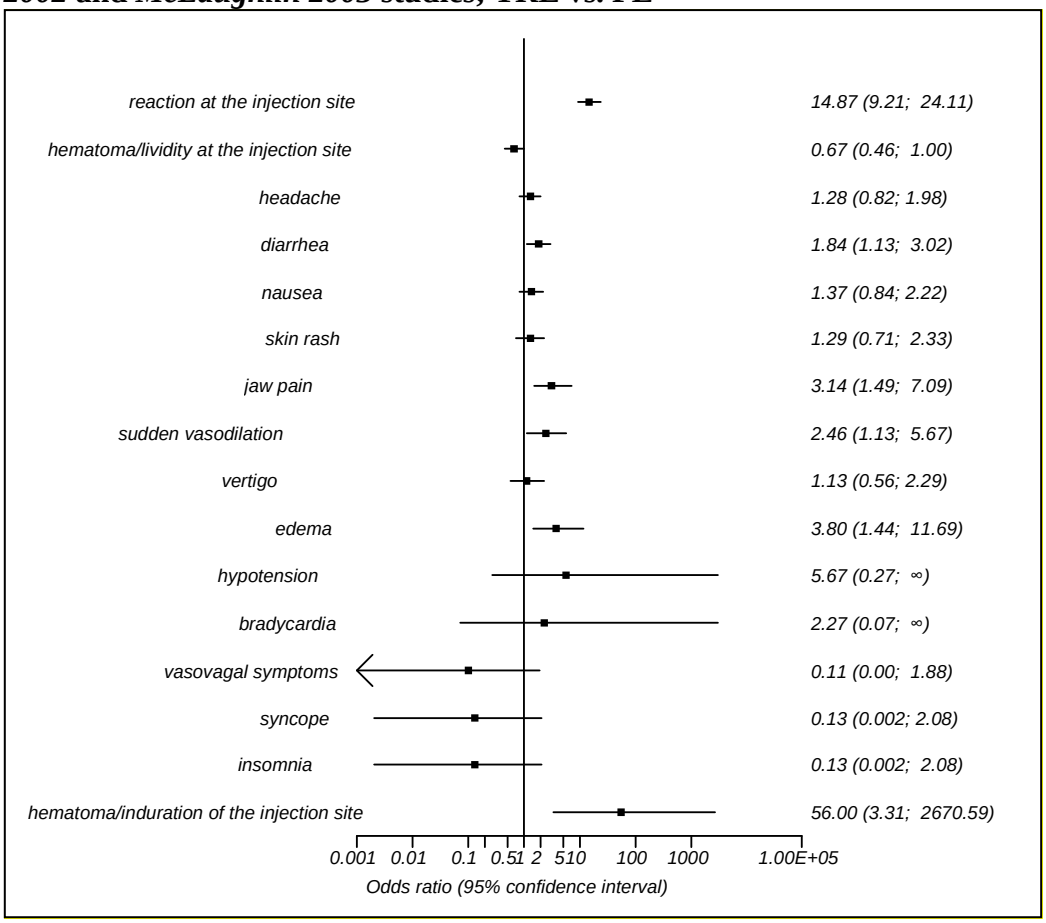
Figure 49.
Metaanalysis for the total number of patients, in whom vomiting was observed; TRE vs. PL



The odds ratio calculated in the metaanalysis is 1.05 (95% CI: 0.50 to 2.21), p = 0.96. It means that the odds of occurrence of this endpoint in the TRE group is similar to this odds in the PL group. The result is not statistically significant.

Odds ratios calculated for the remaining adverse events are presented below.

Figure 50.
Odds ratios for specific adverse events calculated from the results of the *Simonneau 2002* and *McLaughlin 2003* studies; TRE vs. PL



The odds of occurrence of insomnia, syncope, vasovagal symptoms or hematoma or lividity of the injection site is lower in the group treated with treprostinil and is 13%, 13%, 11% and 67% of the respective odds in the control group. The odds ratio for insomnia or syncope is 0.13 (95% CI: 0.00 to 2.08), for vasovagal symptoms 0.11 (95% CI: 0.00 to 1.88), for hematoma or lividity of the injection site 0.67 (95% CI: 0.46 to 1.00). Only the result for hematoma or lividity of the injection site reached statistical significance. In order to avoid one additional case of hematoma or lividity of the injection site treprostinil must be administered instead of placebo to 11 patients for 12 weeks; NNH = 11 (95% CI: 6 to 203).

The odds of occurrence of the remaining adverse events is higher in the TRE group as compared to the placebo group. The odds ratios calculated for the following adverse events reached statistical significance:

- reaction at the injection site: OR = 14.84 (95% CI: 9.21 to 24.11), NNH = 2 (95% CI: 2 to 2)
- diarrhea: OR = 1.84 (95% CI: 1.13 to 3.02), NNH = 11 (95% CI: 6 to 42)
- jaw pain: OR = 3.14 (95% CI: 1.49 to 7.09), NNH = 12 (95% CI: 8 to 28)
- sudden vasodilation: OR = 2.46 (95% CI: 1.13 to 5.67), NNH = 17 (95% CI: 9 to 77)
- edema: OR = 3.8 (95% CI: 1.44 to 11.69), NNH = 16 (95% CI: 9 to 42)
- hematoma/induration of the injection site: OR = 56.00 (95% CI: 3.31; 2670.59), NNH = 2 (95% CI: 2 to 3).

3.7. Bosentan vs. sildenafil

3.7.1. Results of search for the studies

Only one single-center, randomized, double-blind study fulfilling the inclusion criteria was identified, in which bosentan (BOS) was directly compared with sildenafil (SIL) in patients with pulmonary arterial hypertension: SERAPH. Credibility of this clinical trial scored 5 points in the *Jadad* scale. The observation period was 16 weeks.

3.7.2. Description of the population

In the SERAPH study patients with pulmonary hypertension, both primary and associated with connective tissue diseases, such as scleroderma or systemic lupus erythematosus, in WHO functional class III were enrolled. In all patients diagnosis of PAH was based on the results of heart catheterization and defined as mean pulmonary artery pressure over 25 mmHg. In addition in all patients symptoms of pulmonary arterial hypertension were present despite conventional treatment with diuretics, digoxin and anticoagulants and the 6-minute walk distance ranged from 150 to 450 m.
Among the exclusion criteria elevated liver enzymes (> 3 times above the upper limit of normal values), previous treatment with bosentan or sildenafil and necessity of treatment with prostanoids were listed.

Baseline characteristics of the patients enrolled in the SERAPH study are presented in the table below.

Table 127.
Baseline characteristics of the patients enrolled in the SERAPH study; BOS vs. SIL

Parameter	BOS	SIL
Number of patients	12	14
Mean age (SD) [years]	41.1 (nd)	44.4 (nd)
Percentage of men	16.7%*	21.4%*
Percentage of patients with primary PAH	91.7%*	85.7%*
Percentage of patients with PAH associated with scleroderma	8.3%*	7.1%*
Percentage of patients with PAH associated with systemic lupus erythematosus	0.0%*	7.1%*
Mean time from diagnosis (SD) [months]	31 (40)	40 (44)
Percentage of patients treated with warfarin	92%	93%
Percentage of patients treated with diuretics	50%	71%
Percentage of patients treated with digoxin	66%	43%
Percentage of patients treated with calcium channel blockers	42%	7%
Mean 6-minute walk distance (SD) [m]	304.6 (74.1)	290 (88.5)

* Calculation based on available data

In the SERAPH study 26 patients with PAH were enrolled, of whom 12 were assigned to the bosentan group and 14 to the sildenafil group. Mean age of patients in the bosentan and sildenafil group was 41 and 44 years, respectively, time from diagnosis of PAH: 31 and 40 months and the percentage of men 17% and 21%, respectively. Patients with primary PAH constituted the majority of the population: 92% in the BOS group and 86% in the SIL group; those treated with warfarin: 92% and 93%.

The authors of the SERAPH study found no statistically significant differences in baseline characteristics of the patients assigned to the bosentan group and the sildenafil group.

3.7.3. Description of the interventions

In the SERAPH study the patients were randomly assigned to the bosentan group (BOS) or the sildenafil group (SIL). In both therapeutic groups all patients received additional conventional treatment with warfarin, diuretics, digoxin or calcium channel blockers.

The patients in the BOS group received bosentan twice daily at an initial dose of 62.5 mg for a period of four weeks, after which the dose was increased to 125 mg twice daily. The initial dose of sildenafil was 50 mg twice daily. After four weeks the dose of the drug was increased to 50 mg three times daily. The study was double-blind.

The observation period was 16 weeks.

3.7.4. Analysis of efficacy

3.7.4.1. Mortality

In the SERAPH clinical trial only one patient in the sildenafil group died during an observation period of 16 weeks. In the bosentan group no deaths were observed.

The odds ratio calculated using the *Peto* method is 0.16 (95% CI: 0.003 to 7.96). It means that the odds of death is lower in the bosentan group and is 16% of this odds in the sildenafil group. The result is not statistically significant.

3.7.4.2. Quality of life

In the SERAPH study quality of life was assessed using the *Kansas City Cardiomyopathy Quality-of-Life* questionnaire, consisting of 23 questions rated in the 5-point *Liekert* scale (in which 1 represents maximum limitation and 5 – no limitations) related to eight domains (physical symptoms, symptoms stability, social limitation, self-efficacy, quality of life, functional status and clinical summary). Total score ranged from 0 to 100; higher score reflected better health status.

Mean changes from baseline scores and mean difference in this change between the groups (bosentan and sildenafil) are presented in the table below.

Table 128.
Quality of life; BOS vs. SIL

Intervention	N	Change from baseline score		Mean difference in change between the groups (95% CI); BOS vs. SIL
		Mean	(95% CI)	
BOS	12	6	-6 to 17	-22 (-35 to -9)
SIL	13	27	19 to 36	

In the SERAPH study quality of life after an observation period of 16 weeks was improved both in the bosentan group and in the sildenafil group; however, change from baseline score was statistically significant in the sildenafil group only.

From the above data it may be concluded that increase of the quality of life score assessed using the *Kansas City Cardiomyopathy Quality-of-Life* questionnaire was lower by 22 points in the bosentan group as compared to the sildenafil group. Mean difference in change from baseline score between the assessed therapeutic groups was -22 points (95% CI: -35 to -9; p = 0.002). The result was statistically significant. However, results need to be interpreted cautiously as above analysis was not intention-to-treat (one patient who died in sildenafil group was excluded).

3.7.4.3. Results of the 6-minute walk test

In the SERAPH clinical trial exercise capacity of the patients was assessed using the 6-minute walk test. The observation period with regard to this endpoint was 16 weeks.

Mean changes in exercise capacity from the baseline values in the bosentan group and the sildenafil group are presented below.

Table 129.
Results of the 6-minute walk test; BOS vs. SIL

Intervention	N	Baseline distance [m]		Change from baseline (SD) [m]		Mean difference in change between the groups (95% CI); BOS vs. SIL
		Mean	SD	Mean	95% CI	
BOS	12	304.6	74.1	59	29 to 89	-55 (-108 to -2)
SIL	13	290*	88.5*	114	67 to 160	

* Data for 14 patients in the sildenafil group

After 16 weeks of observation in both groups (bosentan and sildenafil) a statistically significant increase in exercise capacity assessed using the 6-minute walk test was noted.

Mean difference in change of this parameter between the therapeutic groups as calculated by the authors of the SERAPH study was -55 meters (95% CI: -108 to -2; p = 0.044), increase of the 6-minute walk distance was therefore lower by 55 meters in the bosentan group as compared to the sildenafil group. The result was statistically significant. The results need to be interpreted cautiously as above analysis was not intention-to-treat (one patient who died in sildenafil group was excluded).

3.7.4.4. Borg Dyspnea Score

Severity of dyspnea was assessed in the SERAPH study using the *Borg Dyspnea Score*, in which lower score reflects lower severity of the symptoms. The patients were observed for a period of 16 weeks.

Baseline scores and changes from baseline values in both therapeutic groups are presented in the table below.

Table 130.
Borg Dyspnea Score; BOS vs. SIL

Intervention	N	Baseline score		Change from baseline score		Mean difference in change between the groups (95% CI); BOS vs. SIL
		Mean	SD	Mean	95% CI	
BOS	12	3.7	1.6	0.2	-1.4 to 1.7	1.7 (-0.24 to 3.64)
SIL	13	4.8*	2.4*	-1.5	-3.0 to 0.0	

* Data for 14 patients in the sildenafil group

** Calculation based on available data

In an observation period of 16 weeks no statistically significant change from baseline value of the *Borg Dyspnea Score* was noted in any of the assessed therapeutic groups

Mean difference in change between the groups as calculated from the data presented in the SERAPH study is 1.7 points (95% CI: -0.24 to 3.64), in disfavor of bosentan. However, the result is not statistically significant. The results need to be interpreted cautiously as above analysis was not intention-to-treat (one patient who died in sildenafil group was excluded).

3.7.4.5. Cardiac index

Among the investigated hemodynamic parameters only cardiac index was assessed in the SERAPH study. The observation period was 16 weeks.

The table below presents mean baseline values of this parameter, changes from baseline and the difference in change between the bosentan group and the sildenafil group after 16 weeks of observation.

Table 131.
Mean values of cardiac index; BOS vs. SIL

Intervention	N	Baseline value [l/min/m^2]		Change from baseline [l/min/m^2]		Mean difference in change between the groups (95% CI); BOS vs. SIL
		Mean	SD	Mean	95% CI	
BOS	12	2.2	0.1	0.3	0.1 to 0.4	0 (-0.2 to 0.2)
SIL	13	2.3*	0.1*	0.3	0.1 to 0.4	

* Data for 14 patients in the sildenafil group

After 16 weeks of observation of patients with pulmonary arterial hypertension both in the bosentan group and in the sildenafil group cardiac index increased from baseline value by 0.3 l/min/m^2 and the result was statistically significant. No differences in this parameter were observed between the assessed groups. Mean difference of changes was 0 l/min/m^2 (95% CI: -0.2 to 0.2). The results need to be interpreted cautiously as above analysis was not intention-to-treat (one patient who died in sildenafil group was excluded).

3.7.5. Assessment of safety

In assessment of safety in the SERAPH study frequency of adverse events and necessity of unplanned hospitalizations, discontinuation of treatment or change of the dose of administered drugs were taken into account.

Numbers and percentages of patients, in whom specific events were observed during an observation period of 16 weeks, are presented below.

Table 132.
Assessment of safety; BOS vs. SIL

Parameter	BOS			SIL			Statistical significance of differences between the groups; BOS vs. SIL
	N	n	Percen-tage	N	n	Percen-tage	
All adverse events	12	3*	12%*	14	1*	7%*	n.s.
Palpitation	12	0	0%	14	1*	7%*	n.s.
Hemoptysis	12	1	8%*	14	0	0%	n.s.
Necessity of diuretic dose increase due to symptoms of fluid retention	12	2	17%*	14	0	0%	n.s.
Hepatic disorders	12	0	0%	14	0	0%	n.s.
Withdrawal from the study	12	0	0%	14	0	0%	n.s.
Necessity of hospitalization	12	3	12%*	14	0	0%	n.s.
Necessity of change in dosage of the investigated drugs	12	0	0%	14	0	0%	n.s.

* Calculation based on available data

In the SERAPH clinical trial frequency of adverse events and unplanned hospitalizations was slightly higher in the bosentan group as compared to the sildenafil group. The authors of the study observed no cases of hepatic disorders, withdrawal from the study or necessity of change in dosage of the investigated drugs in any of the assessed therapeutic groups.

The odds ratio for all adverse events assessed together is 4.33 (95% CI: 0.28 to 244.61); the odds of occurrence of any adverse event in the bosentan group is therefore 4.33 times higher than this odds in the SIL group; however, the result is not statistically significant.

The odds of occurrence of hemoptysis or necessity of increase of dose of diuretics due to symptoms of fluid retention is 8.73 and 9.55 times higher in the bosentan group than the respective odds in the sildenafil group; OR_{Peto} = 8.73 (95% CI: 0.17 to 445.08) for hemoptysis and OR_{Peto} = 9.55 (95% CI: 0.56 to 163.09) for diuretic dose increase. None of the results reached statistical significance.

The odds ratio for palpitation calculated using the *Peto* method is 0.16 (95% CI: 0.003 to 7.96), which means that the odds of occurrence of this endpoint in the bosentan group is 16% of this odds in the sildenafil group. However, the result is not statistically significant.

The odds of unplanned hospitalization in the bosentan group is 10.54 times higher as compared to the sildenafil group. The odds ratio calculated using the *Peto* method is 10.54 (95% CI: 0.99 to 112.35) and the result is not statistically significant.

3.8. Epoprostenol vs. iloprost

3.8.1. Results of search for the studies

Epoprostenol (EPO) was directly compared to iloprost (ILO) only in one randomized, cross-over study fulfilling the inclusion criteria: *Scott 1990*. The identified clinical trial was carried out in a single center. No blinding was used in the *Scott 1990* study and its *Jadad* credibility score was 2 points.

3.8.2. Description of the population

Patients participating in the *Scott 1990* study were those with severe primary pulmonary hypertension who did not respond to previous treatment with vasodilators and were qualified for cardiopulmonary transplantation. Patients with significant worsening of such symptoms as dyspnea and fatigue, classified in NYHA *(New York Heart Association)* II, III or IV functional class, were enrolled. In all patients pulmonary hypertension associated with other diseases was excluded by means of chest X-ray, ventilation-perfusion scintigraphy, pulmonary scintigraphy and heart catheterization. In none of the patients proximal obliteration of pulmonary arteries by thrombi was revealed by pulmonary scintigraphy or angiography.

Baseline characteristics of the patients enrolled in the *Scott 1990* study are presented below.

Table 133.
Baseline characteristics of the patients enrolled in the *Scott 1990* study; EPO vs. ILO

Parameter	Value
Number of patients	12
Mean age (SD) [years]	37.6 (11.1)
Percentage of men	50%*
Percentage of patients with primary PAH	100%*
Mean time from diagnosis (SD) [months]	33.5 (32.9)
Percentage of patients treated with vasodilators	100%

* Calculation based on available data

Twelve patients with primary PAH diagnosed 33.5 month prior to enrollment (on average) participated in the *Scott 1990* study; 50% of them were men and mean age was 37.6 years. All patients were treated with vasodilators and most of them received also diuretics and oral anticoagulants.

3.8.3. Description of the interventions

Participants of the *Scott 1990* study were randomly assigned to two therapeutic groups: epoprostenol (EPO) or iloprost (ILO). The patients usually received three doses of the assigned drug; after a pause of 15 minutes they were crossed over to the other group.

Both drugs were administered in intravenous infusion. The initial dose of epoprostenol was 2 ng/kg/min and was increased every 15 minutes by another 2 ng/kg/min. Iloprost was administered at an initial dose of 1.5 ng/kg/min. Every 15 minutes the dose was increased by another 1.5 ng/kg/min. Both epoprostenol and iloprost were administered until peripheral arterial pressure or pulmonary vascular resistance was reduced by 20% or adverse events were observed. Before each subsequent infusion of epoprostenol hemodynamic measurements were performed.

Mean maximum dose of EPO was 6 (SD = 2) ng/kg/min and that of ILO: 3.4 (SD = 1.8) ng/kg/min.

3.8.4. Analysis of efficacy

In the *Scott 1990* study only hemodynamic parameters (i.e. secondary endpoints) were evaluated, including mean pulmonary artery pressure, mean pulmonary vascular resistance, cardiac index and arterial blood oxygen saturation. Efficacy of the drugs was assessed after discontinuation of treatment with anticoagulants. All patients were fasting for 8 hours before catheterization and were administered intravenous diazepam at a dose of 5-10 mg. The observation period was 45 minutes.

Detailed results are presented in the table below.

Table 134.
Mean values of hemodynamic parameters; EPO vs. ILO

Parameter	Intervention	N	Baseline value		Final value		Mean difference between the groups (95% CI); EPO vs. ILO
			Mean	SD	Mean	SD	
Mean pulmonary artery pressure [mmHg]	EPO	12	67.6	13.8	63.8	18.0	0.8 (-12.07 to 13.67)*
	ILO	12			63.0	13.9	
Pulmonary vascular resistance [mmHg/min/l]	EPO	12	17.1	6.5	12.5	6.0	-0.7 (-5.5 to 4.1)*
	ILO	12			13.2	6.0	
Cardiac index [l/min/m^2]	EPO	12	1.9	0.7	2.8	0.7	0.3 (-0.26 to 0.86)*
	ILO	12			2.5	0.7	
Arterial blood oxygen saturation [%]	EPO	12	57.1	8.1	63.3	7.2	-3.2 (-8.1 to 1.7)*
	ILO	12			66.5	4.8	

* Calculation based on available data

In both therapeutic groups values of mean pulmonary artery pressure and pulmonary vascular resistance after 45 minutes of treatment were lower than baseline values.

Difference in final values of mean pulmonary artery pressure between the groups was 0.8 mmHg (95% CI: -12.07 to 13.67), in disfavor of epoprostenol; the result is not statistically significant.

Mean difference in pulmonary vascular resistance between the groups (EPO and ILO) was -0.7 mmHg/l/min (95% CI: -5.5 to 4.1), i.e. the value was lower by 0.7 mmHg in the epoprostenol group as compared to the iloprost group; however, the result is not statistically significant.

Mean value of cardiac index was higher by 0.3 l/min/m^2 in the epoprostenol group as compared to the iloprost group. Mean difference was 0.3 l/min/m^2 (95% CI: -0.26 to 0.86) and the result is not statistically significant.

After 45 minutes of treatment arterial blood oxygen saturation was lower by 3.2 p.p. in the EPO group as compared to the ILO group. Mean difference in final values of this parameter was -3.2 p.p. (95% CI: -8.1 to 1.7). The result did not reach statistical significance.

3.8.5. Assessment of safety

The authors of the *Scott 1990* study reported the number of patients, in whom adverse events were observed during treatment with epoprostenol or iloprost.
Numbers and percentages of patients, in whom adverse events were observed during 45 minutes of treatment, are presented below.

Table 135.
Assessment of safety; EPO vs. ILO

Parameter	EPO			ILO			Statistical significance of differences between the groups; EPO vs. ILO
	N	n	Percen-tage	N	n	Percen-tage	
Headache	12	3	25%*	12	2	17%*	n.s.*
Abdominal pain	12	1	8%*	12	0	0%	n.s.*
Vomiting	12	0	0%	12	1	8%*	n.s.*

* Calculation based on available data

The *Peto* odds ratio for headache is 1.62 (0.24 to 11.17), which means that the odds of occurrence of this adverse event is higher in the epoprostenol group and is 162% of this odds in the iloprost group. The result is not statistically significant.

The odds ratio calculated using the *Peto* method for abdominal pain is 7.39 (95% CI: 0.15 to 372.38); the odds of occurrence of this endpoint is therefore 7.39 times higher in the epoprostenol group as compared to the iloprost group and the result is not statistically significant.

The odds of occurrence of vomiting is lower in the EPO group and is 14% of this odds in the ILO group; OR_{Peto} = 0.14 (95% CI: 0.003 to 6.82). The result is not statistically significant.

4. DISCUSSION AND LIMITATIONS

Available data

The analysis of efficacy and safety of bosentan, epoprostenol, iloprost, sildenafil and treprostinil in treatment of pulmonary arterial hypertension was based on the results of 19 randomized, controlled clinical studies. The observation period ranged from 45 minutes to 28 weeks.

Adult patients with primary PAH or PAH associated with other diseases (most often with connective tissue diseases) constituted the largest group of patients in the analyzed studies. For three comparisons the number of patients ranged from 12 to 42 (epoprostenol vs. iloprost, bosentan vs. sildenafil, sildenafil vs. placebo in children) and for the others – from 215 to 495. One of the studies included fetuses in the 3rd trimester and newborns up to three days of age.

Credibility of the clinical trials included in the analysis as assessed using the 5-point Jadad scale ranged from 2 to 5 points.

Methods applied and results obtained

Analysis of efficacy and safety was carried out according to "Guidelines on Health Technology Assessment (HTA)". At first the analysis included primary clinical studies taken into consideration in three credible systematic reviews *(Kanthapillai 2004, Paramonthayan 2005, Liu 2006),* to which other primary clinical studies published after the final search dates reported in those reviews were then added.

The most important health-related effects evaluated in the clinical trials included in the analysis were: mortality, quality of life, effect of the treatment on exercise capacity, change of severity of dyspnea and assessment of safety.

Effect of the applied treatment on mortality was assessed in all comparisons excepting epoprostenol vs. iloprost. Performed metaanalyses made it possible to conclude that only for the comparisons of epoprostenol vs. placebo in patients with primary PAH and sildenafil vs. placebo in children the results were statistically significant and confirmed reduction of mortality as a result of use of the investigated drug.

Quality of life was evaluated in 5 studies for 5 compared therapies: two of them concerned adult patients with primary PAH (epoprostenol vs. placebo *(Barst 1996)* and sildenafil vs. placebo *(Sastry 2004))*, while the other comparisons pertained to patients with PAH of various etiology (iloprost vs. placebo *(Olschewski 2002)*, treprostinil vs. placebo *(Simonneau 2002)* and bosentan vs. sildenafil *(SERAPH)).* The authors of the studies used 4 different questionnaires for assessment of quality of life. For patients with primary PAH treated with epoprostenol or sildenafil statistically significant improvement with respect to some of the evaluated aspects, such as dyspnea, emotional reaction, sleep and fatigue, were demonstrated in comparison with placebo. In the studies comparing iloprost or treprostinil to placebo, patients with various types of PAH were enrolled. Statistically significantly higher improvement was demonstrated for treprostinil vs. placebo only for the part related to physical condition, while differences between the groups with respect to global result were not statistically significant. In the SERAPH trial, comparing bosentan with sildenafil, it was demonstrated that the effect of sildenafil on the assessed parameter is higher than that of bosentan.

Influence of the treatment on exercise capacity was evaluated in 15 clinical studies pertaining to 6 comparisons. Exercise capacity was not assessed for the comparison of sildenafil vs. placebo in children and epoprostenol vs. iloprost. The assessment was carried out by various means: the NYHA/WHO functional classification (in 11 studies), the 6-minute walk test (13 studies) and the treadmill test (2 studies). In the population of patients with various types of PAH statistically significantly higher improvement in exercise capacity was demonstrated for bosentan, iloprost, sildenafil and treprostinil as compared to placebo. In some studies analysis in subgroups was also performed. In patients with primary PAH treatment with iloprost or epoprostenol proved significantly more efficacious than placebo, while in patients with PAH associated with connective tissue diseases the same effect was demonstrated for epoprostenol. In addition, in the *SERAPH* study, also concerning PAH associated with connective tissue diseases, higher efficacy of sildenafil as compared to bosentan was demonstrated.

Change in severity of dyspnea was analyzed in 11 studies concerning 6 comparisons. This endpoint was not assessed only for the following comparisons: sildenafil vs. placebo in children and epoprostenol vs. iloprost. Assessment of dyspnea was performed using the Borg Dyspnea Score, the Dyspnea – Fatigue Rating and the Mahler Dyspnea Index. Statistically significantly higher reduction of dyspnea was demonstrated for treatment with epoprostenol, iloprost and treprostinil; for the comparison of treprostinil vs. placebo in a subgroup of patients with primary PAH no difference in efficacy was found between the assessed groups. Similarly, no significant differences in reduction of dyspnea were demonstrated between the groups for the comparison of bosentan vs. placebo, while the comparison of sildenafil vs. placebo in adult patients produced ambiguous results (in the *Bharani 2003* study statistically significantly higher reduction of dyspnea was observed in the sildenafil group as compared to the placebo group, while in the *SUPER 1* study the results were the opposite). No statistically significant difference in reduction of severity of dyspnea was demonstrated between bosentan and sildenafil.

Assessment of safety was carried out for all the comparisons excepting sildenafil vs. placebo in children, due to a short observation period. No statistically significant differences between the bosentan or sildenafil group and the placebo group were demonstrated with respect to incidence of adverse events in adult patients; for the comparisons of epoprostenol, iloprost or treprostinil vs. placebo some adverse events were observed statistically significantly more often in the experimental groups than in the control groups. In patients treated with epoprostenol the incidence of jaw pain, diarrhea and nausea was significantly higher than in patients receiving placebo. In the studies comparing iloprost with placebo serious syncope, flushing and jaw pain occurred statistically significantly more often in the experimental group, while for the comparison of treprostinil vs. placebo the same applied to diarrhea, jaw pain, flushing, edema and local reactions related to drug administration, i.e. reaction, hematoma or induration at the injection site.

In the studies comparing bosentan with sildenafil and epoprostenol with iloprost no statistically significant differences in incidence of adverse events were found. It should be noted that 4 drug manufacturers (Actelion, GlaxoSmithKline, Pfizer, United Therapeutics Corporation) presented their respective *Periodic Safety Update Reports;* however, these data are deemed confidential and therefore are not included in this analysis. Access to these reports is granted to the Consultation Board of the Agency for Health Technology Assessment in Poland, which prepares recommendations for the Minister of Health.

Identified limitations and their effect on interpretation of the results
The most important limitations of identified evidence may be related to the number and

baseline characteristics of the patients enrolled in some studies, used therapeutic doses of the investigated drugs, evaluated endpoints, various credibility of the studies as well as relatively short observation periods.

In many of the studies included in the analysis patients with PAH of various etiology were enrolled without subsequent analysis in subgroups. Moreover, only 2 of the identified studies with very short observation periods pertained to children (a total number of 42 children) and in one of them *(Baquero 2006)* fetuses were also included.

Three comparisons (sildenafil vs. placebo in children, bosentan vs. sildenafil, epoprostenol vs. iloprost) were based on studies, in which a small number of patients participated (12, 26 and 42 patients, respectively), which may limit their external validity and therefore make it difficult to demonstrate superiority of one of the drugs or to generalize the conclusions of the analysis for the whole population concerned (e.g. children), in which a given treatment may be possibly used.

It should be also noted that different doses of the drugs were used in particular studies (this is true for treprostinil, sildenafil, iloprost and epoprostenol) and that doses or pharmaceutical forms of drugs used in some studies differed from those registered by EMEA (for sildenafil and iloprost).

Various and relatively short periods of observation (from ca. 1 hour to 28 weeks) may constitute another serious limitation, making it difficult, or in some cases impossible, to assess one of the most important health-related outcomes, i.e. mortality. It should be noted that some authors regard exercise capacity as an important prognostic parameter, especially in idiopathic pulmonary hypertension. This endpoint was evaluated (using the NYHA/WHO functional classification or the 6-minute walk test) for 6 of the compared therapeutic options. However, demonstration of a relation between mortality and exercise capacity would require a separate analysis, which in turn is not an objective of this report.

The studies included in efficacy and safety analysis are of various credibility as evaluated using the Jadad scale. The main cause of lower credibility was lack of double-blind design, which may result in insufficient elimination of potential confounders. Six (out of 19) clinical trials were not double-blind *(Barst 2006, Rubin 1990, Barst 1996, Badesch 2000, Olschewski 2002, Scott 1990).* Moreover, in 2 studies no information was provided as to patients lost from the study *(Singh 2006, Scott 1990)* and in 8 studies the method of randomization was not described *(Rubin 2002, Barst 1996, Thurm 1991, Olschewski 2002, Bharani 2003, Singh 2006, McLaughin 2003, Scott 1990).*

No therapeutic options related to combination treatment (i.e. simultaneous use of two or more drugs) were taken into consideration in this analysis. This decision was consistent with the application of the Minister of Health, which pertained to monotherapy only, as well as with "Guidelines on diagnostics and treatment of pulmonary arterial hypertension" (2005) of the European Society of Cardiology, in which such therapy is considered a relatively new option.

Obtained results as compared with other analyses concerning the same problem

Three credible systematic reviews pertaining to the problem of treatment of pulmonary arterial hypertension were identified:

1. Liu C, Chen J., *"Endothelin receptor antagonists for pulmonary arterial hypertension"*, Cochrane Database of Systematic Reviews 2006,
2. Paramothayan NS, Lasserson TJ, Wells AU, Walters EH *"Prostacyclin for pulmonary hypertension in adults"*, Cochrane Database of Systematic Reviews 2005

3. Kanthapillai P, Lasserson TJ, Walters EH, *"Sildenafil for pulmonary hypertension"*, Cochrane Database of Systematic Reviews 2004

In the systematic review of *Liu 2006* efficacy and safety of the whole group of endothelin receptor antagonists (to which, among others, bosentan belongs) was evaluated. Both in this analysis and in the review mentioned above positive effect of treatment on exercise capacity (as measured using the 6-minute walk test or the NYHA classification) was demonstrated along with no effect on mortality (mainly due to a short observation period) and no statistically significant difference in incidence of adverse events as compared to placebo. The results for assessment of reduction of severity of dyspnea as measured using the Borg Dyspnea Score were different: in the *Liu 2006* review statistically significantly higher reduction of this parameter was noted for treatment with bosentan as compared to placebo; however, this result was obtained for the whole group of patients, treated with a dose of 125 or 250 mg twice daily, while in this analysis treatment effects for the registered dose (125 mg twice daily) were assessed and found statistically insignificant.

In the systematic review of *Paramothayan 2005* drugs classified as prostacyclins were evaluated: epoprostenol, iloprost, treprostinil and beraprost, of which beraprost was not included in this analysis. For the remaining three drugs in both reports the same studies were taken into account and similar endpoints were assessed. In both analyses treatment with epoprostenol, iloprost or treprostinil was found to have no significant effect on mortality, while statistically significantly higher improvement in exercise capacity and decrease of severity of dyspnea as compared to placebo (assessed in a mixed group of patients) was demonstrated, especially for therapy with inhaled iloprost and epoprostenol. Analyzes performed in the *Paramothayan 2005* review made it possible to conclude that treatment with treprostinil results in no statistically significant change in exercise capacity or severity of dyspnea in patients with primary PAH, which is consistent with the results of this analysis. In both reviews statistically significantly higher improvement in quality of life was demonstrated for treatments with epoprostenol and iloprost as compared to placebo. For group treated with treprostinil no significant improvement in this parameter was found as compared to control group.

In the review of *Kanthapillai 2004*, in which (among others) efficacy of sildenafil was compared to that of placebo, 2 studies were taken into account, both with a small number of participants and a short observation period (two other studies pertained to other comparisons). In that report statistically significantly higher improvement in two aspects of quality of life (dyspnea and fatigue) as well as in exercise capacity as measured using the 6-minute walk test and reduction of dyspnea were noted in the group treated with sildenafil as compared to placebo. Efficacy of sildenafil with respect to reclassification into a lower NYHA class or improvement in emotional function (being a part of assessment of quality of life) was not demonstrated. In this analysis another 2 later studies were taken into account, including one large multicenter double-blind study (SUPER-1). In contrast to conclusions of the *Kanthapillai 2004* review, in this analysis statistically significant differences in efficacy were noted between sildenafil and placebo with respect to improvement in exercise capacity according to the NYHA/WHO classification, while no difference in reduction of dyspnea was found.

Another systematic review, i.e. Shah PS, Ohlsson A. „*Sildenafil for pulmonary hypertension in neonates*" *Cochrane Database of Systematic Reviews 2007*, published in July 2007, should also be taken into consideration. Two small randomized studies with short observation periods (42 and 72 hours) were taken into account in that review: *Baquero 2006* and *Herrea 2006*, of which the latter was available only in abstract form. Higher efficacy of sildenafil as compared

to the control group was demonstrated in that review with respect to mortality and improvement in arterial blood oxygen saturation, which is consistent with this analysis. Nevertheless, further studies are required in order to establish optimal dosage of the drug and assess safety as well as compare sildenafil with other pulmonary vasodilators; long term observation of children with respect to neurological development is also necessary.

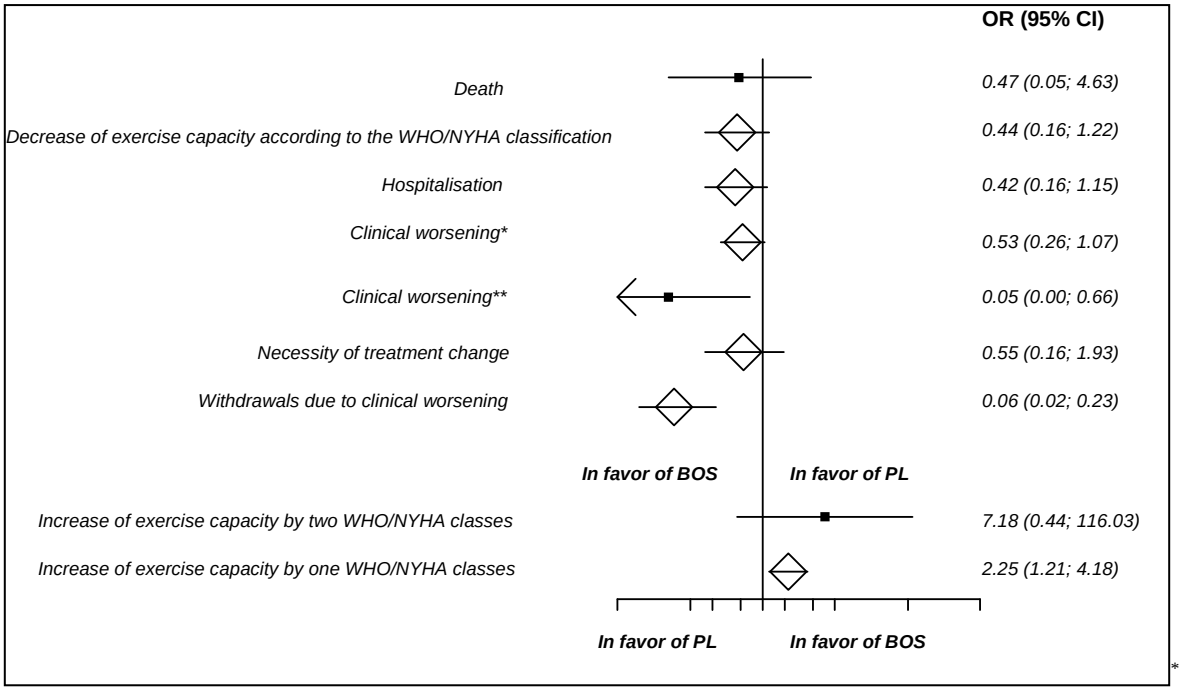
It should also be noted that the *National Institute for Health and Clinical Excellence* (NICE) is currently preparing a report titled *"Drugs for the treatment of pulmonary arterial hypertension"*, scheduled for publication in April 2008.

It should be taken into consideration the initial completion date of the report (that is 2007) and the possibility of an appearance of new evidence in this area and changes in drug licenses.

5. FINAL CONCLUSIONS

Bosentan vs. placebo

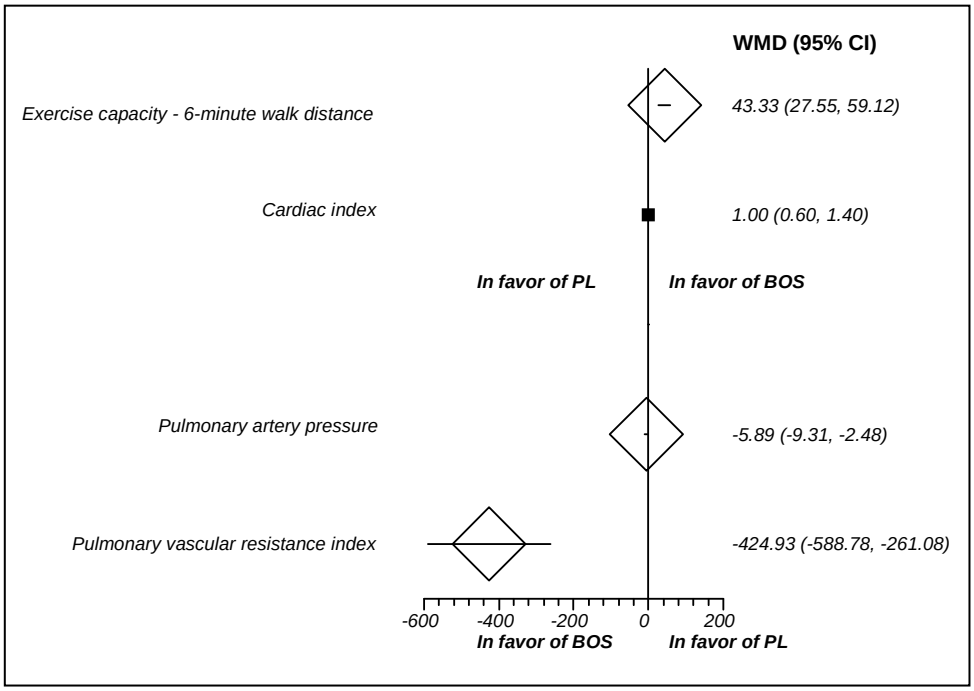
Analysis of bosentan vs. placebo was based on 4 multicenter randomized trials, in which a total number of 408 patients with pulmonary arterial hypertension were enrolled, of whom 249 patients were randomized to receive bosentan and 159 patients – placebo.



* Clinical worsening defined as death, necessity of pulmonary transplantation, hospitalization due to PAH, necessity of introduction of additional treatment and/or lack of clinical improvement, exacerbation of the symptoms resulting in the patient's withdrawal from the study or atrial septostomy.

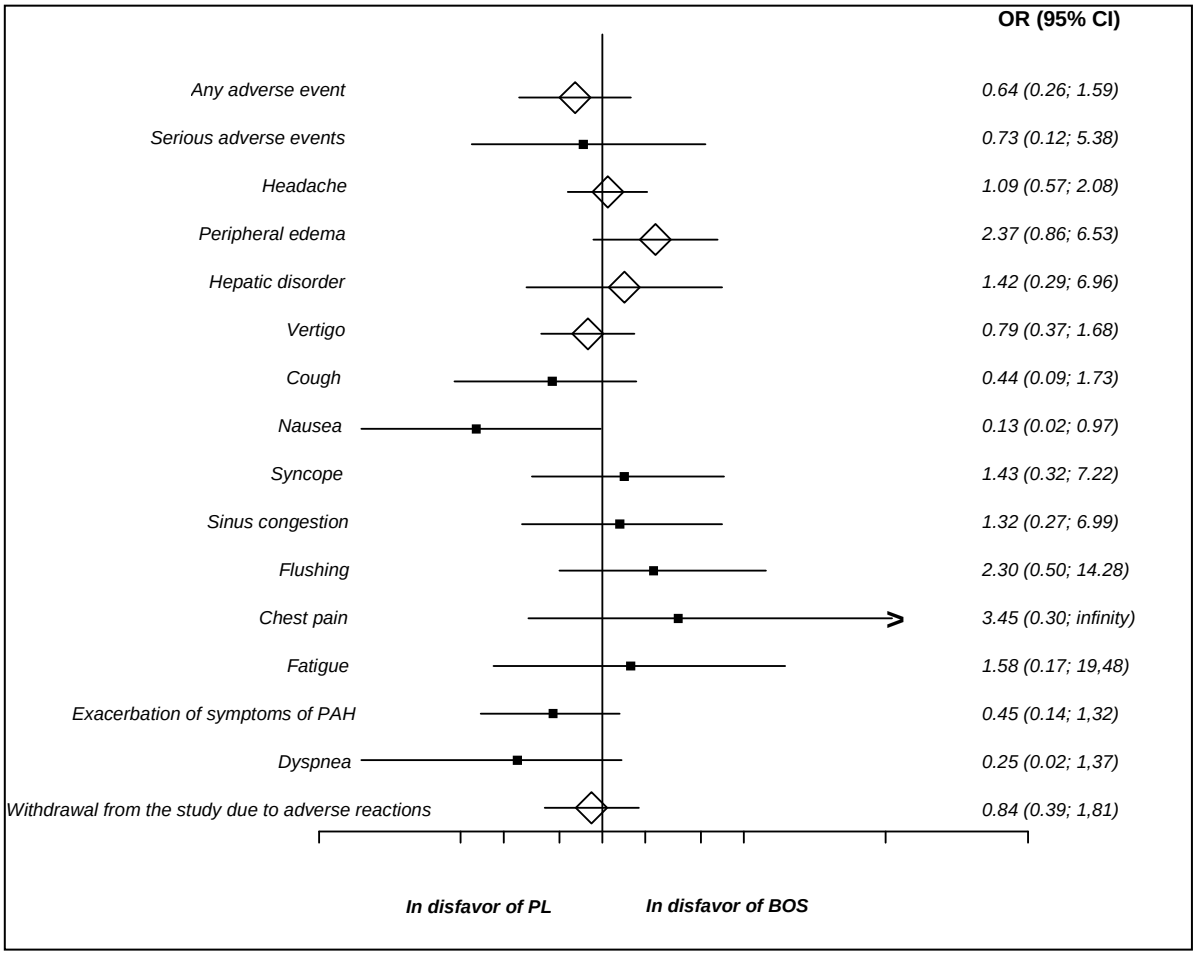
** Clinical worsening defined as development of right ventricular failure or exacerbation of the symptoms of PAH.

In this analysis statistically significant differences were noted between the bosentan group and the placebo group in an observation period of 12-18 weeks with respect to increase of exercise capacity by one WHO/NYHA class, defined as reclassification of the patient from functional class III to class II. The odds of occurrence of this endpoint was 2.25 times higher in the bosentan group as compared to the placebo group. The odds ratio is 2.25 (95% CI: 1.21 to 4.18) and the NNT is 7 (95% CI: 4 to 21). No significant differences between the assessed therapeutic groups were demonstrated with respect to increase of exercise capacity by two functional classes or decrease of exercise capacity according to the WHO/NYHA classification, or with respect to mortality, frequency of hospitalization, clinical worsening (defined as death, necessity of pulmonary transplantation, hospitalization due to PAH, necessity of introduction of additional treatment and/or lack of clinical improvement, exacerbation of the symptoms resulting in the patient's withdrawal from the study or atrial septostomy) and necessity of treatment change.



Mean difference in change of exercise capacity (evaluated using the 6-minute walk test) was 43.33 m (95% CI: 27.55 to 59.12) in an observation period of 16-28 weeks. Increase of exercise capacity is therefore higher by 43.33 meters in patients treated with bosentan as compared to those receiving placebo. The result is statistically significant. No significant differences between the assessed therapeutic groups were noted with respect to severity of dyspnea, which in the included studies was assessed using the Borg Dyspnea Score.

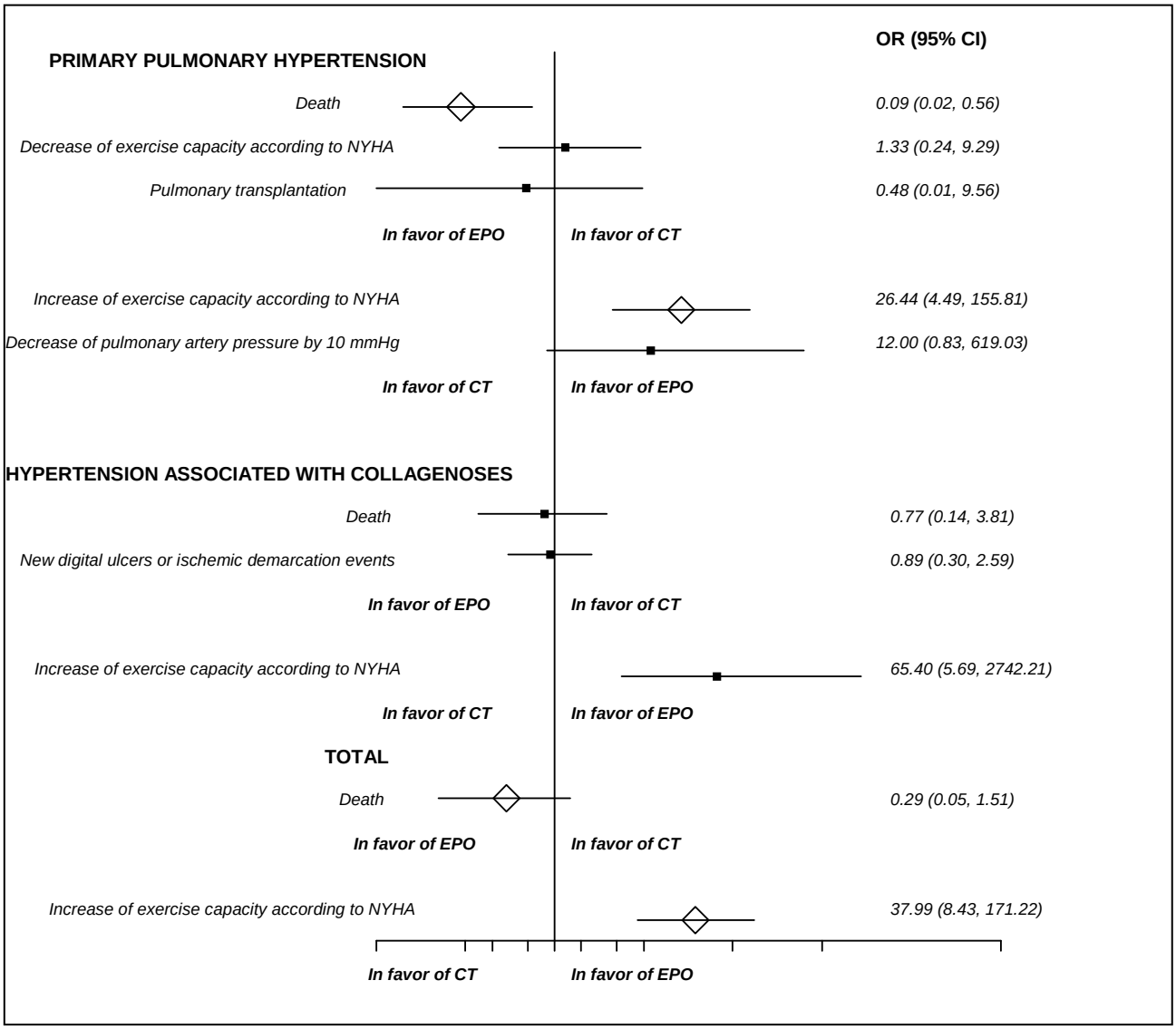
However, there is a statistically significant difference between the assessed groups in favor of bosentan with respect to effect on hemodynamic parameters. Weighted mean difference in change of pulmonary artery pressure between the bosentan group and the placebo group is 5.89 mmHg (95% CI: -9.31 to -2.48), while that in pulmonary vascular resistance index is 424.93 dyn*s*cm^{-5} (95% CI: -588.78 to -261.08). Mean difference in change of cardiac index calculated from the results of a single clinical trial is 1.00 (95% CI: 0.60 to 1.40), in favor of the bosentan group.



Assessment of safety of bosentan as compared to placebo demonstrated no statistically significant differences with respect to serious adverse events or all adverse events evaluated together, including vertigo, cough, syncope, sinus congestion, flushing, chest pain, fatigue, exacerbation of symptoms of PAH, dyspnea and withdrawal due to adverse events. The odds of occurrence of nausea in the group treated with BOS is 13% of this odds in the PL group, and the result is statistically significant.

Epoprostenol vs. placebo

In searched medical databases three primary randomized clinical studies fulfilling the inclusion criteria were identified, in which epoprostenol used in combination with conventional treatment (EPO) was compared to conventional treatment alone (CT) in patients with pulmonary arterial hypertension (N = 215). As a part of sensitivity analysis separate metaanalyses were performed for the whole population of patients and for two subgroups: patients with primary PAH (2 studies; N = 104) and those with PAH associated with collagenoses (1 study; N = 111).

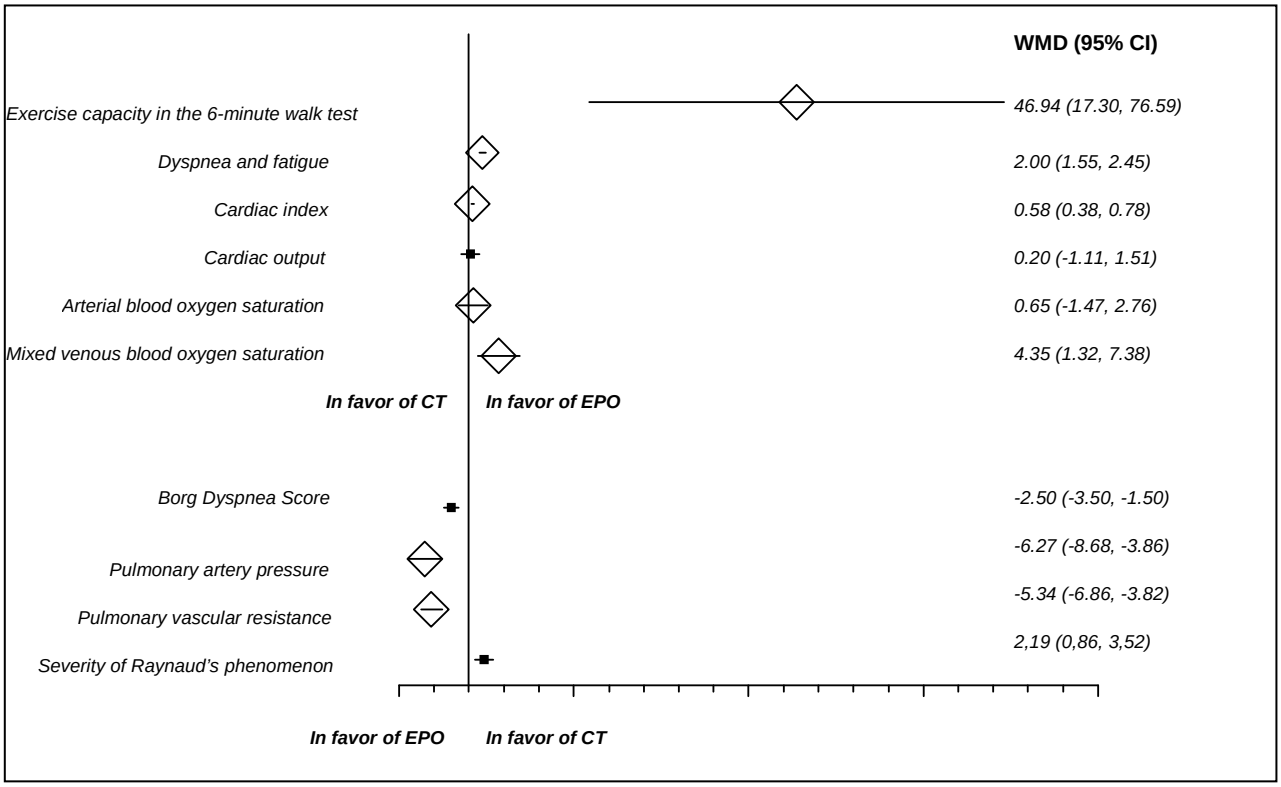


From this metaanalysis it may be concluded that for patients with primary PAH the odds of death in an observation period of 8-12 weeks was lower in the group of epoprostenol in combination with conventional treatment and was 9% of this odds in the group of conventional treatment alone. The result is statistically significant; OR = 0.09 (95% CI: 0.02 to 0.56); NNT = 5 (95% CI: 4 to 13). No statistically significant differences between the groups with respect to this endpoint were demonstrated for the population of patients with PAH associated with connective tissue diseases or for the whole population of patients.

In one of the clinical trials statistically significant improvement in quality of life assessed using the *Chronic Heart Failure Questionnaire* (in which higher score reflects improved quality of life) was demonstrated in patients with primary PAH. After an observation period of 12 weeks the difference in median values between the assessed groups was 7.0 points (95% CI: 4.0 to 10.0) for dyspnea, 5.0 points (95% CI: 3.0 to 7.0) for fatigue, 7.0 points (95% CI: 3.0; 10.0) for emotional function and 2.5 points (95% CI: 1.0 to 4.0) for control of the symptoms, in favor of the group receiving epoprostenol and conventional treatment. Quality of life assessed using the *Nottingham Health Profile* questionnaire, in which lower score represents higher quality of life, was statistically significantly improved in two out of six areas. Difference in median values between the groups was -14.7 points (95% CI: -24.5 to -4.9) for emotional reaction and -21.7 points (95% CI: -34.3 to -9.1) for sleep in favor of the EPO group.

The odds of increase of exercise capacity according to the NYHA *(New York Heart Association)* classification (i.e. of reclassification into a lower NYHA class) in the whole population of patients was nearly 38 times higher in the group receiving epoprostenol with conventional treatment as compared to the group of conventional treatment alone; OR = 37.99 (95% CI: 8.43; 171.22); NNT = 3 (95% CI: 2 to 4). For patients with primary PAH the odds ratio is 26.44 (95% CI: 4.49 to 155.81); NNT = 3 (95% CI: 2 to 4) and for patients with PAH associated with collagenoses: OR = 65.40 (95% CI: 5.69 to 2742.21); NNT = 3 (95% CI: 2 to 4). It means that the odds of improvement in exercise capacity according to the NYHA classification in the group of epoprostenol with conventional treatment was 26.44 and 65.40 times higher than the respective odds in the group of conventional treatment alone. The results are statistically significant.

No statistically significant differences between the assessed groups were demonstrated with respect to frequency of pulmonary transplantation or new digital ulcers or ischemic demarcation events. From the results of a single study it was estimated that in patients with PAH associated with collagenoses severity of *Raynaud's* phenomenon was higher by 2.19 points (95% CI: 0.86 to 3.52) in the epoprostenol group as compared to the conventional treatment group. The result is statistically significant.

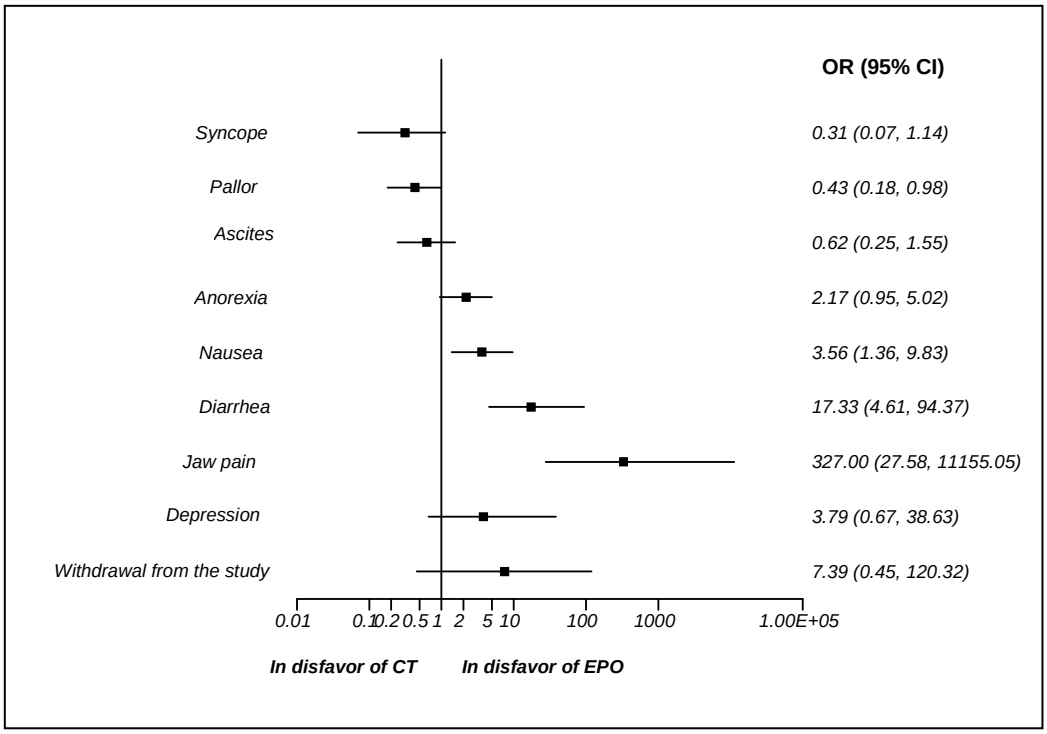


Weighted mean difference in change of the 6-minute walk distance for patients with primary PAH was 46.94 m (95% CI: 17.30 to 76.59), in favor of the group of epoprostenol with conventional treatment. The result was statistically significant. In patients with PAH associated with connective tissue diseases the difference between the median final values of this parameter was 108 m (95% CI: 55.2 to 180.0); the 6-minute walk distance after 12 weeks of observation was therefore longer by 108 m in the group of epoprostenol and conventional treatment as compared to conventional treatment alone.

Statistically significantly higher reduction of dyspnea and fatigue estimated in two clinical trials and dyspnea assessed using the Borg Dyspnea Score in one study also favor the epoprostenol group. Weighted mean difference in change of the score was 2 points (95% CI:

1.55 to 2.45) and 2.5 points (95% CI: -3.5 to -1.5), respectively, in favor of the group of epoprostenol in combination with conventional treatment.

In performed analysis statistically significantly higher improvement in hemodynamic parameters, such as pulmonary artery pressure, pulmonary vascular resistance and cardiac index, was demonstrated in the group of epoprostenol and conventional treatment. For the whole population of patients weighted mean difference in change of pulmonary artery pressure is -6.27 mmHg (95% CI: -8.68 to -3.86), that of pulmonary vascular resistance: -5.34 mmHg/l/min (95% CI: -6.86 to -3.82) and that of cardiac index: 0.58 l/min/m^2 (95% CI: 0.38 to 0.78). For mixed venous blood oxygen saturation the result reached statistical significance for the whole population of patients: WMD = 4.35 p.p. (95% CI: 1.32 to 7.38) and for the population of patients with PAH associated with collagenoses: WMD = 4.69 p.p. (95% CI: 0.94 to 8.30). Weighted mean difference in change of this parameter is not statistically significant for patients with primary PAH; neither is mean difference in cardiac output in patients with primary PAH (evaluated from the results of a single study) nor arterial blood oxygen saturation, regardless of the population of patients.



In safety assessment no significant differences between the therapeutic groups were found with respect to frequency of withdrawal from the study or the following adverse events: syncope, ascites, anorexia or depression. The odds of occurrence of pallor was lower in the group of epoprostenol and conventional treatment and was 43% of this odds in the group of conventional treatment alone; OR = 0.43 (95% CI: 0.18 to 0.98), NNT = 5 (95% CI: 3 to 48).

The odds of occurrence of nausea, diarrhea or jaw pain was found to be higher in the group of epoprostenol and conventional treatment as compared to the group of conventional treatment alone; OR = 3.56 (95% CI: 1.36 to 9.83); NNH = 5 (95% CI: 3 to 13) for nausea, OR = 17.33 (95% CI: 4.61 to 94.37); NNH = 3 (95% CI: 2 to 4) for diarrhea and OR=327.00 (95% CI: 27.58 to 11155.05), NNH = 2 (95% CI: 2 to 2) for jaw pain. The results are statistically significant.

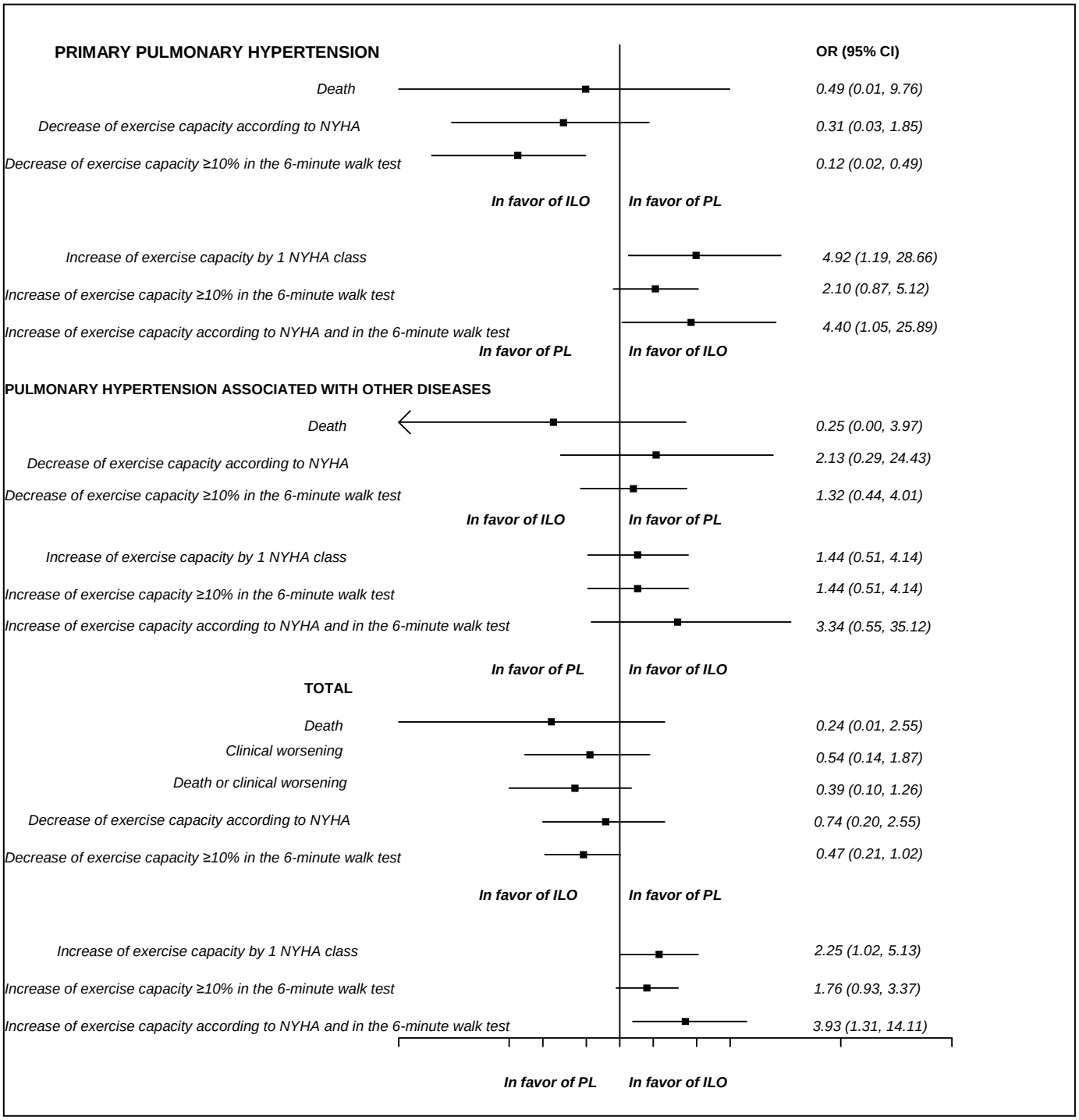
Iloprost vs. placebo

In comparative analysis of efficacy and safety of iloprost vs. placebo in patients with PAH only two randomized clinical trials were taken into account, of which only one allowed for assessment of primary endpoints; all patients in that study received oral vasodilators in addition to the assigned treatment. The analysis included a total number of 216 patients: 107 assigned to the iloprost group and 109 in the placebo group.

The analysis of efficacy after 12 weeks of observation demonstrated statistically significantly higher increase of exercise capacity in the iloprost group as compared to the placebo group; for the odds of improvement by one NYHA functional class in the population of patients with primary PAH OR = 4.92 (95% CI: 1.19 to 28.66), NNT = 6 (95% CI: 4 to 24) and for the whole population OR = 2.25 (95% CI: 1.02 to 5.13), NNT = 9 (95% CI: 5 to 79). For patients with PAH associated with other diseases no statistically significant differences between the therapeutic groups with regard to this endpoint were demonstrated.

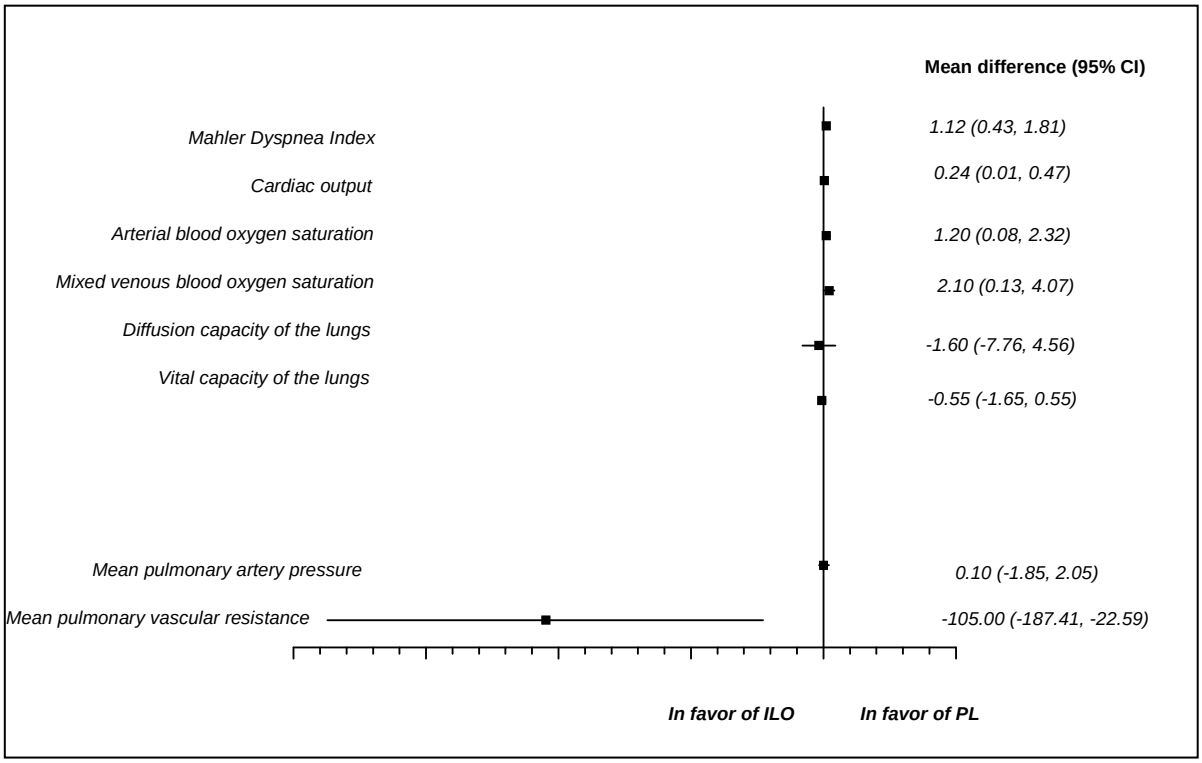
After an observation period of 12 weeks the odds of reduction of exercise capacity (measured using the 6-minute walk test) by at least 10% for patients with primary PAH in the iloprost group was 12% of this odds in the placebo group; OR = 0.12 (95% CI: 0.02 to 0.49); NNT = 4 (95% CI: 3 to 8) and the result was statistically significant. No significant differences between the iloprost group and the placebo group with respect to occurrence of reduction of exercise capacity (measured using the 6-minute walk test) by at least 10% were found for patients with PAH associated with other diseases or the whole population of patients.

For the composite endpoint of increase of exercise capacity according to the NYHA classification and as measured by the 6-minute walk test it was demonstrated that the odds of occurrence of this endpoint in the iloprost group after 12 weeks of observation was 4.40 times higher for patients with primary PAH and 3.93 times higher for the whole population of patients as compared to the placebo group. For patients with primary PAH OR = 4.40 (95% CI: 1.05 to 25.89), NNT = 7 (95% CI: 4 to 41) and for the whole population OR = 3.93 (95% CI: 1.31 to 14.11), NNT = 9 (95% CI: 5 to 28). The results were statistically significant. For patients with PAH associated with other diseases no significant differences between the assessed therapeutic groups were demonstrated.



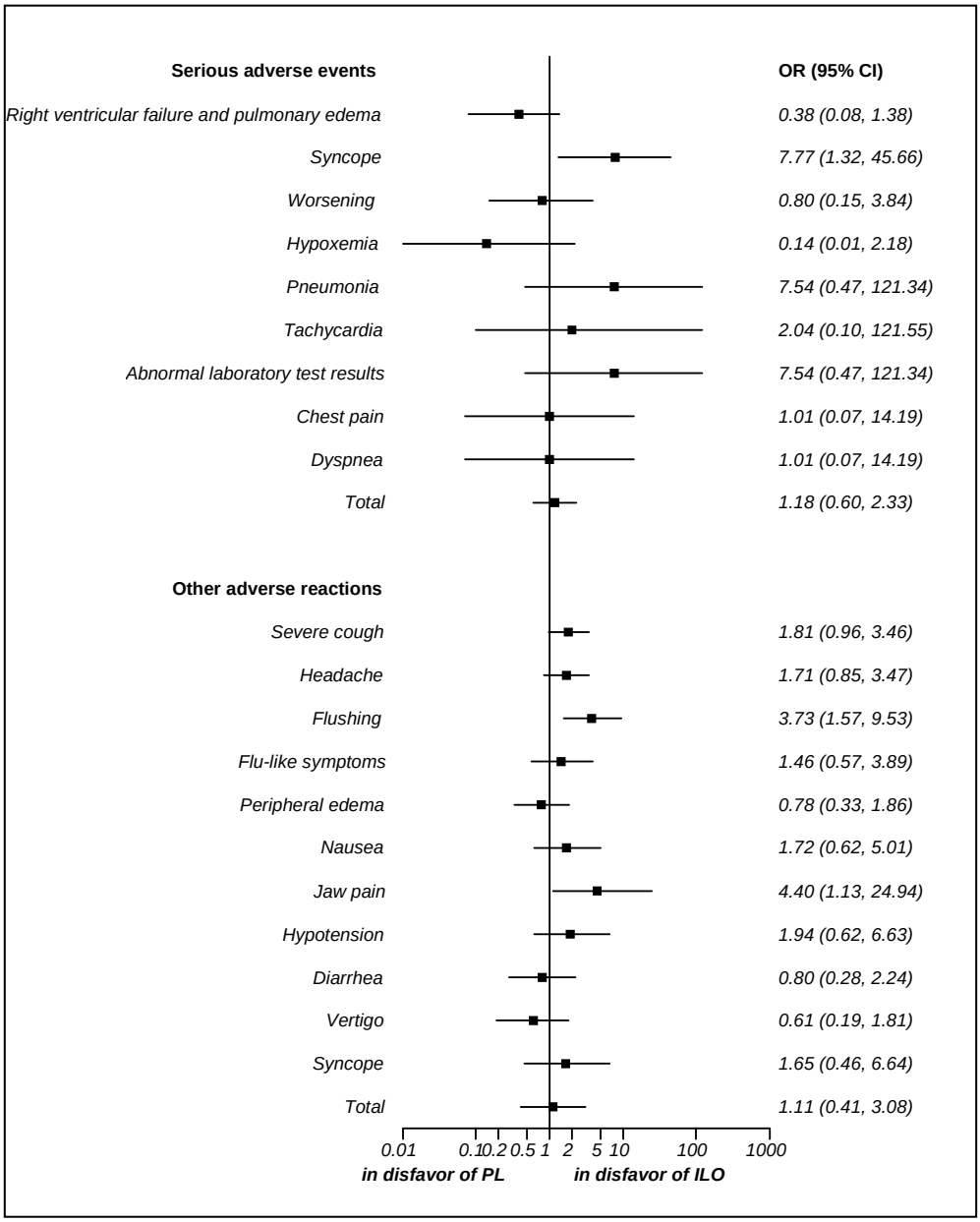
Mean difference in change of the score for dyspnea (the Mahler Dyspnea Index) for the whole population of patients was 1.12 points (95% CI: 0.43 to 1.81), in favor of the iloprost group. The result was statistically significant.

No statistically significant differences between the assessed groups were found with regard to the following endpoints: death, exacerbation of symptoms of the disease, improvement in exercise capacity by two NYHA functional classes, decrease of exercise capacity according to the NYHA classification or increase of exercise capacity by at least 10%. In the analyzed clinical trial no pulmonary transplantation was necessary in any of the patients with pulmonary hypertension observed for 12 weeks.



In the whole population of patients statistically significant improvement in values of hemodynamic parameters measured before inhalation (i.e. mean difference in change of pulmonary vascular resistance, cardiac output, arterial blood oxygen saturation and mixed venous blood oxygen saturation) was also observed. Mean difference in change was -105.00 dyn · s · cm^{-5} (95% CI: -187.41 to -22.59) for pulmonary vascular resistance, 0.24 l/min (95% CI: 0.01 to 0.47) for cardiac output, 120 p.p. (95% CI: 8; 232) for arterial blood oxygen saturation and 210 p.p. (95% CI: 13 to 407) for mixed venous blood oxygen saturation. No statistically significant differences were found between the iloprost group and the placebo group with respect to mean difference in change of mean pulmonary artery pressure. The differences between the therapeutic groups were also not significant for such parameters as vital capacity and diffusion capacity of the lungs.

Quality of life assessed with the *EuroQol* questionnaire improved after 12 weeks of observation of patients with PAH in the iloprost group and remained the same in the placebo group. No statistically significant difference between the assessed therapeutic groups was noted (p = 0.11). Mean quality of life score in the VAS *EuroQol* scale was statistically significantly improved in the iloprost group and slightly worsened in the placebo group. The authors of the *Olschewski 2002* study reported a statistically significant difference between the groups (p = 0.026).



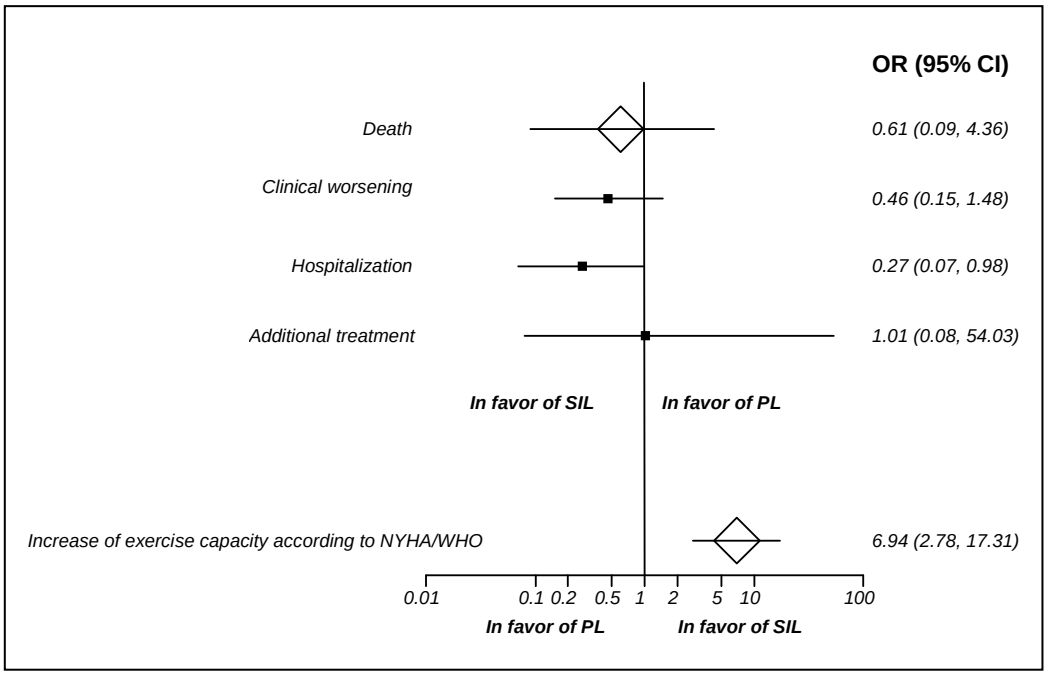
Assessment of safety of the compared interventions demonstrated statistically significantly higher incidence of serious syncope in the iloprost group as compared to the placebo group. The odds ratio was 7.77 (95% CI: 1.32 to 45.66); the odds of occurrence of this endpoint was therefore 7.77 times higher in the iloprost group as compared to the placebo group; NNH = 23 (95% CI: 10 to 83). In an observation period of 12 weeks no statistically significant differences were found with respect to other serious adverse events, including right ventricular failure, reaction of worsening (defined as an event causing concern for possible exacerbation of symptoms of the disease), hypoxemia, pneumonia, tachycardia, abnormal laboratory test results, chest pain, dyspnea and all serious adverse events evaluated together.

For other adverse events a higher odds of occurrence of flushing and jaw pain (3.73 times and 4.40 times, respectively) was noted in the iloprost group as compared with the placebo group. The odds ratio for occurrence of flushing was 3.73 (95% CI: 1.57 to 9.53) and for jaw pain – 4.40 (95% CI: 1.13 to 24.94). The results were statistically significant. The NNH for flushing was 6 (95% CI: 4 to 14) and for jaw pain: 12 (95% CI: 6 to 54). No statistically significant differences between the groups were noted with regard to other adverse events, such as severe

cough, headache, flu-like symptoms, peripheral edema, nausea, hypotension, diarrhea, vertigo, syncope and all adverse events evaluated together.

Sildenafil vs. placebo – adult patients

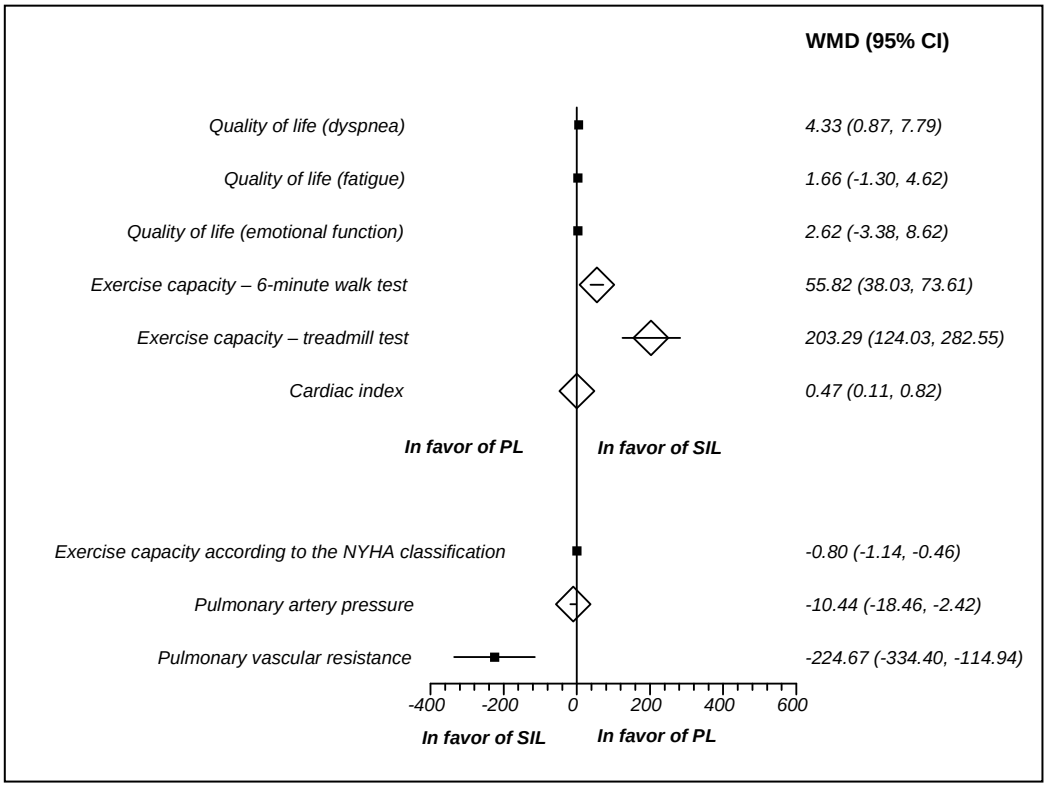
Four randomized, double-blind clinical studies were identified, in which sildenafil was compared to placebo in treatment of pulmonary arterial hypertension in adult patients. The analysis included a total number of 379 patients, of whom 258 were assigned to the sildenafil group and 121 received placebo. In most studies conventional treatment was used in both therapeutic groups in addition to the investigated drugs.



Statistically significant differences in efficacy were observed between the interventions with respect to increase of exercise capacity according to the NYHA/WHO classification, i.e. reclassification into a lower NYHA/WHO functional class. The odds ratio calculated in a metaanalysis of the results of two studies is 6.94 (95% CI: 2.78 to 17.31); the odds of occurrence of this endpoint after an observation period of 6-12 weeks was therefore nearly 7 times higher in the sildenafil group as compared to the placebo group; NNT = 4 (95% CI: 3 to 6). After an observation period of 6 weeks the difference between mean values of exercise capacity in both groups according to the NYHA classification as calculated from the results of a single clinical trial was -0.8 classes (95% CI: -1.14 to -0.46), in favor of the sildenafil group.

It was also observed that in an observation period of 12 weeks sildenafil as compared to placebo decreased the risk of hospitalization due to pulmonary arterial hypertension by 73%; OR = 0.27 (95% CI: 0.07 to 0.98); NNT = 15 (95% CI: 7 to 86).

No statistically significant differences were noted between the sildenafil group and the placebo group with regard to mortality, clinical worsening (defined as death, necessity of hospitalization, necessity of pulmonary transplantation due to PAH or introduction of additional treatment with epoprostenol or bosentan) or necessity of introduction of additional treatment with bosentan or epoprostenol.



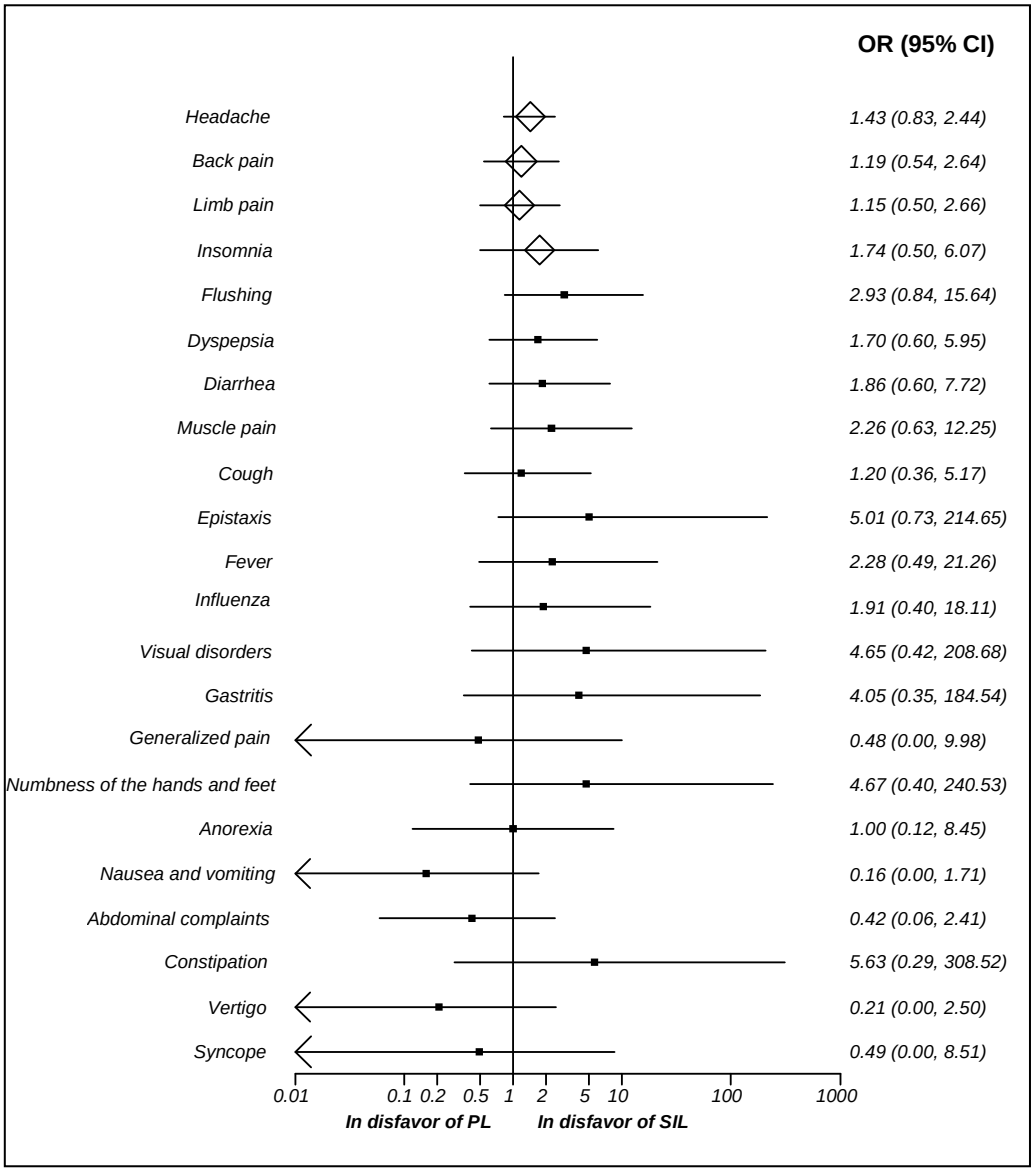
However, in performed analysis statistically significant differences were observed between the sildenafil group and the placebo group with respect to exercise capacity evaluated using the 6-minute walk test and the treadmill test. After an observation period of 2-12 weeks weighted mean difference between the groups in change of exercise capacity (from baseline values) assessed in the 6-minute walk test was 55.82 m (95% CI: 38.03 to 73.61) and for the treadmill test in an observation period of 6 weeks – 203.29 s (95% CI: 124.03 to 282.55), in favor of sildenafil.

Sildenafil as compared to placebo statistically significantly improved quality of life in the aspect of dyspnea, as evaluated using the *Chronic Heart Failure Questionnaire.* The difference of mean values between the groups was 4.33 points (95% CI: 0.87 to 7.79), in favor of the sildenafil group. No statistically significant differences between the groups were demonstrated with regard to quality of life in the aspect of fatigue or emotional function.

From the results of a single study it was also concluded that reduction of severity of dyspnea (measured using the Borg Dyspnea Score) was higher by 1.23 points in the sildenafil group as compared to the placebo group. Mean difference in change was -1.23 points ($p < 0.01$). Nevertheless, in another clinical trial no statistically significant differences in this regard were noted between the evaluated interventions.

In performed analysis significantly higher improvement in hemodynamic parameters was found in the sildenafil group as compared to the placebo group. Weighted mean difference in change of pulmonary artery pressure for patients, of whom the majority were patients with primary PAH, those with PAH associated with other diseases and for both populations combined is -3.87 mmHg (95% CI: -5.63 to -2.11); -17.26 mmHg (95% CI: -23.55 to -10.96) and -10.44 mmHg (95% CI: -18.46 to -2.42), respectively, in favor of sildenafil. Increase of cardiac index was higher by 0.47 l/min/m^2 in the sildenafil group as compared to the placebo group. Weighted mean difference in change of this parameter between the assessed interventions is 0.47 l/min/m^2 (95% CI: 0.11 to 0.82). Mean difference in change of pulmonary vascular resistance as calculated from the results of a single study is

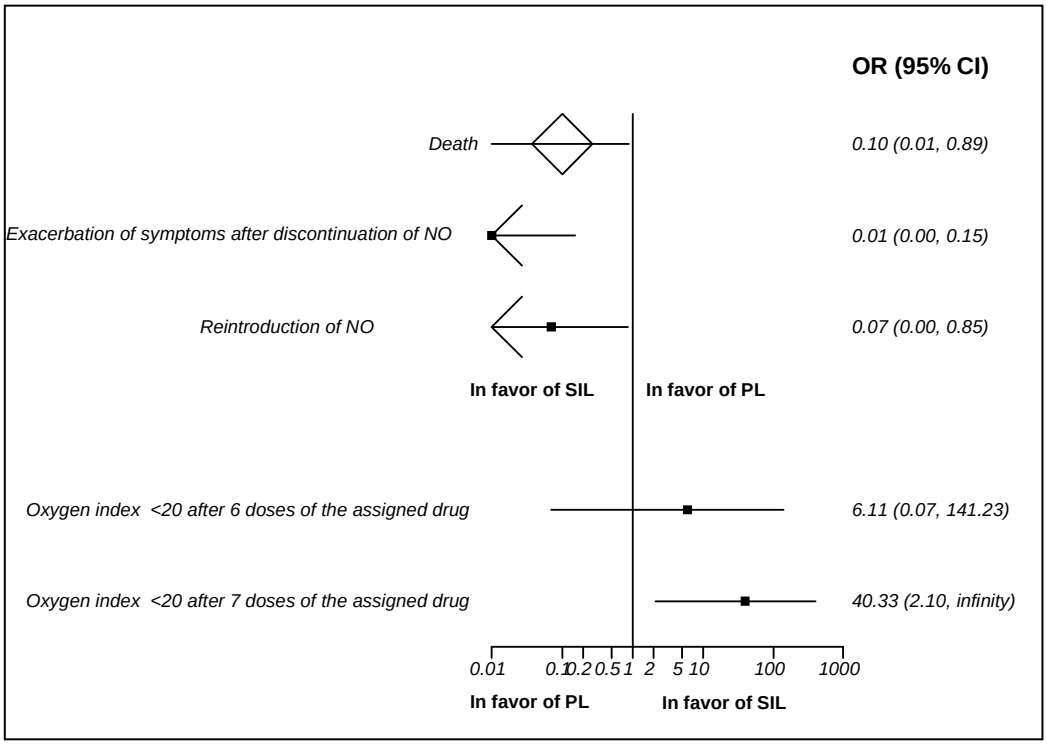
-224.67 dyn*s/cm^5 (95% CI: -334.4 to -114.94); reduction of this parameter was therefore higher by 224.67 dyn*s/cm^5 in the sildenafil group as compared to the placebo group.



Analysis of safety of sildenafil as compared to placebo demonstrated no statistically significant differences between the assessed groups with respect to frequency of the following adverse events: headache, back pain, limb pain, insomnia, flushing, dyspepsia, diarrhea, muscle pain, cough, epistaxis, fever, influenza, visual disorders, gastritis, generalized pain, numbness of the hands and feet, anorexia, nausea and vomiting, abdominal complaints, constipation, vertigo or syncope.

Sildenafil vs. placebo – children

Two primary randomized double-blind clinical studies fulfilling the inclusion criteria were identified, in which sildenafil was compared to placebo in children, newborns or fetuses above 35.5 weeks of gestational age with pulmonary arterial hypertension. The analysis included a total number of 44 patients, of whom 22 were assigned to the sildenafil group and 20 received placebo. The observation period was 4-42 hours.



From the results of the analysis performed it was concluded that the odds of death during an observation period of 4-42 hours was statistically significantly lower in the sildenafil group and was 10% of this odds in the placebo group; OR = 0.10 (95% CI: 0.01 to 0.89); NNT = 4 (95% CI: 3 to 13).

From the results of a single clinical trial, in which the patients were previously treated with nitric oxide, it was evaluated that the odds of exacerbation of symptoms of pulmonary hypertension in an observation period of 4 hours following discontinuation of NO was lower in the sildenafil group and was 1% of this odds in the placebo group. The odds ratio for exacerbation of symptoms of the disease is 0.1 (95% CI: 0.00 to 0.15); NNT = 2 (95% CI: 2 to 3). The result is statistically significant. Significant differences between the compared therapeutic groups were also noted with respect to necessity of reintroduction of treatment with nitric oxide; OR = 0.07 (95% CI: 0.00 to 0.85); NNT = 4 (2 to 22) and decrease of oxygen index below 20 after administration of 7 doses of the assigned drug; OR = 40.33 (95% CI: 2.10 to infinity); NNT = 2 (95% CI: 2 to 3). For decrease of oxygen index below 20 after administration of 6 doses of the assigned drug the differences between the sildenafil group and the placebo group were not statistically significant.

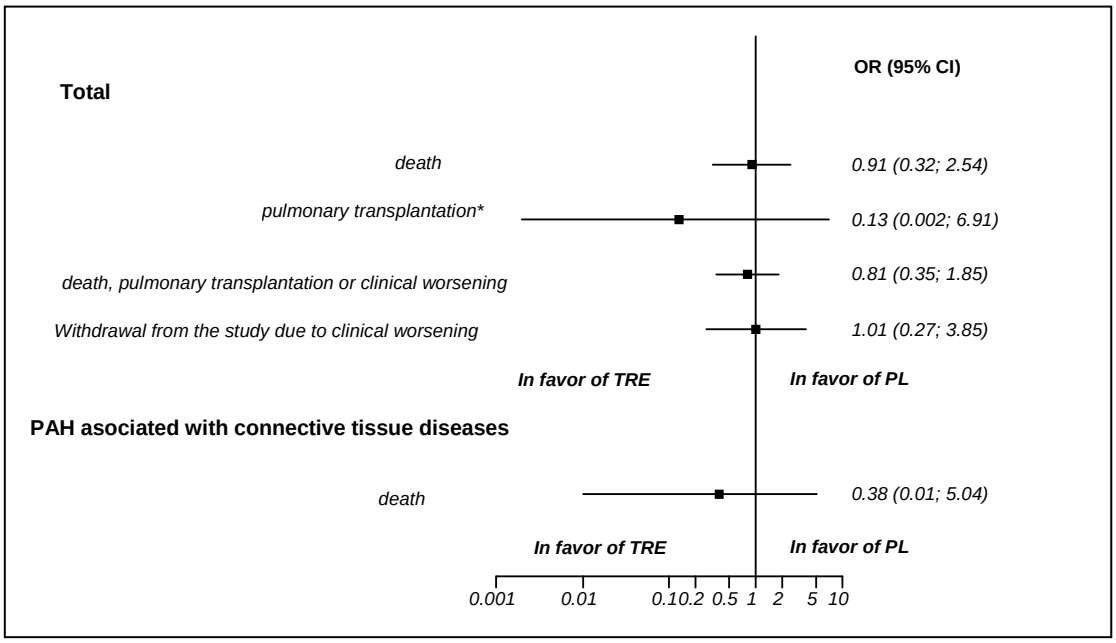
In patients treated with nitric oxide mean difference in change of pulmonary artery pressure between the sildenafil group and the placebo group in an observation period of 1 hour was -23.7 mmHg ($p < 0.001$); increase of mean pulmonary artery pressure was therefore lower by 23.7 mmHg in the sildenafil group as compared to the placebo group. The result is statistically significant.

In summary, only two clinical studies were included in the above analysis, both with very short observation periods (4 and 42 hours), performed in a small population (44 patients in both studies combined) of children and newborns with pulmonary arterial hypertension. In performed analysis significant differences were found between the therapeutic groups, in favor of the sildenafil group, with respect to mortality, exacerbation of symptoms of PAH after discontinuation of previous treatment with nitric oxide, necessity of reintroduction of treatment with nitric oxide, decrease of oxygen index < 20 after administration of seven doses

of the drug and mean pulmonary artery pressure. No assessment of safety of the compared therapeutic options was performed due to short observation periods in the identified studies.

Treprostinil vs. placebo

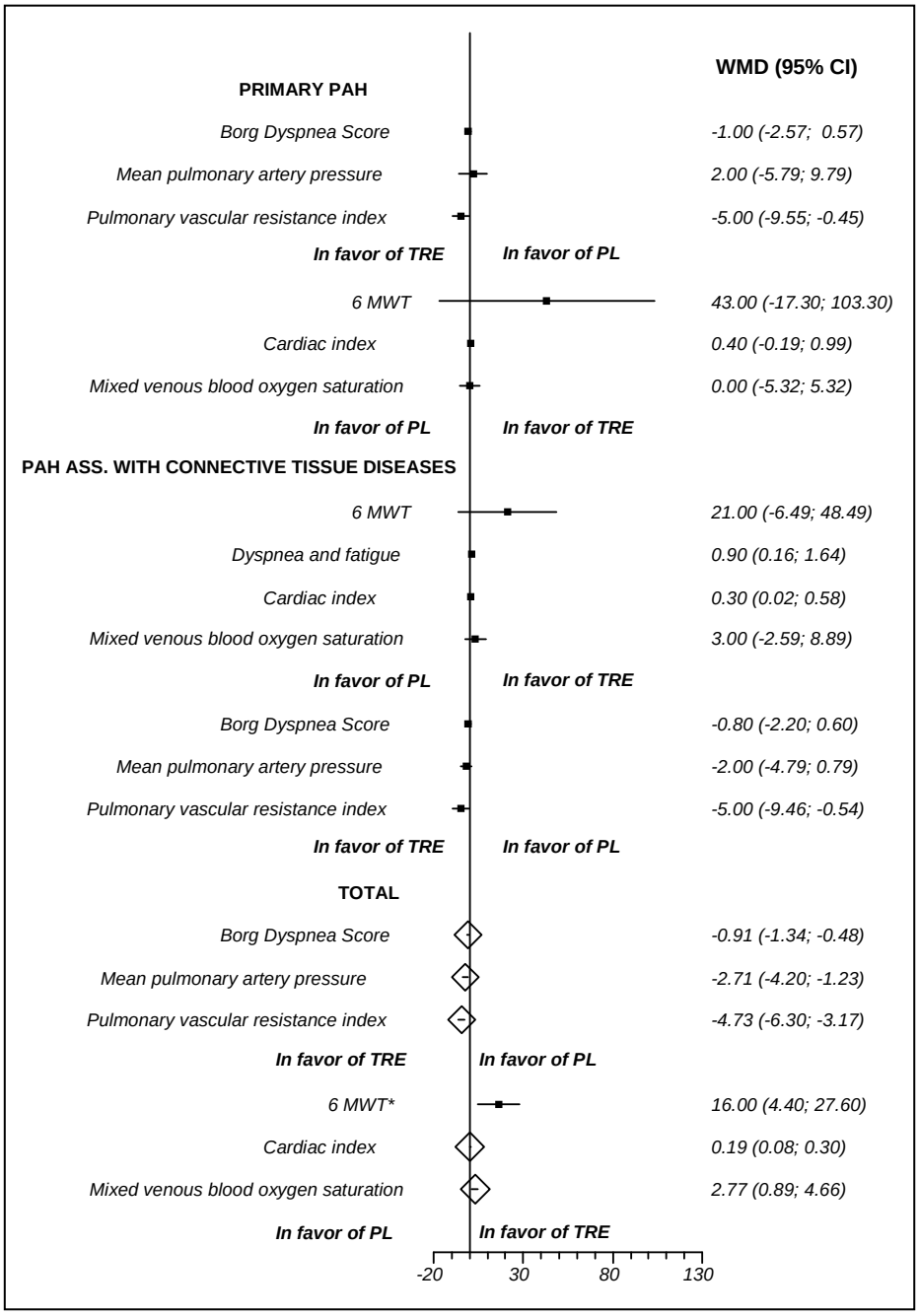
Two randomized clinical trials were taken into account in comparative analysis of efficacy and safety of treprostinil vs. placebo in treatment of patients with pulmonary arterial hypertension *(Simonneau 2002* and *McLaughlin 2003).* The analysis included a total number of 495 patients: 250 assigned to the treprostinil group and 245 to the placebo group. All patients received additional conventional treatment. As a part of sensitivity analysis, apart from a metaanalysis of the whole population of patients, a separate analysis for patients with PAH associated with connective tissue diseases was performed (a subgroup of patients in the *Simonneau 2002* study; N = 90).



* Odds Ratio calculated using the *Peto* method

The analysis of efficacy based on the results of the *Simonneau 2002* study with an observation period of 12 weeks demonstrated no significant differences between the treprostinil group and the placebo group with regard to mortality (either for the whole population of patients or the patients with PAH associated with connective tissue diseases), pulmonary transplantation, a composite endpoint of death, pulmonary transplantation or clinical worsening, or withdrawal from the study due to clinical worsening. Efficacy of treprostinil as compared to placebo in reducing mortality was not demonstrated – the difference in mortality between the groups was statistically insignificant.

Quality of life was assessed in a single study using the *"Minnesota Living with Heart Failure Questionnaire"*, in which physical and psychical condition of the patient as well as their emotional and social function is evaluated. After 12 weeks of treatment statistically significantly higher improvement in quality of life with regard to physical condition was demonstrated in the treprostinil group as compared to the control group ($p = 0.0064$). No statistically significant difference between the groups was observed with regard to the results of the whole questionnaire ($p = 0.17$).



* median value was specified for the population of patients described in the *Simonneau 2002* study

In both studies exercise capacity was assessed using the 6-minute walk test (6MWT). From the results of a single study *(Simonneau 2002)* it was concluded that after 12 weeks of observation increase of the 6-minute walk distance was higher by 16 m in the treprostinil group as compared to the placebo group. Mean difference in median change was 16 m (95% CI: 4.4 to 27.6), p = 0.006 and the result is statistically significant.

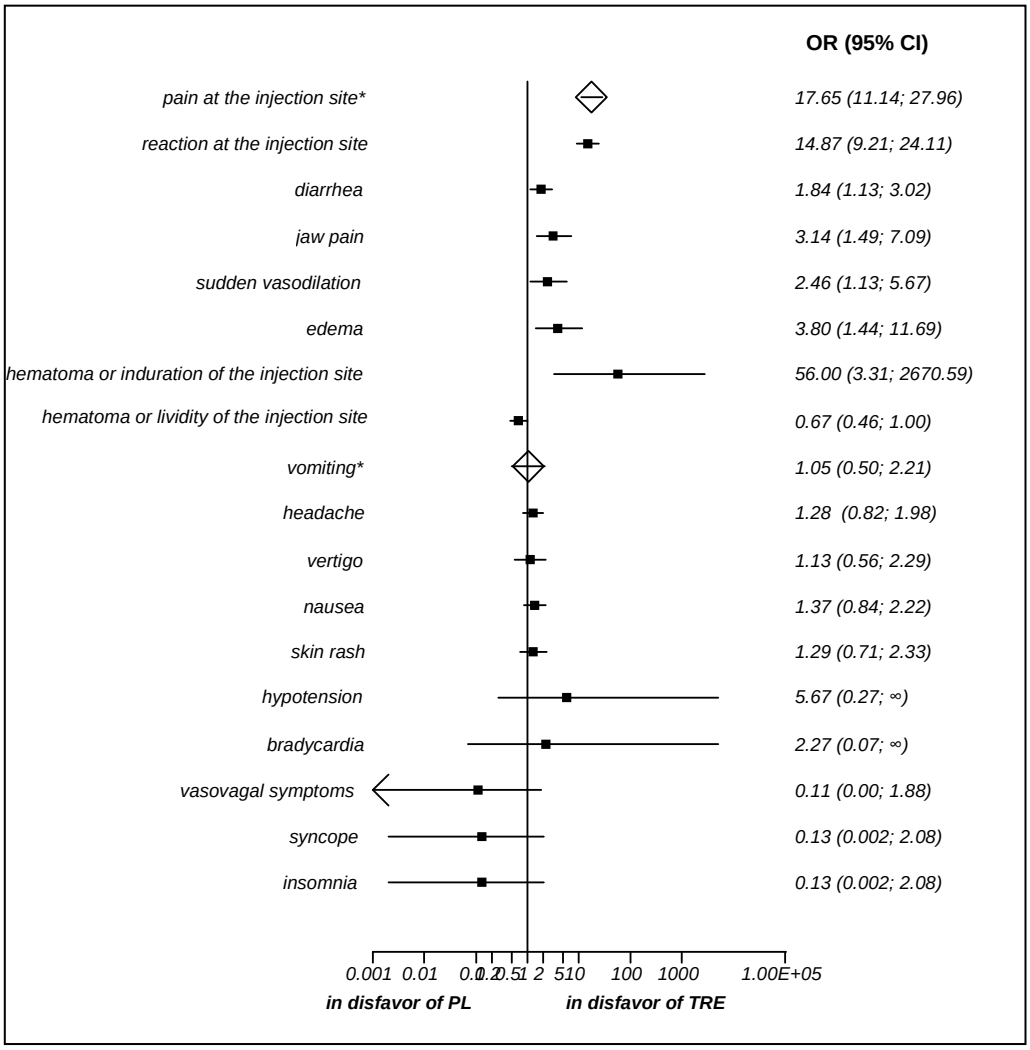
Severity of dyspnea was evaluated using the Borg Dyspnea Score and the Dyspnea – Fatigue Rating. For the whole population of patients weighted mean difference in change of the Borg Dyspnea Score was -0.91 points (95% CI: -1.34 to -0.48) in favor of the treprostinil group and the result is statistically significant. For the subpopulations of patients (those with primary PAH and those with PAH associated with connective tissue diseases) differences between the groups were not statistically significant.

From the results of a single study it was also demonstrated that reduction in Dyspnea – Fatigue Rating is statistically significantly higher in the treprostinil group as compared to the placebo group, both for the whole population of patients and for patients with PAH associated with connective tissue diseases. Mean difference in change between the groups was 1.3 points (p = 0.0001) and 0.9 (95% CI: 0.16 to 1.64), respectively. For patients with primary PAH no statistically significant differences between the groups with regard to this endpoint were noted.

In performed analysis statistically significant differences between the treprostinil group and the placebo group were observed for the whole population of patients with regard to all hemodynamic parameters. Weighted mean difference in change of mean pulmonary artery pressure was -2.7 mmHg (95% CI: -4.20 to -1.23), that of pulmonary vascular resistance index was -4.73 units/m^2 (95% CI: -6.30 to -3.17), of cardiac index – 0.19 l/min/m^2 (95% CI: 0.08 to 0.30) and of mixed venous blood oxygen saturation – 2.77% (95% CI: 0.89 to 4.66), in all cases in favor of the treprostinil group.

For patients with primary PAH mean difference in change of pulmonary vascular resistance index between the groups was -5 units/m^2 (95% CI: -9.55 to -0.45) in favor of treprostinil. No statistically significant differences were noted between the groups with respect to the remaining hemodynamic parameters (mean pulmonary artery pressure, cardiac index and mixed venous blood oxygen saturation).

For hemodynamic parameters assessed in patients with PAH associated with connective tissue diseases differences between the groups were statistically significant for pulmonary vascular resistance index (mean difference in change was -5.00 units/m^2 (95% CI: -9.46 to -0.54) in favor of treprostinil) and cardiac index (mean difference in change: 0.30 l/min/m^2 (95% CI: 0.02 to 0.58) in favor of treprostinil). For that subpopulation of patients no statistically significant differences were found between the treprostinil group and the placebo group with respect to mean pulmonary artery pressure and mixed venous blood oxygen saturation.

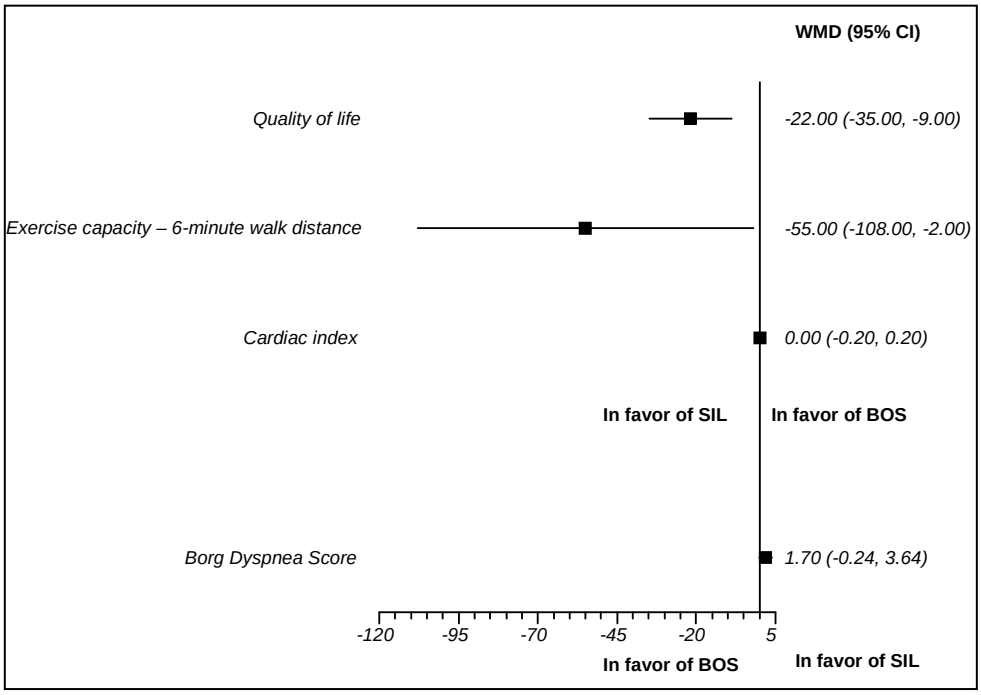


* the result presented in the figure was obtained in a metaanalysis of 2 studies

In safety assessment no statistically significant differences between the therapeutic groups were found with respect to frequency of the following adverse events: hematoma or lividity at the injection site, vomiting, headache, vertigo, nausea, skin rash, hypotension, bradycardia, vasovagal symptoms, syncope or insomnia. In the group treated with treprostinil the oddss of occurrence of reaction at the injection site, diarrhea, jaw pain, sudden vasodilation, edema or hematoma or induration of the injection site were higher than the respective oddss in the control group. OR = 14.87 (95% CI: 9.21 to 24.11), NNH = 2 (95 CI: 2 to 2) for reaction at the injection site; OR = 1.84 (95% CI: 1.13 to 3.02), NNH = 11 (95% CI: 6 to 42) for diarrhea; OR = 3.14 (95% CI: 1.49 to 7.09), NNH = 12 (95% CI: 8 to 28) for jaw pain; OR = 2.46 (95% CI: 1.13 to 5.67), NNH = 17 (95% CI: 9 to 77) for sudden vasodilation; OR = 3.8 (95% CI: 1.44 to 11.69), NNH = 16 (95% CI: 9 to 42) for edema; OR=56.00 (95% CI: 3.31; 2670.59), NNH = 2 (95% CI: 2 to 3) for hematoma or induration of the injection site. The results are statistically significant.

Bosentan vs. sildenafil

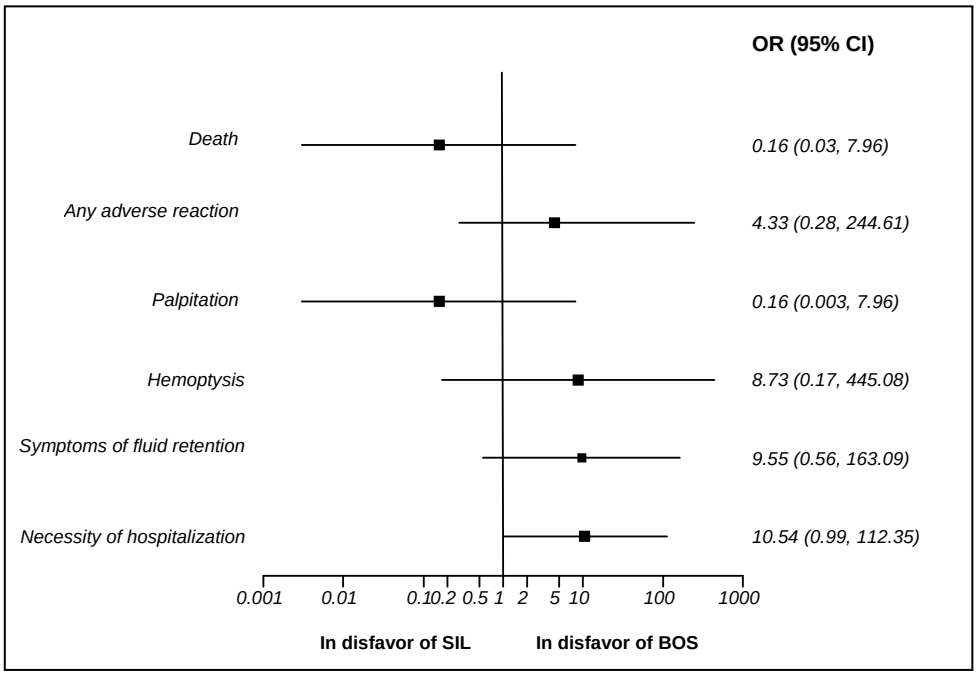
Only one randomized double-blind clinical study was identified, in which bosentan was directly compared to sildenafil. The analysis included 26 patients with PAH, of whom 12 were assigned to the bosentan group and 14 to the sildenafil group. All patients received additional conventional treatment with warfarin, diuretics, digoxin or calcium channel blockers. The observation period was 16 weeks.



Analysis of efficacy demonstrated statistically significantly higher improvement in quality of life (evaluated using the *Kansas City Cardiomyopathy Quality-of-Life* questionnaire) in the sildenafil group as compared to the bosentan group. After an observation period of 16 weeks mean difference in change of the score between the bosentan group and the sildenafil group was -22 points (95% CI: -35 to -9).

Mean difference in change of exercise capacity (measured using the 6-minute walk test) between the bosentan group and the sildenafil group was -55 meters (95% CI: -108 to -2), in disfavor of the bosentan group; the result reached statistical significance.

No statistically significant differences between the assessed therapeutic groups were found with respect to mortality, the Borg Dyspnea Score or cardiac index. The results need to be interpreted cautiously as above analysis was not intention-to-treat (one patient who died in sildenafil group was excluded).

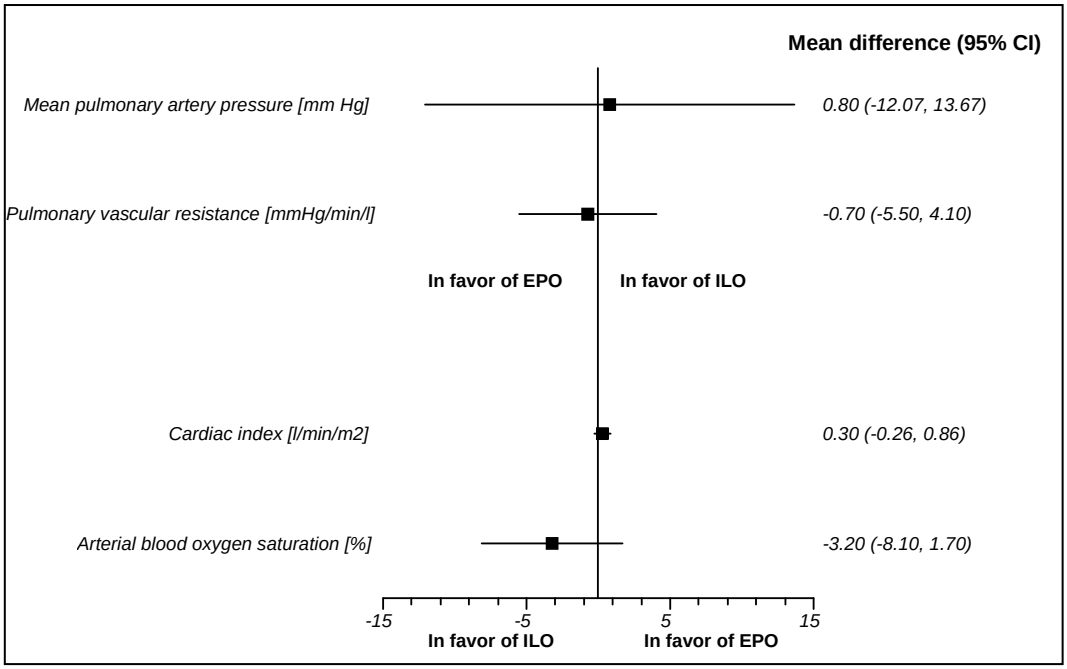


Assessment of safety of the compared therapeutic options demonstrated no statistically significant differences between the bosentan group and the sildenafil group with respect to palpitation, hemoptysis, necessity of increase of dose of diuretics due to symptoms of fluid retention or all adverse events evaluated together, or necessity of hospitalization.

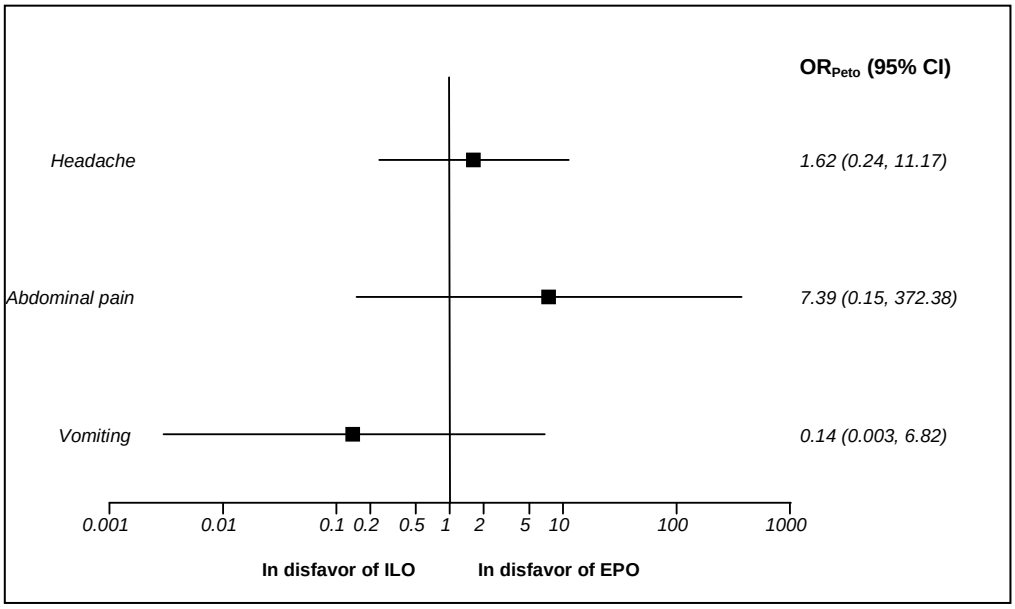
Epoprostenol vs. iloprost

Epoprostenol was directly compared to iloprost only in one randomized cross-over clinical study. The identified clinical trial was not double-blind. The study enrolled 12 patients with severe primary pulmonary hypertension who did not respond to previous treatment with vasodilators and were qualified for cardiopulmonary transplantation. The observation period was 45 minutes.

Analysis of efficacy demonstrated no statistically significant differences between the epoprostenol group and the iloprost group with respect to the following hemodynamic parameters: mean pulmonary artery pressure, pulmonary vascular resistance, cardiac index or arterial blood oxygen saturation.



In assessment of safety of the compared therapeutic options no statistically significant differences between the groups were found with respect to frequency of the following adverse events: headache, abdominal pain and vomiting.



In summary, performed analysis demonstrated no statistically significant differences between the epoprostenol group and the iloprost group with respect to either efficacy or safety. However, it should be noted that credibility of the analysis may be limited due to a very small population of patients with primary PAH (12 patients), a short observation period (45 minutes) and relatively low general credibility of the clinical trial taken into account (2 points in the *Jadad* scale).

Summary

Nineteen randomized clinical trials, in which a total number of 1795 patients with PAH participated, were included in the systematic review. Summary of evidence according to the GRADE proposal is presented in the annexes.

Performed systematic review and metaanalysis made it possible to conclude that two drugs out of five investigated interventions (bosentan, epoprostenol, iloprost, sildenafil and treprostinil) are significantly more efficacious than conventional treatment or placebo with respect to mortality in short observation periods. For the comparison of epoprostenol vs. conventional treatment in patients with primary PAH, in an observation period of 8-12 weeks, the odds ratio is 0.09 (95% CI: 0.02 to 0.56), NNT = 5 (4 to 13), while for the comparison of sildenafil vs. placebo in children and fetuses, in an observation period of 4-42 hours OR = 0.10 (95% CI: 0.01 to 0.89), NNT = 4 (95% CI: 3 to 13). It should be noted that proper assessment of survival rate of patients with PAH requires randomized clinical trials with longer observation periods (over 6 months).

For all comparisons assessment of quality of life was based on the results of single studies, in which different scales were used. For this endpoint statistically significant differences in favor of the investigated drugs were noted for the following comparisons: epoprostenol vs. conventional treatment (the *Chronic Heart Failure Questionnaire* and the *Nottingham Health Profile* in the aspect of emotional reaction and sleep); sildenafil vs. placebo (the *Chronic Heart Failure Questionnaire)* in the aspect of dyspnea and treprostinil vs. placebo in the aspect of physical condition (the *Minnesota Living with Heart Failure Questionnaire).*

In four comparisons: (bosentan vs. placebo, epoprostenol vs. placebo, iloprost vs. placebo and sildenafil vs. placebo) exercise capacity of the patients was evaluated according to the NYHA or WHO classification. Analysis based on the results of 1 to 3 randomized clinical studies for each comparison demonstrated that all the four drugs efficiently increase exercise capacity according to this classification in the whole population of patients with PAH, both primary and associated with other diseases (bosentan vs. placebo: OR = 2.25 (95% CI: 1.21 to 4.18),

NNT = 7 (95% CI: 4 to 21); epoprostenol vs. placebo: 37.99 (95% CI: 8.43 to 171.22), NNT = 3 (95% CI: 2 to 4); iloprost vs. placebo: OR = 2.25 (95% CI: 1.02 to 5.13), NNT = 9 (95% CI: 5 to 79), sildenafil vs. placebo: OR = 6.94 (95% CI: 2.78 to 17.31), NNT = 4 (95% CI: 3 to 6). From a metaanalysis of the results for the total number of patients in 2 studies comparing epoprostenol with conventional treatment and a subgroup of patients in a single clinical trial, in which iloprost was compared to placebo, it may also be concluded that in patients with primary PAH the probability of increase of exercise capacity according to the NYHA/WHO classification was significantly higher both in the epoprostenol group and the iloprost group as compared to the placebo group (epoprostenol vs. placebo: OR = 26.44 (95% CI: 4.49 to 155.81), NNT = 3 (95% CI: 2 to 4); iloprost vs. placebo: 4.92 (95% CI: 1.19 to 28.66)). Exercise capacity according to NYHA/WHO in patients with PAH associated with other diseases was assessed for two comparisons: epoprostenol vs. placebo, based on one study, and iloprost vs. placebo in a subgroup of patients in a single clinical trial. However, statistically significant differences between the therapeutic groups with regard to this outcome were observed only for the comparison of epoprostenol vs. placebo, in favor of epoprostenol (OR = 65.40 (95% CI: 5.69 to 2742.21), NNT = 3 (95% CI: 2 to 4)).

Exercise capacity in the 6-minute walk test was evaluated in 4 randomized studies comparing bosentan to placebo, 2 studies comparing epoprostenol to conventional treatment, a single clinical trial, in which iloprost was compared to placebo, 1 study assessing sildenafil vs. placebo and 2 trials comparing treprostinil to placebo. In performed analyses statistically significant improvement in this parameter was found in four intervention groups (bosentan, iloprost, sildenafil, treprostinil) as compared to the placebo groups in the populations of patients with primary PAH and PAH associated with other diseases evaluated together. Weighted mean difference in change was 43.33 m (95% CI: 27.55 to 59.12) for the comparison of bosentan vs. placebo; 36.4 m (p = 0.004) for iloprost vs. placebo; 55.82 m (95% CI: 38.03 to 73.61) for sildenafil vs. placebo and 16.00 m (95% CI: 4.40 to 27.60) for treprostinil vs. placebo. For patients with primary PAH statistically significant differences between the groups were observed only in case of the comparison of epoprostenol vs. conventional treatment, in favor of the epoprostenol group: WMD = 46.94 m (95% CI: 17.30 to 76.59). In the two remaining comparisons (iloprost vs. placebo and treprostinil vs. placebo) differences between the assessed groups did not reach statistical significance. For patients with PAH associated with other diseases this endpoint was evaluated in three comparisons: epoprostenol vs. placebo – based on a single study, iloprost vs. placebo and treprostinil vs. placebo – based on subgroups of patients in single clinical trials. However, no significant differences between the assessed groups were demonstrated in any of the comparisons.

Severity of dyspnea was evaluated in all the comparisons; however, different scales were used for this assessment. In four comparisons the Borg Dyspnea Score was used (bosentan vs. placebo, epoprostenol vs. placebo, sildenafil vs. placebo and treprostinil vs. placebo), in two comparisons the Dyspnea – Fatigue Rating was additionally applied and in the comparison of iloprost vs. placebo severity of dyspnea was estimated using the Mahler Dyspnea Index. In performed analysis statistically significant differences between the assessed interventions in the Borg Dyspnea Score were found for the following comparisons: epoprostenol vs. conventional treatment – in the population of patients with PAH associated with other diseases: (mean difference in change: -2.5 (95% CI: -3.5 to -1.5)) and treprostinil vs. placebo – in the whole population of patients (WMD = -0.91 (95% CI: -1.34 to -0.48)). For the comparison of sildenafil vs. placebo this endpoint was assessed in two clinical trials. In one study, in which a small number of patients (18 individuals) participated, statistically significantly higher reduction of severity of dyspnea was observed in the sildenafil group as compared to the placebo group (mean difference in change was -1.23 (p < 0.01)), while the

result obtained in a larger clinical trial (a total number of 277 patients) did not reach statistical significance. Reduction of severity of dyspnea and fatigue was significantly higher in the groups of epoprostenol and treprostinil as compared to the control groups. Weighted mean difference in change of this parameter between the epoprostenol group and the control group was 2.00 (95% CI: 1.55 to 2.45) for the whole population of patients, 2.00 (95% CI: 1.00 to 3.00) for patients with primary PAH and 2.00 (95% CI: 2.00 to 3.00) for patients with PAH associated with other diseases; for treprostinil vs. placebo the results were: 1.3 (p = 0.0001) for the whole population of patients and 0.9 (95% CI: 0.16 to 1.64) for patients with PAH associated with other diseases. For patients with primary PAH no significant differences with respect to this endpoint were found between the treprostinil group and the placebo group. Mean difference in change of the Mahler Dyspnea Index between the iloprost group and the placebo group was 1.12 (95% CI: 0.43 to 1.81) in favor of iloprost and the result is statistically significant.

In safety analysis no statistically significant differences were found between the bosentan group and the placebo group as well as the sildenafil group and the placebo group with regard to incidence of any of the assessed adverse events. In assessment of incidence of jaw pain significant differences were observed between the epoprostenol, iloprost and treprostinil groups and the respective control groups, in disfavor of the investigated drugs. The odds of occurrence of jaw pain in the epoprostenol, iloprost and treprostinil group was 327.00, 4.40 and 3.14 times higher than this odds in the respective control group (epoprostenol vs. conventional treatment: OR = 327.00 (95% CI: 27.58 to 11155.05), NNH = 2 (95% CI: 2 to 2); iloprost vs. placebo: OR = 4.40 (95% CI: 1.13 to 24.94), NNH = 12 (6 to 54); treprostinil vs. placebo: OR = 3.14 (95% CI: 1.49 to 7.09), NNH = 12 (8 to 28). In addition, treatment with epoprostenol was related to a statistically significantly higher odds of occurrence of nausea (OR = 3.56 (95% CI: 1.36 to 9.83), NNH = 5 (95% CI: 3 to 13)) and diarrhea (OR = 17.33 (95% CI: 4.62 to 94.37), NNH = 3 (95% CI: 2 to 4) as compared to the conventional treatment group. The risk of serious syncope or flushing is higher for patients treated with iloprost as compared to placebo; the odds ratio is: OR = 7.77 (95% CI: 1.32 to 45.66), NNH = 23 (95% CI: 10 to 83) for serious syncope and 3.73 (95% CI: 1.57 to 9.53), NNH = 6 (95% CI: 4 to 14) for flushing, respectively. Use of treprostinil (as compared to placebo) is related to significantly higher incidence of the following adverse reactions: edema (OR = 3.80 (95% CI: 1.44 to 11.69), NNH = 16 (95% CI: 9 to 42)), pain at the injection site (OR = 17.65 (95% CI: 11.14 to 27.96), NNH = 2 (95% CI: 2 to 2), reaction at the injection site (OR = 14.87 (95% CI: 9.21 to 24.11), NNH = 2 (95% CI: 2 to 2), hematoma or induration at the injection site (OR = 56.00 (95% CI: 3.31 to 2670.59), NNH = 2 (95% CI: 2 to 3) and sudden vasodilation (OR = 2.46 (95% CI: 1.13 to 5.67), NNH = 17 (95% CI: 9 to 77). It should be noted that analysis of safety of the investigated drugs was based on a limited number of randomized clinical studies, with relatively short observation periods. In order to perform a complete safety analysis, more RCTs fulfilling the inclusion criteria of this analysis with longer observation periods (at least 6 months) should be carried out. Analysis of observation studies, without a control group, with longer observation periods, was not an objective of this report.

6. INDEX OF ABBREVIATIONS

ABI	Absolute Benefit Increase
ARR	Absolute Risk Reduction
n.d.	no data (available)
BOS	bosentan
CI	Confidence Interval
DL_{CO}	Diffusion Capacity of the Lungs
EBM	Evidence Based Medicine
EPO	epoprostenol
FVC	Forced Vital Capacity
FEV_1	Forced Expiratory Volume in one second
ILO	iloprost
CT	Conventional Treatment
n.a.	not applicable (calculation not possible)
NNH	Number Needed to Harm; the number of patients, in whom a specific health technology must be used instead of the comparator for a given time to cause one additional adverse outcome
NNT	Number Needed to Treat; the number of patients, in whom a specific health technology must be used instead of the comparator for a given time to cause one additional positive outcome
n.s.	not significant (statistically)
NYHA	New York Heart Association
PL	placebo
RB	Relative Benefit
RBI	Relative Benefit Increase
RR	Relative Risk
RRR	Relative Risk Reduction
SD	Standard Deviation
SIL	sildenafil
PAH	Pulmonary Arterial Hypertension
TRE	treprostinil
VAS	Visual Analogue Scale
VC	Vital Capacity
vs.	versus
WHO	World Health Organization

7. REFERENCES

Introduction and Methods:

1. AGENCJA OCENY TECHNOLOGII MEDYCZNYCH. WYTYCZNE PRZEPROWADZANIA OCENY TECHNOLOGII MEDYCZNYCH (HTA); DOKUMENT DOSTĘPNY NA STRONIE: HTTP://WWW.AOTM.GOV.PL/PLIKI/EDU/WYTYCZNE%20HTA%20W%20AOTM.PDF.
2. THERAPEUTIC GOODS ADMINISTRATION: DRUGS DESIGNATED AS ORPHAN DRUGS; WWW.TGA.GOV.AU/DOCS/HTML/ORPHAND2.HTM
3. FDA: LIST OF ORPHAN DESIGNATIONS AND APPROVALS: WWW.FDA.GOV/ORPHAN/DESIGNAT/LIST.HTM
4. THE PORTAL FOR RARE DISEASES AND ORPHAN DRUGS: WWW.ORPHANET.NET
5. BRADBURN MJ, DEEKS JJ, BERLIN JA, RUSSELL LOCALIO A. MUCH ADO ABOUT NOTHING: A COMPARISON OF THE PERFORMANCE OF META-ANALYTICAL METHODS WITH RARE EVENTS. STAT MED. 2007, 26 (1): 53-77.
6. URZĄD REJESTRACJI PRODUKTÓW LECZNICZYCH, WYROBÓW MEDYCZNYCH I PRODUKTÓW BIOBÓJCZYCH: CHARAKTERYSTYKA PRODUKTU LECZNICZEGO FLOLAN 0,5 I 1,5 MG (19.04.2006R.), CHARAKTERYSTYKA PRODUKTU LECZNICZEGO REMODULIN 5 MG/ML (26.04.2007)
7. GALIÈ N, TORBICKI A, BARST R I WSP. ESC GUIDELINES. GUIDELINES ON DIAGNOSIS AND TREATMENT OF PULMONARY ARTERIAL HYPERTENSION. THE TASK FORCE ON DIAGNOSIS AND TREATMENT OF PULMONARY ARTERIAL HYPERTENSION OF THE EUROPEAN SOCIETY OF CARDIOLOGY; EUROPEAN HEART JOURNAL; 2004; 25; 2243-2278
8. D'ALONZO GE, BARST RJ, AYRES SM I WSP. SURVIVAL IN PATIENTS WITH PRIMARY PULMONARY HYPERTENSION. RESULTS FROM A NATIONAL PROSPECTIVE REGISTRY. ANN INTERN MED 1991; 115: 343-349
9. EUROPEAN MEDICINES AGENCY EMEA, CHARAKTERYSTYKI PRODUKTÓW LECZNICZYCH: REVATIO, TRACLEEAR, VENTAVIS
10. FDA, CENTER FOR DRUG EVALUATION AND RESEARCH, PRODUCT INFORMATION – FLOLAN (NDA 20-444/S-003), REMODULIN (NDA 21-272/S-005), BOZENTAN (NDA 21-290)
11. HUMBERT M, SITBON O, CHAOUAT A I WSP. PULMONARY ARTERIAL HYPERTENSION IN FRANCE RESULTS FROM A NATIONAL REGISTRY. AM J RESPIR CRIT CARE MED VOL 173. PP 1023–1030, 2006
12. JADAD AR, MOORE RA, CARROLL D, JENKINSON C, REYNOLDS DJ, GAVAGHAN DJ, MCQUAY HJ. ASSESSING THE QUALITY OF REPORTS OF RANDOMIZED CLINICAL TRIALS: IS BLINDING NECESSARY? CONTROL CLIN TRIALS. 1996, VOL 17, 1, PP 1-12.
13. MCGOON M, GUTTERMAN D, STEEN V I WSP. SCREENING, EARLY DETECTION, AND DIAGNOSIS OF PULMONARY ARTERIAL HYPERTENSION. ACCP EVIDENCE-BASED CLINICAL PRACTICE GUIDELINES. CHEST 2004;126;14-34
14. MOHER D, COOK DJ, EASTWOOD S, OLKIN I, RENNIE D, STROUP DF. IMPROVING THE QUALITY OF REPORTS OF METAANALYSES OF RANDOMISED CONTROLLED TRIALS: THE QUOROM STATEMENT. QUALITY OF REPORTING OF META-ANALYSES. LANCET. 1999, 354, 9193, 1896-900.
15. NHS REGIONAL DRUG AND THERAPEUTICS CENTRE AN UPDATE ON NEWER AGENTS FOR THE TREATMENT OF PULMONARY HYPERTENSION, 2004
16. RICH S, DANTZKER AR, AYRES AM I WSP. PRIMARY PULMONARY HYPERTENSION: A NATIONAL PROSPECTIVE STUDY. ANNALS OF INTERNAL MEDICINE, 1987; 107: 216 – 223

17. THE COCHRANE COLLBORATION. COCHRANE HANDBOOK FOR SYSTEMATIC REVIEWS OF INTERVENTIONS. WERSJA 4.2.6, DOKUMENT DOSTĘPNY NA STRONIE: HTTP://WWW.COCHRANE.ORG/RESOURCES/HANDBOOK/HANDBOOK4.2.6SEP2006.PDF.

Systematic Reviews:

18. KANTHAPILLAI P, LASSERSON TJ, WALTERS EH, "SYLDENAFIL FOR PULMONARY HYPERTENSION", COCHRANE DATABASE OF SYSTEMATIC REVIEWS 2004

19. LIU C, CHEN J., "ENDOTHELIN RECEPTOR ANTAGONISTS FOR PULMONARY ARTERIAL HYPERTENSION", COCHRANE DATABASE OF SYSTEMATIC REVIEWS 2006,

20. PARAMOTHAYAN NS, LASSERSON TJ, WELLS AU, WALTERS EH "PROSTACYCLIN FOR PULMONARY HYPERTENSION IN ADULTS", COCHRANE DATABASE OF SYSTEMATIC REVIEWS 2005

21. SHAH PS, OHLSSON A. „SYLDENAFIL FOR PULMONARY HYPERTENSION IN NEONATES" COCHRANE DATABASE OF SYSTEMATIC REVIEWS 2007

Clinical Trials included into the Analysis:

22. BADESCH D, BURGESS G, PARPIA T, TORBICKI A ; SYLDENAFIL CITRATE IN PATIENTS WITH PULMONARY ARTERIAL HYPERTENSION (PAH) RESULTS OF A MULTICENTER MULTINATIONAL RANDOMIZED DOUBLE-BLIND PLACEBO CONTROLLED TRIAL BY WHO FUNCTIONAL CLASS (FC) [ABSTRACT]; AMERICAN THORACIC SOCIETY 2005 INTERNATIONAL CONFERENCE; MAY 20-25; SAN DIEGO, CALIFORNIA YR: 2005 PG: [A57] [POSTER: K39]

23. BADESCH DB, BODIN F, CHANNICK RN ET AL; COMPLETE RESULTS OF THE FIRST RANDOMIZED PLACEBO-CONTROLLED STUDY OF BOZENTAN, A DUAL ENDOTHELIN RECEPTOR ANTAGONIST, IN PULMONARY ARTERIAL HYPERTENSIONL; CURRENT THERAPEUTIC RESEARCH 63[4], 227-246. 2002.

24. BADESCH DB, TAPSON VF, MCGOON MD ET AL CONTINUOUS INTRAVENOUS EPOPROSTENOL FOR PULMONARY HYPERTENSION DUE TO THE SCLERODERMA SPECTRUM OF DISEASE. A RANDOMIZED, CONTROLLED TRIAL; ANN INTERN MED 2000; 132(6):425-434.

25. BAQUERO H, SOLIZ A, NEIRA F, VENEGAS ME, SOLA A; ORAL SYLDENAFIL IN INFANTS WITH PERSISTENT PULMONARY HYPERTENSION OF THE NEWBORN: A PILOT RANDOMIZED BLINDED STUDY.; PEDIATRICS. 2006 APR;117(4):1077-83.

26. BARST RJ, LANGLEBEN D, BADESCH D ET AL; TREATMENT OF PULMONARY ARTERIAL HYPERTENSION WITH THE SELECTIVE ENDOTHELIN-A RECEPTOR ANTAGONIST SITAXSENTAN; J AM COLL CARDIOL 2006; 47(10):2049-2056.

27. BARST RJ, RUBIN LJ, LONG WA ET AL.; A COMPARISON OF CONTINUOUS INTRAVENOUS EPOPROSTENOL (PROSTACYCLIN) WITH CONVENTIONAL THERAPY FOR PRIMARY PULMONARY HYPERTENSION. THE PRIMARY PULMONARY HYPERTENSION STUDY GROUP.; N ENGL J MED 1996; 334(5):296-302.

28. BHARANI A, MATHEW V, SAHU A, LUNIA B; THE EFFICACY AND TOLERABILITY OF SYLDENAFIL IN PATIENTS WITH MODERATE-TO-SEVERE PULMONARY HYPERTENSION.; INDIAN HEART J 2003; 55(1):55-59.

29. CHANNICK RN, SIMONNEAU G, SITBON O ET AL; EFFECTS OF THE DUAL ENDOTHELIN-RECEPTOR ANTAGONIST BOZENTAN IN PATIENTS WITH PULMONARY HYPERTENSION: A RANDOMISED PLACEBO-CONTROLLED STUDY; LANCET 2001; 358(9288):1119-1123.

30. DENTON CP, HUMBERT M, RUBIN L, BLACK CM; BOZENTAN TREATMENT FOR PULMONARY ARTERIAL HYPERTENSION RELATED TO CONNECTIVE TISSUE DISEASE: A SUBGROUP ANALYSIS OF THE PIVOTAL CLINICAL TRIALS AND THEIR OPEN-LABEL EXTENSIONS.; ANN RHEUM DIS 2006; 65(10):1336-1340.

31. GALIE N, BEGHETTI M, GATZOULIS MA ET AL; BOZENTAN THERAPY IN PATIENTS WITH EISENMENGER SYNDROME: A MULTICENTER, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED STUDY; CIRCULATION 2006; 114(1):48-54.

32. GALIE N, BURGESS G, PARPIA T, BARST R; EFFECTS OF SYLDENAFIL ON 1 YEAR SURVIVAL OF PATIENTS WITH IDIOPATHIC PULMONARY ARTERIAL HYPERTENSION (PAH) [ABSTRACT]; AMERICAN THORACIC SOCIETY 2005 INTERNATIONAL CONFERENCE; MAY 20-25; SAN DIEGO, CALIFORNIA YR: 2005 PG: [C88]
33. GALIE N, GHOFRANI HA, TORBICKI A, BARST RJ, RUBIN LJ, BADESCH D, FLEMING T, PARPIA T, BURGESS G, BRANZI A, GRIMMINGER F, KURZYNA M, SIMONNEAU G; SYLDENAFIL USE IN PULMONARY ARTERIAL HYPERTENSION (SUPER) STUDY GROUP. SYLDENAFIL CITRATE THERAPY FOR PULMONARY ARTERIAL HYPERTENSION; N ENGL J MED. 2005 NOV 17;353(20):2148-57.
34. GALIE N, HINDERLITER AL, TORBICKI A ET AL; EFFECTS OF THE ORAL ENDOTHELIN-RECEPTOR ANTAGONIST BOZENTAN ON ECHOCARDIOGRAPHIC AND DOPPLER MEASURES IN PATIENTS WITH PULMONARY ARTERIAL HYPERTENSION. J AM COLL CARDIOL 2003; 41(8):1380-1386.
35. GATZOULIS MA, BEGHETTI M, GALIE N ET AL.; BOZENTAN SHOWS PERSISTENT BENEFIT IN FUNCTIONAL CLASS AND EXERCISE CAPACITY AMONGST EISENMENGER PATIENTS IN THE BREATHE-5 OPEN LABEL EXTENSION STUDY. WORLD CONGRESS OF CARDIOLOGY [ABSTRACT]. 2006.
36. HINDERLITER AL, WILLIS PW, BARST RJ ET AL.; EFFECTS OF LONG-TERM INFUSION OF PROSTACYCLIN (EPOPROSTENOL) ON ECHOCARDIOGRAPHIC MEASURES OF RIGHT VENTRICULAR STRUCTURE AND FUNCTION IN PRIMARY PULMONARY HYPERTENSION. PRIMARY PULMONARY HYPERTENSION STUDY GROUP. CIRCULATION 1997; 95(6):1479-1486.
37. LANGLEBEN D, BARST RJ, BADESCH D ET AL.; CONTINUOUS INFUSION OF EPOPROSTENOL IMPROVES THE NET BALANCE BETWEEN PULMONARY ENDOTHELIN-1 CLEARANCE AND RELEASE IN PRIMARY PULMONARY HYPERTENSION. CIRCULATION 1999; 99(25):3266-3271.
38. MCLAUGHLIN VV, SITBON O, BADESCH DB ET AL. SURVIVAL WITH FIRST-LINE BOZENTAN IN PATIENTS WITH PRIMARY PULMONARY HYPERTENSION. EUR RESPIR J 2005; 25(2):244-249.
39. MCLAUGHLIN VALLERIE V.; GAINE SEAN P. ; BARST ROBYN J. ; OUDIZ RONALD J. ; BOURGE ROBERT C. ; FROST ADAANI ; ET AL.; EFFICACY AND SAFETY OF TREPROSTINIL: AN EPOPROSTENOL ANALOG FOR PRIMARY PULMONARY HYPERTENSION.; J CARDIOVASC PHARMACOL. 2003 FEB;41(2):293-9.
40. NAMACHIVAYAM P, THEILEN U, BUTT WW, COOPER SM, PENNY DJ, SHEKERDEMIAN LS.; SYLDENAFIL PREVENTS REBOUND PULMONARY HYPERTENSION AFTER WITHDRAWAL OF NITRIC OXIDE IN CHILDREN.; AM J RESPIR CRIT CARE MED. 2006 NOV 1;174(9):1042-7. EPUB 2006 AUG 17.
41. OLSCHEWSKI H, SIMONNEAU G, GALIE N ET AL.; INHALED ILOPROST FOR SEVERE PULMONARY HYPERTENSION. N ENGL J MED 2002; 347(5):322-329.
42. OUDIZ RJ,SCHILZ RJ,BARST RJ,GALIE N,RICH S,RUBIN LJ, ET AL. TREPROSTINIL, A PROSTACYCLIN ANALOGUE, IN PULMONARY ARTERIAL HYPERTENSION ASSOCIATED WITH COLLAGENVASCULAR DISEASE; CHEST 2004; 126 (2): 420–7.
43. PEPKE-ZABA J, BROWN MCJ, PARPIA T, GILBERT C, BURGESS G THE IMPACT OF SYLDENAFIL CITRATE ON HEALTH-RELATED QUALITY OF LIFE IN PATIENTS WITH PULMONARY ARTERIAL HYPERTENSION (PAH) RESULTS OF A MULTICENTER, MULTINATIONAL, RANDOMIZED DOUBLE-BLIND, PLACEBO CONTROLLED TRIAL [ABSTRACT]; AMERICAN THORACIC SOCIETY 2005 INTERNATIONAL CONFERENCE; MAY 20-25; SAN DIEGO, CALIFORNIA YR: 2005 PG: [B16]
44. RAYMOND RJ, HINDERLITER AL, WILLIS PW ET AL. ECHOCARDIOGRAPHIC PREDICTORS OF ADVERSE OUTCOMES IN PRIMARY PULMONARY HYPERTENSION. J AM COLL CARDIOL 2002; 39(7):1214-1219.
45. RUBIN L, BURGESS G, PARPIA T, SIMONEAU G; EFFECTS OF SYLDENAFIL ON 6 MINUTE WALK DISTANCE (6MWD) AND WHO FUNCTIONAL CLASS (FC) AFTER 1 YEAR OF

TREATMENT [ABSTRACT]; AMERICAN THORACIC SOCIETY 2005 INTERNATIONAL CONFERENCE; MAY 20-25; SAN DIEGO, CALIFORNIA YR: 2005 PG: [B16]

46. RUBIN LJ, BADESCH DB, BARST RJ ET AL.; BOZENTAN THERAPY FOR PULMONARY ARTERIAL HYPERTENSION. N ENGL J MED 2002; 346(12):896-903.
47. RUBIN LJ, MENDOZA J, HOOD M ET AL.; TREATMENT OF PRIMARY PULMONARY HYPERTENSION WITH CONTINUOUS INTRAVENOUS PROSTACYCLIN (EPOPROSTENOL). RESULTS OF A RANDOMIZED TRIAL. ANN INTERN MED 1990; 112(7):485-491.
48. SASTRY BKS, NARASIMHAN C, REDDY K, RAJU S. CLINICAL EFFICACY OF SYLDENAFIL IN PRIMARY PULMONARY HYPERTENSION; JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY 2004;43(7):1149–53.
49. SCOTT JP, HIGENBOTTAM T, WALLWORK J; THE ACUTE EFFECT OF THE SYNTETHIC PROSTACYCLIN ANALOGUE ILOPROST IN PRIMARY PULMONARY HYPERTENSION; BR J CLIN PRACT 1990; 44: 220-6.
50. SIMONNEAU G, BARST R, GALIE N, NAEJIE R, RICH S, BOURGE RC, ET. AL.; CONTINUOUS SUBCUTANEOUS INFUSION OF TREPROSTINIL, A PROSTACYCLIN ANALOGUE, IN PATIENTS WITH PULMONARY ARTERIAL HYPERTENSION.; AMERICAN JOURNAL OF RESPIRATORY CRITICAL CARE MEDICINE 2002;165(3):800–4.
51. SINGH TP, ROHIT M, GROVER A, MALHOTRA S, VIJAYVERGIYA R. A RANDOMIZED, PLACEBO-CONTROLLED, DOUBLE-BLIND, CROSSOVER STUDY TO EVALUATE THE EFFICACY OF ORAL SYLDENAFIL THERAPY IN SEVERE PULMONARY ARTERY HYPERTENSION; AM HEART J. 2006 APR;151(4):851.E1-5.
52. SITBON O, BADESCH DB, CHANNICK RN ET AL . EFFECTS OF THE DUAL ENDOTHELIN RECEPTOR ANTAGONIST BOZENTAN IN PATIENTS WITH PULMONARY ARTERIAL HYPERTENSION: A 1-YEAR FOLLOW-UP STUDY. CHEST 2003; 124(1):247-254.
53. THURM CA, WIGLEY FM, DOLE WP, WISE RA.; FAILURE OF VASOLDILATOR INFUSION TO ALTER PULMONARY DIFFUSING CAPACITY IN SYSTEMIC SCLEROSIS. AM J MED 1991; 90(5):547-552.
54. WILKINS MR, PAUL GA, STRANGE JW., TUNARIU N, GIN-SING W, BANYA WA SYLDENAFIL VERSUS ENDOTHELIN RECEPTOR ANTAGONIST FOR PULMONARY HYPERTENSION (SERAPH) STUDY; AMERICAN JOURNAL OF RESPIRATORY AND CRITICAL CARE MEDICINE 2005; 171(11):1292-7.

8. ANNEXES

8.1. Characteristics of the systematic reviews used

Table 136.
Characteristic of the *Kanthapillai 2004* review

Title	**Sildenafil for pulmonary hypertension**
Authors	Kanthapillai P, Lasserson TJ, Walters EH
Journal/ database	*Cochrane Database of Systematic Reviews* 2004, Issue 4. Art. No.: CD003562. DOI: 10.1002/14651858.CD003562.pub2.
Last update	August 1st, 2004
Date of the last search	October 13th, 2005 (date of the last addition of new studies, no date of the last search specified)
Aim	Evaluation of efficacy and safety of sildenafil administered in any form to patients with primary or secondary pulmonary hypertension
Inclusion criteria for the studies	Double- or single-blind RCTs, in which efficacy and safety of sildenafil in treatment of primary or secondary PAH was assessed.
Population	Patients (adults and children) treated with anticoagulants, with a diagnosis of pulmonary hypertension; only those studies, in which average pulmonary artery pressure exceeded 25 mmHg, were included; studies, in which the patients suffered from other serious diseases, were not included.
Intervention	• sildenafil vs. placebo • sildenafil vs. prostacyclin • sildenafil + prostacyclin vs. prostacyclin • sildenafil + inhaled NO[3] vs. NO • high dose vs. low dose of sildenafil
Endpoints (according to the protocol)	• Primary: o improvement in the NYHA classification • Secondary: o Hemodynamic parameters (CO^4 level, pulmonary artery pressure and others) o Arterial blood gasometry (ABG) o Exercise capacity o Quality of life/ health status o Dyspnea o Mortality o Hospitalizations/ necessity of interventions

[3] nitric oxide
[4] carbon oxide

	o Adverse events
Included studies	**Bharani 2003** o sildenafil vs. placebo o Randomized, double-blind, cross-over study o 2 x 2 weeks o N = 9 **Ghofrani 2002** o NO + sildenafil (12.5 or 50 mg), NO + sildenafil (12.5 or 50 mg) + iloprost o randomized, open-label study (no blinding) o 120 minutes in the groups of sildenafil alone and 180 in the sildenafil + iloprost groups o N = 30 **Ghofrani 2002a** o iloprost vs. sildenafil o randomized parallel open-label study without blinding o 60 minutes o N = 16 **Sastry 2004** o sildenafil vs. placebo o randomized, double-blind, cross-over study o 6 weeks (without the wash-out phase) o N = 22

Results

Endpoint	**Relative outcome measure**	**Result + 95% CI/SD**
Primary:		
improvement in the NYHA classification – in favor of sildenafil (cross-over)	OR	6.33 [0.26; 152.86]; ns.
Secondary:		
Hemodynamic parameters – as compared to placebo: cardiac index (cross-over)	l/m^2	0.65 [0.41; 0.89]
pulmonary artery pressure (cross-over)	mmHg	-11.14 [-17.56; -4.72]
pulmonary vascular resistance as compared to prostacyclin (cross-over)	WMD	4.40 [-23.72; 32.52]; ns.
Exercise capacity – in favor of sildenafil as compared to placebo: treadmill (cross-over study)	seconds	211.70 [153.78; 269.62]
treadmill (parallel study)		246.00 [52.64; 439.36]
6-minute walk test – in favor of sildenafil as compared to placebo	meters	93.37 (26.54)
Dyspnea (CHFQ) (cross-over) – in favor of placebo	CHFQ	4.33 [1.21; 7.45]

	Dyspnea (the Borg Dyspnea Score: 0-10) as compared to placebo after the 6-minute walk test – in favor of sildenafil (cross-over)	the Borg Dyspnea Score	-1.55 [-2.51; -0.59]
	Fatigue (cross-over) – in favor of sildenafil	CHFQ	1.66 [0.08; 3.24]
	Emotional function (cross-over) – in favor of sildenafil	CHFQ	2.62 [-0.12; 5.36]; ns.
Conclusions of the authors, comments	The review was based on 4 small short-term studies; the results should therefore be interpreted with much care. No statistically significant result for any primary endpoint was observed.		
Comments of the AHTAPol	Contrary to the protocol, studies without blinding were included. The study of SUPER-1 (RCT, N=277, 12 weeks) was not included since it was published after the last search for the studies in the review.		

Table 137.
Characteristics of the *Paramothayan 2005* review

Title	**Prostacyclin for pulmonary hypertension in adults**
Authors	Paramothayan NS, Lasserson TJ, Wells AU, Walters EH
Journal/ database	*Cochrane Database of Systematic Reviews* 2005, Issue 2. Art.No.:CD002994. DOI: 10.1002/14651858.CD002994.pub2.
Last update	July 11th, 2005
Date of the last search	July 11th, 2005 (date of the last addition of new studies, no date of the last search specified)
Aim	Evaluation of efficacy and safety of prostacyclin and its analogues in primary PAH and secondary PAH associated with vascular collagenoses, primarily with systemic scleroderma and CREST.
Inclusion criteria for the studies	Double- or single-blind studies with a control group (parallel or cross-over), in which efficacy and safety of prostacyclin (or its analogues) in primary PAH or secondary PAH associated with vascular collagenoses was assessed.
Population	Adult patients with a diagnosis of primary PAH or secondary PAH associated with vascular collagenoses.
Intervention	• intravenous epoprostenol + conventional treatment vs. conventional treatment • intravenous iloprost + conventional treatment vs. conventional treatment • oral, inhaled or subcutaneous prostacyclin analogues vs. placebo
Endpoints (according to the protocol)	• Primary: o Exercise capacity – results of the 6-minute walk test o Improvement in the NYHA classification • Secondary: o Hemodynamic parameters (CO^5 level, pulmonary artery pressure and others) o Pulmonary function tests o Symptoms and signs of PAH o Dyspnea (the Borg Dyspnea Score and others) o Mortality o Adverse events
Included studies	**Badesch 2000** o intravenous epoprostenol + conventional treatment vs. conventional treatment o randomized, controlled, open-label study (blinded to investigators)

[5] carbon oxide

- 12 weeks
- N = 111

Barst 1996

- intravenous epoprostenol + conventional treatment vs. conventional treatment
- randomized, controlled, open-label study (blinded to investigators)
- 12 weeks
- N = 81

Barst 2003

- beraprost + conventional treatment vs. placebo + conventional treatment
- RCT; double-blind
- 52 weeks
- N = 116

Galiè 2002

- beraprost + conventional treatment vs. placebo + conventional treatment
- RCT; double-blind
- 12 weeks
- N = 130

McLaughlin 2003

- subcutaneous treprostinil vs. placebo
- RCT; double-blind
- 8 weeks
- N = 26

Olschewski 2002

- inhaled iloprost + conventional treatment vs. placebo + conventional treatment
- RCT; double-blind
- 12 weeks
- N = 203

Rubin 1990

- intravenous prostacyclin vs. conventional treatment
- RCT;
- 8 weeks (randomized phase), 18 months (non-randomized phase)
- N = 23

Simonneau 2002

- subcutaneous treprostinil + conventional treatment vs. placebo + conventional treatment
- RCT; double-blind
- 12 weeks
- N = 470

Thurm 1991

- i.v. iloprost vs. placebo
- RCT; double-blind
- 3 days
- N = 14

Results

Endpoint	Relative outcome measure	Result + 95% CI
<u>Intravenous prostacyclin vs. conventional treatment</u>		
Primary:		
Exercise capacity – 6-minute walk test – in favor of prostacyclin	SMD (meters)	0.69 [0.40; 0.97] (ca. 90 m)

Improvement in the NYHA classification – in favor of prostacyclin	OR	37.99 [8.43; 171.22];
Secondary:		
Change of pulmonary artery pressure – in favor of prostacyclin	WMD (mmHg)	-6.30 [-8.68; -3.92]
Change of pulmonary vascular resistance – in favor of prostacyclin	WMD (mmHg/l/min)	-5.32 [-6.83; -3.82]
Change of cardiac index – in favor of prostacyclin	WMD (l/min/m^2)	0.58 [0.38; 0.78]
Change of cardiac output – in favor of prostacyclin	WMD (l/min)	0.22 [-0.71; 1.15]; ns.
Systemic arterial oxygen saturation – in favor of prostacyclin	WMD (%)	0.64 [-1.40; 2.69]; ns.
Change of systemic oxygen transport – in favor of prostacyclin	WMD (ml/min)	63.94 [-110.02; 237.9]; ns.
Mortality – in favor of prostacyclin	OR	0.32 [0.06; 1.58]; ns.
Intravenous iloprost vs. conventional treatment		
Primary: no results		
Secondary:		
Carbon oxide diffusion capacity – in favor of conventional treatment	WMD (ml/min/ mmHg)	-1.58 [-7.67; 4.51]; ns.
Vital capacity at rest – in favor of conventional treatment	WMD (l)	-0.55 [-1.63; 0.53]; ns.
Inhaled iloprost vs. placebo:		
Primary:		
Exercise capacity – 6-minute walk test – change from baseline – in favor of iloprost	m	36.40 [12.04; 60.76]
Improvement in the NYHA classification – in favor of iloprost	OR	2.13 [1.02; 4.48]
Secondary:		
Change of pulmonary artery pressure in relation to baseline values – in favor of iloprost	WMD	-4.40 [-6.65; -2.15]; ns.
Change of pulmonary vascular resistance in relation to baseline values – in favor of iloprost	WMD	-335 [-417.86; -252.14]
Change of cardiac output – in favor of iloprost	WMD	0.74 [0.48; 1.00]
Dyspnea (the Mahler Dyspnea Index) – in favor of iloprost	WMD	1.12 [0.43; 1.81]
Mortality – in favor of iloprost	OR	0.19 [0.02; 1.69]; ns.
Clinical worsening – in favor of iloprost	OR	0.54 [0.17;
Adverse events – in favor of placebo	OR	1.18 [0.63; 2.21]; ns.
Subcutaneous treprostinil vs. placebo		
Primary:		

	Exercise capacity – results of the 6-minute walk test	WMD (m)	n.a.
	Secondary:		
	Dyspnea	WMD	n.a.
	Change of pulmonary artery pressure in relation to baseline values – in favor of treprostinil	WMD	-2.71 [-4.20; -1.23]
	Change of pulmonary vascular resistance in relation to baseline values – in favor of treprostinil	WMD	-4.73 [-6.31; -3.15]
	Change of cardiac index in relation to baseline values – in favor of treprostinil	WMD	0.19 [0.08; 0.30]
	Mortality	OR	1.01 [0.35; 2.94]; ns.
	Quality of life	WMD	n.a.
	Dyspnea	WMD	n.a.
	Withdrawal from the study due to clinical worsening	OR	1.02 [0.32; 3.20]; ns.
	Withdrawal from the study due to adverse events – in favor of placebo	OR	13.47 [2.57; 70.48]
	Adverse events	OR	1.05 [0.50; 2.21]; ns.
	Oral beraprost vs. placebo		
Conclusions of the authors, comments	Although relative effects with respect to exercise capacity seem significant, they are much less pronounced in studies with a control group receiving placebo. Improvement in exercise capacity is higher in subgroups of patients with primary PAH than those with secondary PAH. Despite positive effects with regard to this outcome, the Barst 2003 study (concerning beraprost, which was not a subject of this analysis) demonstrated that after 12 months the effect was no longer statistically significant. As to mortality, the results were not statistically significant for any of the investigated interventions. Thus, there is no reason to consider prostacyclin an alternative for transplantation. Prostacyclin or its analogues improve the NYHA class; however, there is much doubt whether this may be treated as improvement in quality of life (for which there is usually no data). Serious adverse events of prostacyclin and its analogues (based not only on RCTs): o increased probability of sepsis, o catheter-related thrombosis (PAH associated with connective tissue diseases), o edema due to venous stenosis. Less serious adverse events include (among others) jaw pain, diarrhea, and headache. Better assessment of adverse events would require studies with longer observation period.		

Table 138.
Characteristics of the Liu 2006 review

Title	**Endothelin receptor antagonists for pulmonary arterial hypertension**
Authors	Liu C, Chen J
Journal/ database	*Cochrane Database of Systematic Reviews 2006*, Issue 3. Art.No.:CD004434. DOI: 10.1002/14651858.CD004434.pub3.
Last update	May 22nd, 2006
Date of the last search	August 1st, 2005 (date of the last addition of new studies, no date of the last search specified)
Aim	Evaluation of efficacy and safety of endothelin receptor antagonists in treatment of pulmonary arterial hypertension.
Inclusion criteria for the studies	Randomized or quasi-randomized clinical trials.

Population	Adults and children with a diagnosis of PAH requiring treatment, to whom anticoagulants were administered.
Intervention	Endothelin receptor antagonists in comparison with any other intervention.
Endpoints (according to the protocol)	• Primary: o 6-minute walk distance o WHO or NYHA (New York Heart Association) functional class – improvement in the classification o Borg Dyspnea Score, Dyspnea – Fatigue Rating o mortality Secondary: o Hemodynamic parameters (mean pulmonary artery pressure and others) o Pulmonary function tests o Adverse events
Included studies	**Barst 2004** o sitaxsentan vs. placebo o RCT; double-blind o 12 weeks o N = 178 **Barst 2004a** o As above (?) **Barst 2004b** o As above (?) **Channick 2001** o bosentan vs. placebo o RCT; triple-blind o 12 weeks o N = 32 **Galiè 2003** o bosentan vs. placebo o RCT; triple-blind o 16 weeks o N = 85 **Humbert 2004** o bosentan + intravenous epoprostenol vs. placebo + intravenous epoprostenol o RCT; double-blind o 16 weeks o N = 33 **Rubin 2002** o bosentan vs. placebo o RCT; triple-blind o 16 weeks o N = 213 **Wilkins 2005** o bosentan vs. sildenafil o Randomized trial; double-blind o 16 weeks o N = 26

Results	**Endpoint**	**Relative outcome measure**	**Result + 95% CI**	
	<u>Endothelin receptor antagonists vs. placebo</u>			

	Primary:			
	Exercise capacity – 6-minute walk test – in favor of ERA	WMD (meters)	37.08 [22.37; 51.08]	
	Improvement in the NYHA classification – in favor of ERA	RR	1.60 [1.17; 2.19];	
	Change of the Borg Dyspnea Score – in favor of ERA	WMD	-0.83 [-1.65; -0.01]	
	Mortality – in favor of placebo	RR	1.32 [0.36; 4.86]; ns.	
	Secondary:			
	Change of pulmonary artery pressure in relation to baseline values – in favor of ERA	WMD	-4.36 [-6.77; -1.94]	
	Change of pulmonary vascular resistance in relation to baseline values – in favor of ERA	WMD	-286.73 [-369.1; -204.36]	
	Change of cardiac index in relation to baseline values – in favor of ERA	WMD	0.51 [0.22; 0.81]	
	Hepatic toxicity – in favor of placebo	OR	1.44 [0.57; 3.66]; ns.	
	ERA vs. sildenafil			
	Primary:			
	Exercise capacity – 6-minute walk test – in favor of sildenafil	WMD	-55.00 [-109.92; -0.08]	
	Mortality – in favor of bosentan	OR	0.36 [0.01; 9.68]; ns.	
	Secondary:			
	Symptoms of PAH	WMD	1.70 [-0.42; 3.82]; ns.	
	Change of cardiac index in relation to baseline values	WMD	0.00 [-0.14; 0.14]; ns.	
Conclusions of the authors, comments	Pulmonary arterial hypertension is related to high mortality. The studies demonstrated that anticoagulants are the only drugs reducing mortality (in the perspective of long-term observational studies). However, this is true for primary PAH only – the authors of the review did not identify any studies that would confirm efficacy of anticoagulants in secondary PAH. Transplantation remains the most efficacious method in terms of mortality. A significant observed adverse event (reported in the Krum 1999 study) was elevation of hepatic transaminase level in 16.5% of patients receiving 500 mg of bosentan twice daily. However, with lower doses (125 and 250 mg twice daily) of bosentan no significant elevation of this enzyme was observed.			

8.2. Assessment of the systematic reviews used – the QUOROM questionnaire

Table 139.
QUOROM – assessment of the "Sildenafil for pulmonary hypertension (Review)"

Category	Subcategory	Description	Present in the text? (Y/N)	Page number
Title		**Identification of the report as a metaanalysis (or systematic review) of randomized clinical trials**	☑	1
Abstract	Aim	Structured format used	☑	1
		Clinical question clearly defined	☑	1
	Data sources	Database or other information source specified	☑	1
	Methodology of the review	Inclusion criteria (population, intervention, main outcomes, study design), methods used for validity assessment, data abstraction, study characteristics and combining results presented in enough detail as to make the analysis reproducible	☑	1

	Results	Characteristics of the included and excluded RCTs presented along with qualitative and quantitative results (e.g. estimations, confidence intervals) and subgroup analysis	☑	1
	Conclusions	Key findings presented	☑	1
Introduction		**Clinical problem clearly described, the biological rationale for the intervention and the rationale for the review presented**	☑	2
Methods	Search	Information sources (e.g. databases, registers, personal files, experts, agencies, hand-searching) and restrictions applied (years, type and language of the publication) described in detail	☑	3
	Study selection	Inclusion and exclusion criteria specified (population, intervention, main outcomes, study design)	☑	2-3
	Validity assessment	Criteria and methods of assessment (e.g. masked conditions, quality assessment) presented	☑	3
	Data abstraction	Appropriate methods applied (e.g. completed independently, in duplicate)	☑	3
	Study characteristics	Sufficient description of study design, participant characteristics, details of intervention, outcome definition and methods of assessment of clinical heterogeneity	☑	4, 9-12
	Quantitative data synthesis	The principal measures of effect (e.g. relative risk), methods of combining results (statistical testing and confidence intervals), handling of missing data, assessment of statistical heterogeneity, rationale for any a priori sensitivity or subgroup analysis and bias assessment presented	☑	3-4, 15-19
Results	Course of metaanalysis	Reasons for exclusion of publications at subsequent stages of selection specified	☐	-
	Study characteristics	Descriptive data for each trial (e.g. age, sample size, intervention, dose, duration, follow-up) presented	☑	9-12
	Quantitative data synthesis	Agreement on the selection and validity assessment; simple summary results (for each treatment group in each trial, for each primary outcome); data needed to calculate effect sizes and confidence intervals in intention-to-treat analysis (e.g. a 2x2 table containing the numbers of patients, mean values with SD, percentages of patients) presented	☑	15-19
Discussion		Key findings summarized; clinical inferences based on internal and external validity discussed; the results interpreted in light of the totality of available evidence; potential biases in the review process (e.g., publication bias) described; future research suggested	☑	6

Table 140.
QUOROM – assessment of the "Prostacyclin for pulmonary hypertension in adults (Review)"

Category	Subcategory	Description	Present in the text? (Y/N)	Page number
Title		Identification of the report as a metaanalysis (or systematic review) of randomized clinical trials	☑	1
Abstract		Structured format used	☑	1
	Aim	Clinical question clearly defined	☑	1
	Data sources	Database or other information source specified	☑	1
	Methodology of the review	Inclusion criteria (population, intervention, main outcomes, study design), methods used for validity assessment, data abstraction, study characteristics and combining results presented in enough detail as to make the analysis reproducible	☑	1
	Results	Characteristics of the included and excluded RCTs presented along with qualitative and quantitative results (e.g. estimations, confidence intervals) and subgroup analysis	☑	1
	Conclusions	Key findings presented	☑	1
Introduction		Clinical problem clearly described, the biological rationale for the intervention and the rationale for the review presented	☑	2-3
Methods	Search	Information sources (e.g. databases, registers, personal files, experts, agencies, hand-searching) and restrictions applied (years, type and language of the publication) described in detail	☑	3-4
	Study selection	Inclusion and exclusion criteria specified (population, intervention, main outcomes, study design)	☑	3
	Validity assessment	Criteria and methods of assessment (e.g. masked conditions, quality assessment) presented	☑	4
	Data abstraction	Appropriate methods applied (e.g. completed independently, in duplicate)	☑	4
	Study characteristics	Sufficient description of study design, participant characteristics, details of intervention, outcome definition and methods of assessment of clinical heterogeneity	☑	4
	Quantitative data synthesis	The principal measures of effect (e.g. relative risk), methods of combining results (statistical testing and confidence intervals), handling of missing data, assessment of statistical heterogeneity, rationale for any a priori sensitivity or subgroup analysis and bias assessment presented	☑	27-61
Results	Course of metaanalysis	Reasons for exclusion of publications at subsequent stages of selection specified	☑	4, 22-24
	Study characteristics	Descriptive data for each trial (e.g. age, sample size, intervention, dose, duration, follow-up) presented	☑	4, 18-24
	Quantitative data synthesis	Agreement on the selection and validity assessment; simple summary results (for each treatment group in each trial, for each primary outcome); data needed to calculate effect sizes and confidence intervals in intention-to-treat analysis (e.g. a 2x2 table containing the numbers of patients, mean values with SD, percentages of patients) presented	☑	5-10, 18-22
Discussion		Key findings summarized; clinical inferences based on internal and external validity discussed; the results interpreted in light of the totality of available evidence; potential biases in the review process (e.g., publication bias) described; future research suggested	☑	10-13

Table 141.
QUOROM – assessment of the "Endothelin receptor antagonists for pulmonary arterial hypertension (Review)"

Category	Subcategory	Description	Present in the text? (Yes/No)	Page number
Title		Identification of the report as a metaanalysis (or systematic review) of randomized clinical trials	Yes	1
Abstract		Structured format used	Yes	1
	Aim	Clinical problem clearly defined	Yes	1
	Data sources	Database or other information source specified	Yes	1
	Methodology of the review	Inclusion criteria (population, intervention, main outcomes, study design), methods used for validity assessment, data abstraction, study characteristics and combining results presented in enough detail as to make the analysis reproducible	No	
	Results	Characteristics of the included and excluded RCTs presented along with qualitative and quantitative results (e.g. estimations, confidence intervals) and subgroup analysis	No	
	Conclusion	Key findings presented	Yes	1
Introduction		Clinical problem clearly described, the biological rationale for the intervention and the rationale for the review presented	Yes	
Methods	Search	Information sources (e.g. databases, registers, personal files, experts, agencies, hand-searching) and restrictions applied (years, type and language of the publication) described in detail	Yes	3
	Study selection	Inclusion and exclusion criteria specified (population, intervention, main outcomes, study design)	Yes	3
	Validity assessment	Criteria and methods of assessment (e.g. masked conditions, quality assessment) presented	Yes	3
	Data abstraction	Appropriate methods applied (e.g. completed independently, in duplicate)	No	
	Study characteristics	Sufficient description of study design, participant characteristics, details of intervention, outcome definition and methods of assessment of clinical heterogeneity	Yes	4
	Quantitative data synthesis	The principal measures of effect (e.g. relative risk), methods of combining results (statistical testing and confidence intervals), handling of missing data, assessment of statistical heterogeneity, rationale for any *a priori* sensitivity or subgroup analysis and bias assessment presented	Yes	4

Results	Course of metaanalysis	Reasons for exclusion of publications at subsequent stages of selection specified	Yes	4
	Study characteristics	Descriptive data for each trial (e.g. age, sample size, intervention, dose, duration, follow-up) presented	Yes	10, 11,12,13,14
	Quantitative data synthesis	Agreement on the selection and validity assessment; simple summary results (for each treatment group in each trial, for each primary outcome); data needed to calculate effect sizes and confidence intervals in intention-to-treat analysis (e.g. a 2x2 table containing the numbers of patients, mean values with SD, percentages of patients) presented	Yes	4, 5, 6, 16-22
Discussion		Key findings summarized; clinical inferences based on internal and external validity discussed; the results interpreted in light of the totality of available evidence; potential biases in the review process (e.g., publication bias) described; future research suggested	Yes	6, 7

8.3. Detailed results of search for the studies

Table 142.
Results of search in the PubMed database

Search: January 29th, 2007		
Indication		
#1	pulmonary hypertension	22384
Intervention I: sildenafil		
#2	Sildenafil	2896
#3	Syldenafil	1
#4	Acetildenafil	2487
#5	Desmethylsildenafil	2485
#6	Homosildenafil	2486
#7	Hydroxyhomosildenafil	2487
#8	UK 92480-10	2485
#9	UK-92,480-10	2485
#10	Viagra	2611
#11	Revatio	2485
#12	#2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11	2982
#13	#12 AND #1	339
Intervention II: treprostinil		
#14	Treprostinil	118
#15	Remodulin	83
#16	UT15	0
#17	UT-15	85
#18	#14 OR #15 OR #16 OR #17	124
#19	#18 AND #1	82
Intervention III: iloprost		
#20	Iloprost	1843
#21	Ciloprost	1423
#22	Ventavis	1423
#23	ZK-36374	1428
#24	ZK 36374	1428
#25	ZK36374	1423
#26	#20 OR #21 OR #22 OR #23 OR #24 OR #25	1850
#27	#26 AND #1	224
Intervention IV: bosentan		
#28	Bosentan	1084
#29	Tracleer	814
#30	Ro 47-0203	821
#31	Ro-47-0203	821
#32	#28 OR #29 OR #30 OR #31	1091
#33	#32 AND #1	299
Intervention V: epoprostenol		
#34	Epoprostenol	11055
#35	Epoprostanol	10830
#36	PGI2	12682
#37	Prostaglandin	102131
#38	Prostacyclin	15476

#39	PGX	38
#40	Flolan	10834
#41	#34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40	104518
#42	#41 AND #1	1789
Summary descriptors		
#43	phosphodiesterase inhibitors	67167
#44	#43 and #1	626
#45	vasodilator agents	266511
#46	#45 AND #1	2606
#47	endothelin receptor antagonists	3620
#48	endothelin receptor antagonist	2856
#49	#47 OR #48	4141
#50	#49 AND #1	417
All interventions		
#51	#50 OR #46 OR #44 OR #42 OR #33 OR #27 OR #19 OR #13	4098
#52	#51 Limits: English, French, German, Spanish, Polish, published in the last 2 years, Clinical Trial, Randomized Controlled Trial, Humans	**75**

Table 143.
Results of search in the EmBase database

Search: January 30th, 2007		
Indication		
#1	pulmonary hypertension	29283
Intervention I: sildenafil		
#2	Sildenafil	6282
#3	Syldenafil	1
#4	Acetildenafil	5
#5	Desmethylsildenafil	2
#6	Homosildenafil	6
#7	Hydroxyhomosildenafil	6
#8	UK 92480-10	2
#9	UK-92,480-10	0
#10	Viagra	6339
#11	Revatio	6282
#12	#2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11	6341
#13	#12 AND #1	842
Intervention II: treprostinil		
#14	Treprostinil	408
#15	Remodulin	413
#16	UT15	451
#17	UT-15	451
#18	#14 OR #15 OR #16 OR #17	454
#19	#18 AND #1	378
Intervention III: iloprost		
#20	Iloprost	3295
#21	Ciloprost	3295
#22	Ventavis	3295
#23	ZK-36374	3299
#24	ZK 36374	205
#25	ZK36374	3299
#26	#20 OR #21 OR #22 OR #23 OR #24 OR #25	3299
#27	#26 AND #1	754
Intervention IV: bosentan		

#28	Bosentan	2085
#29	Tracleer	2085
#30	Ro 47-0203	145
#31	Ro-47-0203	2089
#32	#28 OR #29 OR #30 OR #31	2089
#33	#32 AND #1	899
Intervention V: epoprostenol		
#34	Epoprostenol	18124
#35	Epoprostanol	2
#36	PGI2	18855
#37	Prostaglandin	133224
#38	Prostacyclin	22108
#39	PGX	18167
#40	Flolan	18127
#41	#34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40	154263
#42	#41 AND #1	2927
Summary descriptors		
#43	phosphodiesterase inhibitors	4664
#44	#43 and #1	179
#45	vasodilator agents	24888
#46	#45 AND #1	378
#47	endothelin receptor antagonists	1764
#48	endothelin receptor antagonist	6041
#49	#47 OR #48	6414
#50	#49 AND #1	909
All interventions		
#51	#50 OR #46 OR #44 OR #42 OR #33 OR #27 OR #19 OR #13	4136
#52	#51 Limits: English, French, German, Spanish, Polish, published in the last 2 years, Clinical Trial, Randomized Controlled Trial, Humans	**206**

Table 144.
Results of search in the Cochrane database

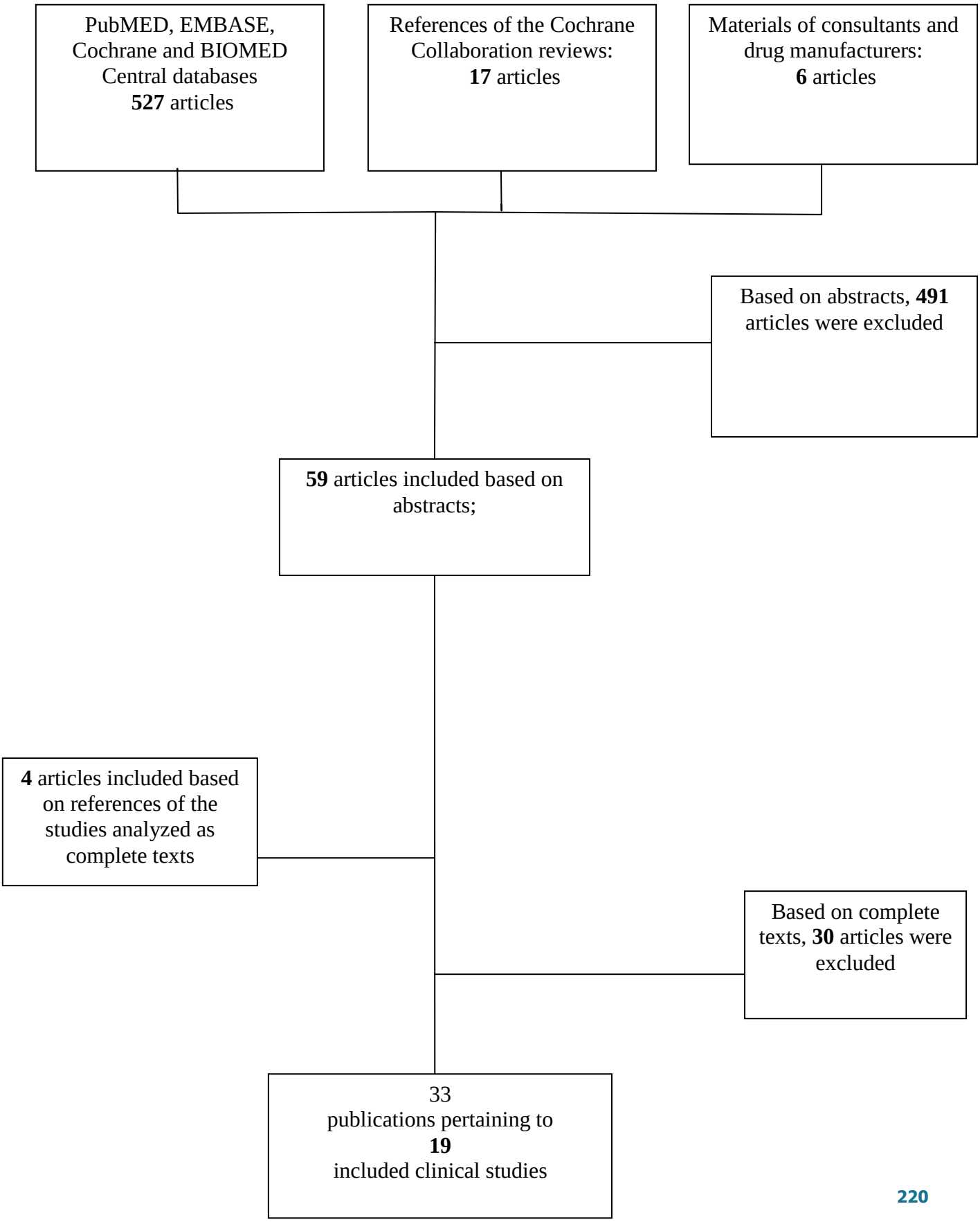
Search: January 30th, 2007		
Indication		
#1	pulmonary hypertension	1209
Intervention I: sildenafil		
#2	Sildenafil OR Syldenafil OR Acetildenafil OR Desmethylsildenafil OR Homosildenafil OR Hydroxyhomosildenafil OR UK 92480-10 OR UK-92,480-10 OR Viagra OR Revatio	412
Intervention II: treprostinil		
#3	Treprostinil OR Remodulin OR UT15 OR UT-15	15
Intervention III: iloprost		
#4	Iloprost OR Ciloprost OR Ventavis OR ZK-36374 OR ZK 36374 OR ZK36374	223
Intervention IV: bosentan		
#5	Bosentan OR Tracleer OR Ro 47-0203 OR Ro-47-0203	58
Intervention V: epoprostenol		
#6	Epoprostenol OR Epoprostanol OR PGI2 OR Prostaglandyn OR Prostacyclin OR PGX OR Flolan	943
Summary descriptors		
#7	phosphodiesterase inhibitors OR vasodilator agents OR endothelin	3706

	receptor antagonists OR endothelin receptor antagonist	
All interventions		
#8	#2 OR #3 OR #4 OR #5 OR #6 OR #7	4768
#9	#1 AND #8	248
#10	#9 Limits: published in the last 2 years	**44**

Table 145.
Results of search in the Biomed Central database

Search: January 29th, 2007		
Indication		
#1	**pulmonary hypertension** (all words) in *all fields*	1025
Intervention I: sildenafil		
#2	sildenafil OR syldenafil OR acetildenafil OR desmethylsildenafil OR UK 92480-10 OR UK-92,480-10 OR viagra OR revatio	200
#3	#1 AND #2	54
Intervention II: treprostinil		
#4	treprostinil OR remodulin OR UT15 OR UT-15	10
#5	#1 AND #4	8
Intervention III: iloprost		
#6	iloprost OR ciloprost OR ventavis OR ZK-36374 OR ZK 36374 OR ZK36374	40
#7	#1 AND #5	24
Intervention IV: bosentan		
#8	bosentan OR Tracleer OR Ro 47-0203 OR Ro-47-0203	75
#9	#1 AND #9	49
Intervention V: epoprostenol		
#10	epoprostenol OR epoprostanol OR PGI2 OR prostaglandin OR prostacyclin OR PGX OR flolan	1263
#11	#1 AND #10	151
All interventions		
#51	#3 OR #5 OR #7 OR #9 OR#11	**202**

8.4. Description of the process of search for primary studies



8.5. Characteristics of the studies included in the analysis

8.5.1. Bosentan vs. placebo

Table 146.
Characteristics of the *Channick 2001* study

Name of the study	*Channick 2001*	
Study design	Multicenter, randomized, double-blind, parallel clinical study	
Jadad score	4	
Inclusion criteria for patients	Severe symptomatic PAH – primary or secondary to scleroderma; WHO functional class III-IV; Previous treatment with vasodilators, anticoagulants, diuretics, cardiac glycosides or oxygen; 6-minute walk distance between 150 and 500 m; Mean pulmonary arterial pressure over 25 mmHg; Pulmonary capillary wedge pressure below 15 mmHg; Pulmonary vascular resistance over 240 dyn/s/cm^5.	
Exclusion criteria for the patients	Functional class IV; Introduction or discontinuation of treatment with anticoagulants, diuretics, cardiac glycosides or oxygen within one month prior to enrollment; Long-term treatment with epoprostenol; Treatment with glibenclamide or cyclosporine within one month prior to enrollment (in order to avoid potential drug interactions).	
Baseline characteristics of the population		
Parameter	**Bosentan**	**Placebo**

Total number of patients	21	11
Mean age (SD) [years]	52.2 (12.2)	47.4 (14.0)
Percentage of men	19%	0%
Percentage of patients with primary PAH	81%	91%
Percentage of patients with PAH secondary to scleroderma	19%	9%
Percentage of patients in WHO functional class III	100%	100%
Percentage of patients in WHO functional class IV	0%	0%
Description of the interventions	Bosentan at a dose of 62.5 mg twice daily for the first four weeks, then at a dose of 125 mg twice daily until any treatment-related adverse events occurred	Placebo
Endpoints	Exercise capacity after 12 weeks of treatment defined as the 6-minute walk distance Cardiovascular hemodynamic parameters (pulmonary vascular resistance, cardiac index, mean pulmonary pressure, pulmonary capillary wedge pressure, mean right ventricular pressure) measured by means of right ventricular catheterization; Borg Dyspnea Score; Change of the WHO functional class; Withdrawal from the study due to exacerbation of the symptoms.	
Observation period	28 weeks	
Information concerning patients lost from the study	25 patients lost from the study, 15 from the bosentan group and 10 from the placebo group	
Description of the randomization method	Computed, using the Almedica system for drug marking	
Description of the method of blinding	Double-blind study, no detailed description	
Comments (conflicts of interest, sources of financing)	none	

Table 147.
Characteristics of the *Rubin 2002* study

Name of the study	*Rubin 2002*		
Study design	Multicenter, randomized, double-blind clinical study with three parallel groups		
Jadad score	3		
Inclusion criteria for patients	Severe, symptomatic PAH – primary or secondary to a connective tissue disease (scleroderma or systemic lupus erythematosus); WHO functional class III-IV (for patients in class IV stable condition required); Previous treatment with vasodilators, anticoagulants, diuretics, cardiac glycosides or oxygen; 6-minute walk distance between 150 and 450 m; Mean pulmonary arterial pressure at rest over 25 mmHg; Pulmonary capillary wedge pressure below 15 mmHg; Pulmonary vascular resistance over 240 dyn/s/cm^5.		
Exclusion criteria for the patients	Introduction or discontinuation of any treatment for pulmonary hypertension within one month prior to enrollment; Treatment with epoprostenol within 3 months prior to enrollment; Treatment with glibenclamide or cyclosporine (in order to avoid potential drug interactions).		
Baseline characteristics of the population			
Parameter	**Bosentan 125 mg**	**Bosentan 250 mg**	**Placebo**
Total number of patients	74	70	69
Mean age (SD) [years]	50.4 (15.9)	47.0 (15.6)	47.2 (16.2)
Percentage of men	23%	19%	22%
Percentage of patients with primary PAH	77%	64%	70%

Percentage of patients with PAH secondary to scleroderma	18%	29%	20%
Percentage of patients with PAH secondary to systemic lupus erythematosus	5%	7%	10%
Percentage of patients in WHO functional class III	89%	92%	94%
Percentage of patients in WHO functional class IV	11%	8%	6%
Description of the interventions	Bosentan (Tracleer) at a dose of 62.5 mg twice daily for the first four weeks, then at a dose of 125 mg twice daily for 12 weeks.	Bosentan (Tracleer) at a dose of 62.5 mg twice daily for the first four weeks, then at a dose of 250 mg twice daily for 12 weeks.	Placebo
Endpoints	Exercise capacity after 16 weeks of treatment defined as the 6-minute walk distance Borg Dyspnea Score (0-10 points, where 10 represents most severe dyspnea); Change of the WHO functional class; Time from randomization to worsening defined as death, pulmonary transplantation, hospitalization due to pulmonary hypertension, lack of improvement or withdrawal from the study due to worsening, necessity of introduction of treatment with epoprostenol or atrial septostomy; Safety (adverse events)		
Observation period	16 weeks + additional 12 weeks (28 weeks)		
Information concerning patients lost from the study	Due to adverse events 6% of patients were lost from the bosentan groups and 7% from the placebo group.		
Description of the randomization method	No description		
Description of the method of blinding	No description		
Comments (conflicts of interest, sources of financing)	The study was financed by the Actelion company (Allschwil, Switzerland). All the authors had financial relations with the Actelion company.		

Table 148.
Characteristics of the *Barst 2006* study

Name of the study	*Barst 2006*	
Study design	With respect to bosentan – randomized, open-label, multicenter (international) study	
Jadad score	3	
Inclusion criteria for patients	1. PAH – idiopathic or associated with connective tissue diseases or congenital heart diseases (operated atrial or ventricular septal defect or patent Botall's duct operated at least a year before enrollment or unoperated secondary atrial septal defect (with oxygen saturation ≥ 88%)). 2. Mean pulmonary arterial pressure ≥ 25 mmHg at rest, pulmonary capillary wedge pressure or left ventricular end-diastolic pressure ≤ 15 mmHg and pulmonary vascular resistance ≥ 3 Wood units 3. baseline 6-MWD ≥ 150 m and ≤ 450 m 4. body mass ≥ 50 kg for patients aged < 18 years	
Exclusion criteria for the patients	Significant interstitial lung disease, portal hypertension, chronic disease of the liver, HIV infection, hepatic disorder (transaminase level > 1.5 times higher than the upper limit), renal insufficiency, history of left ventricular failure or obstructive sleep-apnea syndrome, previous failure with bosentan treatment, use of a PD5 inhibitor, an ET receptor antagonist or any new treatment for PAH within 30 days prior to enrollment.	
Baseline characteristics of the population		
Parameter	**Bosentan**	**Placebo**
Total number of patients	60	62
Mean age (SD) [years]	49 ± 16 (range 18 – 77)	53 ± 15 (range 22-77)
Number of women	47 (78%)	47 (76%)
NYHA class II	22 (37%)	23 (37%)
NYHA class III	37 (62%)	35 (57%)
NYHA class IV	1 (2%)	4 (6%)

Description of the interventions	Bosentan (administered orally): 4 weeks: 62.5 mg twice daily, then increased to 125 mg twice daily	placebo
Endpoints	Primary: change of the 6-MWD after 18 weeks Tests Secondary:<0change of the WHO functional class, time to clinical worsening, change of the Borg Dyspnea Score Assessment of safety – based on adverse events and laboratory tests (hepatic enzymes)	
Observation period	18 weeks	
Information concerning patients lost from the study	8 patients	
Description of the randomization method	Computed randomization	
Description of the method of blinding	None since the drug was available for a specific patient only; Assessment of some parameters (e.g. the 6-MWT, the WHO functional class, the Borg Dyspnea Score) was blinded	
Comments (conflicts of interest, sources of financing)	The authors of the study work as consultants for the sponsor – Encysive Pharmaceutics	

Table 149.
Characteristics of the BREATHE-5 study

Name of the study	BREATHE-5
Study design	Double-blind, multicenter, randomized clinical trial
Jadad score	5
Inclusion criteria for patients	Patients aged over 12 years in NYHA functional class III, with Eisenmenger's syndrome. Arterial blood oxygen saturation between 70 and 90%. 6-MWD between 150 and 450 meters.
Exclusion criteria for the patients	Patent Botall's duct (due to complications in measurement of hemodynamic parameters), combined congenital heart disease, left ventricular failure (left ventricular ejection fraction < 40%); restrictive lung disease (total lung capacity < 70% of the normal value); obstructive pulmonary disease (forced expiratory volume in one second

	[FEV_1] < 70% of the normal value and FEV_1/FVC < 60%), recently diagnosed coronary artery disease	
Baseline characteristics of the population		
Parameter	**Intervention group**	**Control group**
Total number of patients	37	17
Mean age (SD) [years]	37.2 [SD 12]	44.2 [SD 8.5]
Percentage of men	38%	41%
Ventricular septal defects	65%	71%
Atrial septal defects	22%	29%
Atrioventricular septal defects	14%	0%
Description of the interventions	Conventional treatment + bosentan (62.5 mg twice daily for 4 weeks; later 125 mg twice daily)	Conventional treatment + placebo
Endpoints	Hemodynamic parameters; 6-minute walk distance	
Observation period	16 weeks	
Information concerning patients lost from the study	4 patients were lost from the study; the procedure for lost patients was as follows: in case of death, necessity of transplantation or loss from the study the worst outcomes are assumed (e.g. the 6-minute walk distance 0 m); in case of patients lost from the study due to reasons other than worsening of the patient's condition, the last recorded result was repeated in subsequent measurements	
Description of the randomization method	Randomization was controlled by means of packing of the drugs for the study. The patients were randomized in sequence, beginning from the lowest drug number.	
Description of the method of blinding	Placebo looking like bosentan was used. The patients, physicians, monitors and the sponsor's personnel remained "blinded" until the clinical database was closed.	
Comments (conflicts of interest, sources of financing)	7 out of 8 authors declared conflict of interest; the study was supported by Actelion Pharmaceuticals Ltd. Some investigators received grants from the following companies: Actelion, Pfizer, Schering, Encysive, Myogen, GlaxoSmithKline, Lilly, NITROX, NMT Medical and AGA Medical.	

8.5.2. Epoprostenol vs. placebo

Table 150.
Characteristics of the *Rubin 1990* study

Name of the study	*Rubin 1990*	
Study design	Open-label study consisting of two phases: randomized and non-randomized	
Jadad score	3	
Inclusion criteria for patients	Patients with PAH, mainly not responding to or not tolerating other vasodilating therapy.	
Exclusion criteria for the patients	-	
Baseline characteristics of the population		
Parameter	**Intervention group**	**Control group**
Total number of patients	11	12
Mean age (SD) [years]	37.45 [12.65]	35.00 [15.49]
Percentage of men	36%	25%
Percentage of patients in NYHA functional class II	9%	8%
Percentage of patients in NYHA functional class III	82%	50%
Percentage of patients in NYHA functional class IV	9%	42%
Description of the interventions	Intravenous epoprostenol (continuous infusion) + conventional treatment	Conventional treatment
Endpoints	Hemodynamic parameters; the 6-minute walk test	
Observation period	8 weeks (randomized phase) and up to 18 months (non-randomized phase)	

Information concerning patients lost from the study	4 died, 1 lost from the study due to adverse events (pulmonary edema)
Description of the randomization method	The investigator called a central phone number, where a subsequent envelope containing the patients assignment (the experimental or control group) was opened;
Description of the method of blinding	No blinding
Comments (conflicts of interest, sources of financing)	No data concerning conflicts of interest or sources of financing

Table 151.
Characteristics of the *Barst 1996* study

Name of the study	***Barst 1996***	
Study design	Randomized, open-label clinical trial	
Jadad score	3	
Inclusion criteria for patients	Symptomatic PAH	
Exclusion criteria for the patients	-	
Baseline characteristics of the population		
Parameter	**Intervention group**	**Control group**
Total number of patients	41	40
Mean age (SD) [years]	40 (3)	40 (2)
Percentage of men	24%	30%
NYHA class III	76%	73%
NYHA class IV	24%	27%
Description of the interventions	Conventional treatment + prostacyclin	Conventional treatment

Endpoints	Exercise capacity, hemodynamic parameters, quality of life
Observation period	12 weeks
Information concerning patients lost from the study	3 patients underwent pulmonary transplantation (excluded from the study); for 8 patients who died the worst possible results were assumed in the first variant of the analysis (in the second variant those patients were not taken into account);
Description of the randomization method	No description
Description of the method of blinding	No blinding
Comments (conflicts of interest, sources of financing)	The study was partially sponsored by Glaxo Wellcome Inc.; no information concerning conflicts of interest

Table 152.
Characteristics of the *Badesch 2000* study

Name of the study	***Badesch 2000***	
Study design	Randomized, controlled, open-label study	
Jadad score	3	
Inclusion criteria for patients	Pulmonary arterial hypertension secondary to scleroderma; age at least 16 years; 6-minute walk distance at least 50 m; moderate to severe PAH without a diagnosis of thromboembolic disease or interstitial lung disease	
Exclusion criteria for the patients	Any long-term treatment for pulmonary hypertension or scleroderma introduced within a month prior to enrollment; any other treatment for pulmonary hypertension or scleroderma discontinued within a week prior to enrollment excepting anticoagulants; any treatment with prostaglandins.	
Baseline characteristics of the population		
Parameter	**Intervention group**	**Control group**
Total number of patients	56	55
Mean age (SD) [years]	53.00 [13.1]	57.3 [10.3]

Percentage of men	9%	18%
Percentage of patients in NYHA class II	2%	7%
Percentage of patients in NYHA class III	75%	82%
Percentage of patients in NYHA class IV	23%	11%
Description of the interventions	Epoprostenol + conventional treatment	Conventional treatment
Endpoints	Exercise capacity, hemodynamic parameters, survival rate	
Observation period	12 weeks	
Information concerning patients lost from the study	Causes of death specified in both groups.	
Description of the randomization method	Stratified block randomization; the investigators contacted the center in order to assign a patient to a specific group.	
Description of the method of blinding	No blinding	
Comments (conflicts of interest, sources of financing)	The study was financed by Glaxo Wellcome Inc. (participation in data collection and analysis); some of the authors declared conflicts of interest;	

8.5.3. Iloprost vs. placebo

Table 153.
Characteristics of the *Thurm 1991* study

Name of the study	*Thurm 1991*
Study design	Randomized, double-blind, parallel clinical study
Jadad score	3
Inclusion criteria for patients	Pulmonary hypertension secondary to systemic scleroderma fulfilling the criteria of the American College of Rheumatology;

	Raynaud's phenomenon (at least 8 episodes per week).	
Exclusion criteria for the patients	Smoking	
Baseline characteristics of the population		
Parameter	**Iloprost**	**Placebo**
Total number of patients	6	7
Mean age (SD) [years]	55.2 (14.5)	45.7 (8.7)
Percentage of men	17%	29%
Percentage of patients with primary PAH	0%	0%
Percentage of patients with PAH secondary to systemic scleroderma	100%	100%
Description of the interventions	Intravenous iloprost (continuous infusion) at a dose of 0.5-2.0 ng/kg/min for 6 hours on each of 3 days of treatment	Intravenous placebo (continuous infusion) for 6 hours on each of 3 days of treatment
Endpoints	Spirometric measurements and diffusion capacity of the lungs (DL_{CO}) measured by the single breath method (measured twice within 5 minutes in upright position; the measurement was repeated twice after 20 minutes of rest in supine position; the final result was the mean value of the two measurements). Alveolar volume was calculated by helium dilution during a breath hold of 10 seconds.	
Observation period	3 days	
Information concerning patients lost from the study	One patient was lost from the iloprost group due to technical reasons	
Description of the randomization method	None	
Description of the method of blinding	None	
Comments (conflicts of interest, sources of financing)	None	

Table 154.
Characteristics of the *Olschewski 2002* study

Name of the study	*Olschewski 2002*	
Study design	Multicenter, randomized, parallel clinical study	
Jadad score	2	
Inclusion criteria for patients	PAH – primary or secondary to appetite suppressant drugs, scleroderma or chronic thromboembolic disease; NYHA functional class III-IV; 6-minute walking distance (without encouragement) 50-500 m; Mean pulmonary arterial pressure over 30 mmHg; Previous treatment with anticoagulants, diuretics, cardiac glycosides, calcium channel blockers (at a stable dose for at least 6 weeks prior to enrollment) or oxygen;	
Exclusion criteria for the patients	Treatment with the investigated drugs, prostanoids or beta-blockers; Pulmonary capillary wedge pressure at rest over 15 mmHg; Cardiac index at rest below 1.5 or over 4 l/min/m^2 of the body surface area; Vascular diseases; Bilirubin concentration over 3 mg/dl; Creatinine clearance below 30 ml/min; Forced vital capacity (FVC) below 50%; Forced expiratory volume in one second (FEV_1) below the mean normal value minus twice the standard deviation; Clinical instability.	
Baseline characteristics of the population		
Parameter	**Iloprost**	**Placebo**
Total number of patients	101	102
Mean age (SD) [years]	51.2 (13.2)	52.8 (12.0)

Percentage of men	31.7%	33.3%
Percentage of patients with primary PAH	50.5%	50.0%
Percentage of patients with PAH secondary to treatment with appetite suppressant drugs	4.0%	4.9%
Percentage of patients with PAH secondary to vascular collagenosis	12.9%	21.6%
Percentage of patients with PAH secondary to chronic thromboembolic disease	32.7%	23.5%
Percentage of patients in NYHA functional class III	59.4%	57.8%
Percentage of patients in NYHA functional class IV	40.6%	42.2%
Description of the interventions	Iloprost (Ilomedin) administered in inhalation by means of a nebulizer (HaloLite, MedicAid) at a dose of 2.5 or 5.0 µg/ml in one inhalation (depending on tolerance of the first dose). The amount of drug remaining in the nebulizer was discarded after each inhalation. This action was repeated 6-9 times a day. Frequency of inhalations and the dose administered was adjusted individually during the first 8 days of treatment, according to a pre-defined dosage algorithm.	Placebo administered in inhalation by means of a nebulizer
Endpoints	Increase of the 6-minute walk distance by 10%; Functional improvement according to the NYHA classification without clinical worsening or death within 12 weeks of treatment; Change of the 6-minute walk distance; Change of the NYHA functional class; Change of the Mahler Dyspnea Index; Hemodynamic parameters; Quality of life;	

	Clinical worsening; Death; Necessity of transplantation; Adverse events.
Observation period	12 weeks
Information concerning patients lost from the study	Patients lost from the study constituted 4.0% of the iloprost group and 13.7% of the placebo group.
Description of the randomization method	None
Description of the method of blinding	None
Comments (conflicts of interest, sources of financing)	Study sponsored by the Schering company (Berlin, Germany). All the authors had financial relations with Shering.

8.5.4. Sildenafil vs. placebo – adults

Table 155.
Characteristics of the *Bharani 2003* study

Name of the study	***Bharani 2003***
Study design	Prospective, randomized, double-blind, placebo-controlled, cross-over study
Jadad score	4
Inclusion criteria for patients	NYHA functional class ≥ II Systolic pulmonary pressure ≥ 35 mmHg with normal left ventricular function (evaluated by Doppler imaging) Patients with PAH of various etiology
Exclusion criteria for the patients	Contraindications to sildenafil; Reversible cause of PAH, e.g. valvular disease
Baseline characteristics of the population	

Parameter	
Total number of patients	9
Mean age (SD) [years]	32.11 (18 – 60)
Percentage of men	44%
Percentage of patients with idiopathic PAH	33.3% (3)
Percentage of patients with secondary PAH associated with interstitial lung disease	22.2% (2)
Percentage of patients with PAH secondary to chronic thromboembolic disease	11.1% (1)
Percentage of patients with PAH secondary to Eisenmenger's syndrome	33.3% (3)
Percentage of patients in WHO functional class II	33.3% (3)
Percentage of patients in WHO functional class III	55.6% (5)
Percentage of patients in WHO functional class IV	11.1% (1)
Description of the interventions	The patients received sildenafil at a dose of 25 mg or placebo every 8 hours for 2 weeks followed by a pause of 2 weeks and subsequent treatment with the other intervention (cross-over design). In addition the patients received conventional treatment (warfarin, nifedipine, diuretics, digoxin).
Endpoints	Primary: Exercise capacity – 6-MWD Secondary efficacy measures: Change of symptoms, the NYHA class, modified Borg Dyspnea Score, systolic pulmonary arterial pressure at rest
Observation period	2 weeks for each intervention (cross-over design)
Information concerning patients lost from the study	No patients lost from the study

Description of the randomization method	None
Description of the method of blinding	None
Comments (conflicts of interest, sources of financing)	No information

Table 156.
Characteristics of the *Sastry 2004* study

Name of the study	***Sastry 2004***	
Study design	Randomized, double-blind, cross-over clinical study	
Jadad score	4	
Inclusion criteria for patients	Primary pulmonary arterial hypertension; Patients aged 12-65 years; NYHA functional class II or III; Mean pulmonary arterial pressure over 30 mmHg; Ability to perform exercise tests.	
Exclusion criteria for the patients	NYHA functional class IV; Significant left-to-right shunt; Valvular heart disease; Systolic left ventricular failure; Systemic hypertension; Secondary pulmonary hypertension; Other concomitant diseases.	
Baseline characteristics of the population		
Parameter	**Sildenafil**	**Placebo**

Total number of patients	22	
Age range [years]	16 - 55	
Percentage of men	45.5%	
Percentage of patients with primary PAH	100%	
Percentage of patients with secondary PAH	0%	
Percentage of patients in NYHA functional class II	82%	
Percentage of patients in NYHA functional class III	18%	
Description of the interventions	Sildenafil at a dose adjusted to body mass: patients with body mass below 25 kg received sildenafil at a dose of 25 mg 3 times daily, between 26 and 50 kg - 50 mg 3 times daily, over 50 kg - 100 mg 3 times daily. Additional treatment, including digoxin, diuretics and oral anticoagulants, remained at the physician's discretion.	Placebo
Endpoints	Treadmill test (time); Cardiac index; Pulmonary systolic pressure; Quality of life assessed using the Chronic Heart Failure Questionnaire consisting of 16 questions, of which 5 are related to assessment of dyspnea, 4 – fatigue and 7 – emotional function; Adverse events.	
Observation period	6 weeks	
Information concerning patients lost from the study	Two patients were lost – one in the sildenafil group and one in the placebo group	
Description of the randomization method	Computed	
Description of the method of blinding	Patients, physicians and other personnel (e.g. performing echocardiography or supervising exercise tests) were not informed about the patient's assignment.	
Comments (conflicts of interest, sources of financing)	None	

Table 157.
Characteristics of the *Singh 2006* study

Name of the study	*Singh 2006*	
Study design	Single-center, randomized, double-blind, cross-over clinical study	
Jadad score	3	
Inclusion criteria for patients	PAH – idiopathic or secondary to Eisenmenger's syndrome	
Exclusion criteria for the patients	Coronary artery disease; Significant renal or hepatic disorder; Contraindications to sildenafil; PAH related to causes other than listed above.	
Baseline characteristics of the population		
Parameter	**Patients with idiopathic PAH**	**Patients with PAH secondary to Eisenmenger's syndrome**
Total number of patients	10	10
Median age (range) [years]	35 (3 – 45)	15 (4 – 35)
Percentage of men	10%	40%
Percentage of patients in NYHA functional class II	50%	30%
Percentage of patients in NYHA functional class III	50%	60%
Percentage of patients in NYHA functional class IV	0%	10%
Description of the interventions	**Sildenafil**	**Placebo**
	Adults: sildenafil at a dose of 25 mg from the first day of treatment. Drug administered every 6 hours. If no hypotension occurred, the drug was administered at	Placebo. Additional treatment was allowed: digoxin, diuretics

	a dose of 100 mg 3 times daily. Children with a body mass of less than 30 kg: initial dose – 3.125 mg, then 25 mg 3 times daily. Children with a body mass > 30 kg: initial dose – 6.25 mg, then 50 mg 3 times daily. Additional treatment was allowed: digoxin, diuretics and oral anticoagulants.	and oral anticoagulants.
Endpoints	Exercise capacity evaluated using the 6-minute walk test; Clinical improvement; Change of the NYHA functional class (in relation to baseline); Time of exercise; Metabolic equivalent (units) according to the Bruce protocol; Reduction of pulmonary arterial pressure measured by echocardiography.	
Observation period	6 weeks. After a washout period of 2 weeks the patients were crossed over to the other group.	
Information concerning patients lost from the study	None	
Description of the randomization method	Randomization performed by the Department of Pharmacology. No detailed description.	
Description of the method of blinding	Blinding performed by the Department of Pharmacology. No detailed description.	
Comments (conflicts of interest, sources of financing)	None.	

Table 158.
Characteristics of the SUPER-1 study

Name of the study	SUPER-1			
Study design	Multicenter, randomized, double-blind, parallel clinical study			
Jadad score	4			
Inclusion criteria for patients	PAH – idiopathic, associated with connective tissue diseases or secondary to a surgical intervention due to congenital systemic-to-pulmonary shunt performed within 5 years prior to enrollment; Mean pulmonary arterial pressure over 25 mmHg; Pulmonary capillary wedge pressure at rest below 15 mmHg; Conventional treatment.			
Exclusion criteria for the patients	Treatment with intravenous epoprostenol, oral bosentan, intravenous or inhaled iloprost, subcutaneous treprostinil or L-arginine. 6-minute walk distance below 100-450 m.			
Baseline characteristics of the population				
Parameter	**Sildenafil 20 mg**	**Sildenafil 40 mg**	**Sildenafil 80 mg**	**Placebo**
Total number of patients	69	67	71	70
Mean age (SD) [years]	47 (14)	51 (15)	48 (15)	49 (17)
Percentage of men	29%	30%	21%	19%
Percentage of patients with idiopathic PAH	64%	64%	65%	60%
Percentage of patients with PAH secondary to scleroderma	13%	16%	14%	11%
Percentage of patients with PAH secondary to systemic lupus erythematosus	9%	4%	8%	6%

Percentage of patients with PAH secondary to other connective tissue diseases	9%	9%	7%	14%
Percentage of patients in WHO functional class I	0%	0%	0%	1%
Percentage of patients in WHO functional class II	35%	34%	39%	46%
Percentage of patients in WHO functional class III	58%	66%	59%	49%
Percentage of patients in WHO functional class IV	7%	0%	1%	4%
Description of the interventions	Sildenafil at a dose of 20 mg 3 times daily for 12 weeks, then for 6 weeks sildenafil at a dose of 40 mg and 80 mg for the rest of the treatment period	Sildenafil at a dose of 40 mg 3 times daily for 12 weeks, then the same dose for 6 weeks and 80 mg for the rest of the treatment period	Sildenafil at a dose of 80 mg 3 times daily from the second week of treatment. For the first 7 days the patients received sildenafil at a dose of 40 mg 3 times daily.	Placebo
Endpoints	Exercise capacity defined as the 6-minute walk distance; Mean change in pulmonary arterial pressure in relation to baseline values; Borg Dyspnea Score (0 – no dyspnea, 10 – most severe dyspnea); Functional classification of pulmonary arterial hypertension according to WHO; Time from randomization to worsening defined as death, transplantation, hospitalization due to pulmonary arterial hypertension or introduction of additional treatment for PAH with intravenous epoprostenol or oral bosentan; Adverse events.			
Observation period	12 weeks. The study was extended to 1 year.			
Information concerning patients lost from the study	During an observation period of 12 weeks 13 patients were lost; 6 patients refused to participate in the extended study. Over 1 year of observation a total number of 56 patients were lost.			
Description of the randomization method	Central, stratified with respect to the walk distance (< or ≥ 325 m) and etiology of PAH.			
Description of the method of blinding	A double-blinding method was applied.			
Comments (conflicts of interest, sources of financing)	The study was financed by Phizer Global Research and Development (Kent, Great Britain)			

8.5.5. Sildenafil vs. placebo – children

Table 159.
Characteristics of the *Baquero 2006* study

Name of the study	*Baquero 2006*	
Study design	Single-center, randomized, double-blind, parallel clinical study	
Jadad score	5	
Inclusion criteria for patients	Newborns or fetuses above 35.5 weeks of gestational age; Severe hypoxemia and pulmonary hypertension confirmed by echocardiography; Necessity of artificial ventilation and oxygen index ≥ 40; Symptomatic, severe, refractory hypoxemia; Left-to-right shunt confirmed by echocardiography; Pulmonary arterial pressure ≥ 40 mmHg.	
Exclusion criteria for the patients	Congenital abnormalities; Any congenital heart disease, including pulmonary stenosis, atrial septal defect, anomalous pulmonary venous drainage, ventricular septal defect;	
Baseline characteristics of the population		
Parameter	**Sildenafil**	**Placebo**
Total number of patients	7	6
Mean gestational age (SD) [weeks]	38.4 (2.6)	37.2 (1.9)
Percentage of male newborns	57%	50%
Birth weight (SD) [g]	2803 (617)	2710 (554)

Percentage of the newborns born by cesarean section	71%	83%
Percentage of the newborns with meconium aspiration	57%	33%
Percentage of patients with acute respiratory distress syndrome	43%	67%
Description of the interventions	Sildenafil at a concentration of 2 mg/ml. A 50 mg tablet was dissolved in 25 ml of Orabase. Frozen components were deemed outdated after 1 month. The drug was administered by an oropharyngeal tube. The drug at a dose of 1 mg/kg (0.5 ml/kg) was administered not later than 30 minutes after randomization, and then every 6 hours. The dose was doubled (2.0 mg/kg or 1/0 ml/kg) if oxygen index did not improve and arterial blood pressure remained stable after administration of the previous dose.	Placebo solvent (0.5-1 ml/kg) administered by an oropharyngeal tube. Placebo (1 mg/kg or 0.5 ml/kg) was administered not later than 30 minutes after randomization, and then every 6 hours. The dose was doubled if oxygen index did not improve and arterial blood pressure remained stable after administration of the previous dose.
Endpoints	Improvement in oxygen index defined as decrease by at least 6 with relation to the previously calculated value. Decrease of this parameter by more than 10% was considered significant; Gastric tolerance; Arterial blood pressure; Ventilation parameters (oxygen saturation and partial pressure in the alveolar air); Survival.	
Observation period	42 hours after administration of the first dose of the drug.	
Information concerning patients lost from the study	One newborn was lost in the sildenafil group and 5 in the placebo group. The cause of the loss was death.	
Description of the randomization method	Sealed envelopes containing numbers were used.	
Description of the method of blinding	Physicians were not informed, which drug is administered to a specific newborn. Masking was performed at the dispensary by preparing containers for oral solutions looking the same for sildenafil and placebo and marked with a sealed identification code.	
Comments (conflicts of interest, sources of financing)	One of the authors took part in another clinical study concerning sildenafil and sponsored by Phizer.	

Table 160.
Characteristics of the *Namachivayam 2006* study

Name of the study	*Namachivayam 2006*	
Study design	Double-blind, randomized, controlled clinical trial	
Jadad score	4	
Inclusion criteria for patients	Children undergoing artificial ventilation in the pediatric intensive care unit who received inhaled NO at a dose of 10 ppm or higher for at least 12 hours.	
Exclusion criteria for the patients	Previous unsuccessful attempt to discontinue treatment with NO, use of intravenous vasodilators (nitrates), hepatocellular damage, oxygen fraction in the inhaled air above 0.6 at the time of recruitment, congenital heart diseases with anomalous pulmonary or systemic venous drainage and impossibility of measurement of pulmonary artery pressure or the right ventricle.	
Baseline characteristics of the population		
Parameter	**Sildenafil**	**Placebo**
Total number of patients	15	14 (15)
Median age (interquartile range)	0.47 (0.13-1.31)	0.28 (0.1-0.81)
Body mass (interquartile range) [kg]	4.6 (3.1-8.8)	4.0 (3.6-8.8)
Percentage of patients with a congenital heart disease	0.87	0.71
Time of mechanical ventilation before enrollment (interquartile range) [h]	94 (54-122)	70 (36-175)
Description of the interventions	Sildenafil 0.4 mg/kg an hour before discontinuation of NO	Placebo an hour before discontinuation of NO
Endpoints	Relapse of pulmonary hypertension, hemodynamic parameters, duration of the stay in the intensive care unit.	

Observation period	4 hours
Information concerning patients lost from the study	One child died immediately after randomization into the control group (out of 15 randomized into this group).
Description of the randomization method	Random permuted blocks of 10 patients.
Description of the method of blinding	The patients, parents, investigators and analysts were “blinded”. Study drugs were prepared by the pharmaceutical department of the hospital, in which the study was carried out.
Comments (conflicts of interest, sources of financing)	The authors declared no conflicts of interests; no information concerning sources of financing was provided.

8.5.6. Treprostinil vs. placebo

Table 161.
Characteristics of the *McLaughlin 2003* study

Name of the study	***McLaughlin 2003***		
Study design	Study I Multicenter, open-label, short-term study	Study II Multicenter, open-label, short-term study	Study III Multicenter, randomized, double-blind, placebo-controlled study
Jadad score	3		
Inclusion criteria for patients	NYHA functional class III or IV; mean pulmonary arterial pressure ≥ 25 mmHg; pulmonary capillary wedge pressure or left ventricular end-diastolic pressure ≤ 15 mmHg pulmonary vascular resistance > 3 Wood units 6-MWD (in Study III): 50 – 450m		
Baseline characteristics of the population			
Parameter	**Epoprostenol iv. vs. treprostinil iv.**	**Treprostinil iv. vs. treprostinil**	**Treprostinil sc. vs. placebo**

		sc.	
Total number of patients	14	25	26
Age [years]	35±12	42±11	37±17
Age range	12-57	22-71	12-73
Percentage of men, n (%)	4(29)	2(20)	5(19)
Percentage of women, n (%)	10(71)	20 (80)	21(81)
Percentage of patients in NYHA functional class III, n (%)	13(93)	19(76)	25(96)
Percentage of patients in NYHA functional class IV, n (%)	1(7)	6(24)	1(4)
Description of the interventions	Epoprostenol i.v.: beginning from a dose of 2 ng/kg/min up to the maximum tolerated dose at which hemodynamic effects were achieved (6.4±0.8 ng/kg/min Treprostinil i.v.: from the initial dose of 5 up to the final dose of 60 ng/kg/min – maximum tolerated dose was 24.6±4.0 ng/kg/min. The patients were observed for 24h after administration of drugs	Treprostinil: 1st administration: iv. 10ng/kg/min followed by a pause of 150 min. 2nd administration: sc. at doses of: 5, 10 and 20 ng/kg/min (3 cohorts) The patients were observed for 24h after administration of drugs	Dose of treprostinil: from the initial dose of 2.5 ng/kg/min to a maximum of 20 ng/kg/min.
Primary endpoints	Not specified	Not specified	Not specified
Secondary endpoints	Not specified	Not specified	Not specified
Observation period	Ca. 36 hours	Ca. 36 hours	8 weeks
Information concerning patients lost from the study	1	5	4
Description of the randomization method			Not specified

Description of the method of blinding			Not specified
Comments	Hemodynamic parameters were measured and adverse events assessed	Hemodynamic parameters were measured and adverse events assessed	Hemodynamic parameters and exercise capacity were measured; severity of dyspnea and adverse events were assessed
conflicts of interest, sources of financing	Financed by United Therapeutics Corporation		

Table 162.
Characteristics of the *Simonneau 2002* study

Name of the study	*Simonneau 2002*
Study design	Randomized (by permuted blocks), double-blind clinical study
Jadad score	4
Inclusion criteria for patients	PAH – primary or associated with connective tissue diseases or congenital systemic-to-pulmonary shunts; Patients aged 8-75 years; NYHA functional class II, III or IV Hemodynamic parameters: • mean pulmonary arterial pressure ≥ 25 mmHg; • mean pulmonary capillary wedge pressure ≤ 15 mmHg; • pulmonary vascular resistance > 3 mmHg/l/min; No signs or symptoms of thromboembolic disease.
Exclusion criteria for the patients	Significant interstitial pulmonary disease Portopulmonary hypertension or pulmonary hypertension associated with HIV infection Uncontrolled sleep-apnea syndrome History of a disease of the left heart Other diseases associated with pulmonary hypertension (e.g. sickle cell anemia) Baseline exercise capacity below 50 m or over 450 m of the 6-MWD

	New long-term treatment for PAH introduced within previous months Any treatment for PAH discontinued within previous weeks excepting anticoagulants Use of any prostaglandin derivatives within the previous 30 days

Baseline characteristics of the population		
Parameter	**Treprostinil** (plus conventional treatment)	**Placebo** (plus conventional treatment)
Total number of patients	469 (233 – treprostinil group, 236 – placebo group)	
Age range [years]	44.6 ±1.0	44.4 ±0.9
Percentage of men, n (%)	36 (16)	51 (22)
Percentage of women, n (%)	197 (85)	185 (78)
Ethnic groups, n (%): **black** **white** **others**	 13 (6) 198 (85) 22 (9)	 8 (3) 198 (84) 30 (13)
Percentage of patients in NYHA functional class II, n (%)	25 (11)	28 (12)
Percentage of patients in NYHA functional class III, n (%)	190 (82)	192 (81)
Percentage of patients in NYHA functional class IV, n (%)	18 (8)	16 (7)
6-MWD (m)	326 ± 5	327 ± 6
Patients with primary PAH, n (%)	134 (58)	136 (58)
Percentage of patients with PAH associated with connective tissue diseases, n (%)	41 (17)	49 (20)
Percentage of patients with PAH associated with congenital systemic-to-pulmonary shunts, n (%)	58 (25)	51 (22)

Time from diagnosis of PAH (years)	4.3 ± 0.5	3.3 ± 0.5
Description of the interventions	**Treprostinil** plus conventional treatment (oral vasodilators, oral anticoagulants, diuretics and/or digoxin). Treprostinil was administered subcutaneously by means of a microinfusion pump. Initial dose – 1.25 ng/kg/min Maximum dose after 12 weeks– 22.5 ng/kg/min.– according to improvement in PAH signs and severity of adverse events	**Placebo** plus conventional treatment (oral vasodilators, oral anticoagulants, diuretics and/or digoxin)
Primary endpoints	Exercise capacity (6-MWT) Signs of PAH (a composite endpoint – 16 parameters) Dyspnea – Fatigue Rating Death, transplantation or clinical worsening	
Secondary endpoints	Borg Dyspnea Score Hemodynamic parameters Quality of life Adverse events	
Observation period	12 weeks	
Information concerning patients lost from the study	Five patients were switched from subcutaneous treprostinil to intravenous epoprostenol due to worsening	
Description of the randomization method	Permuted blocks	
Description of the method of blinding	None	
Comments (conflicts of interest, sources of financing)	Study financed by United Therapeutics Corporation	

8.5.7. Bosentan vs. sildenafil

Table 163.
Characteristics of the SERAPH 2005 study

Name of the study	SERAPH 2005	
Study design	Double-blind, randomized clinical trial	
Jadad score	5	
Inclusion criteria for patients	Patients in WHO class III, with idiopathic PAH or PAH secondary to connective tissue diseases, qualified for treatment with bosentan;	
Exclusion criteria for the patients	Elevated liver enzymes, previous treatment with bosentan or sildenafil, clinical necessity of treatment with prostanoids;	
Baseline characteristics of the population		
Parameter	**Bosentan**	**Sildenafil**
Total number of patients	14	12
Mean age (range) [years]	44.4 (28-62)	41.1 (27-55)
Percentage of men	21%	17%
Primary PAH	86%	92%
Secondary PAH	14%	8%
BMI (SD)	26.5 (4.5)	26.7 (10.1)
Description of the interventions	Sildenafil (50 mg twice daily for 4 weeks; later 50 mg 3 times daily)	Bosentan (62.5 mg twice daily for 4 weeks; later 125 mg twice daily)
Endpoints	Hemodynamic parameters; the 6-minute walk test, the Borg Dyspnea Score	

Observation period	16 weeks
Information concerning patients lost from the study	Information concerning death of the only patient who did not complete the study.
Description of the randomization method	Computer-generated randomization list.
Description of the method of blinding	Gelatin capsules looking identical.
Comments (conflicts of interest, sources of financing)	A project grant of the British Heart Foundation; 5 out of 13 authors declared conflicts of interest

8.5.8. Epoprostenol vs. iloprost

Table 164.
Characteristics of the *Scott 1990* study

Name of the study	***Scott 1990***	
Study design	Primary, single-center, randomized, cross-over clinical study without blinding	
Jadad score	2	
Inclusion criteria for patients	Patients with severe primary pulmonary hypertension who did not respond to previous treatment with vasodilators and were qualified for cardiopulmonary transplantation; Significant worsening of such symptoms as dyspnea and fatigue, NYHA (New York Heart Association) functional class II, III or IV.	
Exclusion criteria for the patients	Pulmonary hypertension associated with other diseases excluded by chest X-ray, ventilation-perfusion scintigraphy, pulmonary scintigraphy and heart catheterization; Proximal obliteration of pulmonary arteries by thrombi in pulmonary scintigraphy or angiography.	
Baseline characteristics of the population		
Parameter	**Epoprostenol**	**Iloprost**

Total number of patients	12	
Mean age (SD) [years]	37.6 (11.1)	
Percentage of men	50%	
Primary PAH	100%	
Mean time from diagnosis (SD) [months]	33.5 (32.9)	
Description of the interventions	Epoprostenol in infusion at the initial dose of 2 ng/kg/min, increased every 15 minutes by another 2 ng/kg/min.	Iloprost in infusion at the initial dose of 1.5 ng/kg/min. The dose was increased every 15 minutes by another 1.5 ng/kg/min.
Endpoints	Hemodynamic parameters (mean pulmonary artery pressure, pulmonary vascular resistance, cardiac index, arterial blood oxygen saturation); Safety (adverse events)	
Observation period	45 minutes	
Information concerning patients lost from the study	-	
Description of the randomization method	None	
Description of the method of blinding	No blinding	
Comments (conflicts of interest, sources of financing)	None	

8.6. Jadad scale

Table 165.
Jadad scale

Qualitative assessment of an RCT – JADAD scale			Score
Study			
Evaluator			
Was the study randomized?		yes/no (1/0)	
Was the study double-blind?		yes/no (1/0)	
Was the randomization method described and was it correct?		yes/no (1/-1)	
Was the “double-blinding” method described and was it correct?		yes/no (1/-1)	
Was information concerning patients lost or excluded from the study provided?		yes/no (1/0)	
		TOTAL	

8.7. Characteristics of the excluded studies

Table 166.
Characteristics of the excluded studies

Study	Reasons of exclusion
Barbaro 2006	Open-label, observational study
Barst 1994	Open, uncontrolled study without randomization
Barst 1997	Editorial article
Barst 2003	Uncontrolled study without randomization
Fattouch 2005	The study concerned perioperative period; the population of patients did not match the inclusion criteria (patients with pulmonary hypertension associated with mitral stenosis undergoing cardiac surgery); used prostacyclin derivative not specified; sodium nitroprusside used as a comparator.
Fattouch 2006	Perioperative study; the population of patients did not match the inclusion criteria.
Gatzoulis 2004	Open-label study without a control group
Gessler 2001	The aim of the study was comparison of hemodynamic effects of administration of iloprost by means of different nebulizers; no comparators assumed in this analysis were used in the study
Ghofrani 2002	None of the investigated comparators. Sildenafil was compared to sildenafil used in combination with iloprost.
Ghofrani 2002a	Short-term (60 min) study concerning only hemodynamic parameters in patients with pulmonary hypertension secondary to pulmonary fibrosis (the population of patients did not match the inclusion criteria). Duration of the study did not allow for assessment of the primary endpoints.
Hoeper 2004	Uncontrolled study without randomization
Humbert 2004	None of the investigated comparators. Epoprostenol was compared to epoprostenol used in combination with bosentan.
Humbert 2005	Review article
Kramm 2005	Short-term study carried out in the postoperative period in patients with pulmonary hypertension in the course of thromboembolic disease, who underwent pulmonary endarterectomy (the population of patients did not match the inclusion criteria).
McLaughlin 2006	Patients' population inadequate. Patients treated with bosentan were included
Ocal 2005	Study carried out in the perioperative period; type of the prostacyclin used not specified
Olschewski 2003	The aim of the study was comparison of hemodynamic effects of administration of iloprost by means of different nebulizers; no comparators or endpoints assumed in this analysis were used in the study
Provencher 2005	Uncontrolled study without randomization
Provencher 2006	Uncontrolled study without randomization

Radovancevic 2005	No interventions taken into account in this analysis (in the study prostaglandin E1 and nitric oxide were used)
Rosenzweig 2005	Uncontrolled study without randomization
Saygili 2004	Case report
Schulze-Neick 2005	Study without randomization
Sitbon 2004	Uncontrolled study without randomization
Sitbon 2005	Clinical trial with a historical control group
Shim 2006	Inadequate population according to the Venice criteria of PAH
von Scheidt 2006	Study without randomization; no interventions taken into account in this analysis (in the study prostaglandin E1 were used), no comparator
Voswinckel 2006	Short-term (60-180 min) open-label study with inhaled treprostinil
Wensel 2000	Uncontrolled study without randomization
Williams 2005	Study without randomization with a historical control group

8.8. Summary of evidence according to the GRADE proposal

Table 167.
Summary of evidence concerning bosentan, epoprostenol, iloprost, sildenafil and treprostinil as compared to conventional treatment in patients with pulmonary arterial hypertension according to the GRADE proposal

Intervention	Population	Number of the studies	Study design	*Jadad* score (range)	Observation period	Number of patients		Outcome	
						Interven-tion	Control	OR (95% CI)	NNT/NNH (95% CI)
								WMD (95% CI)	
Mortality									
Bosentan	Total	4	RCT	3-5	16-28 weeks	249	159	0.47 (0.05 to 4.63)*	-
Epoprostenol	Total	3	RCT	3	8-12 weeks	106	95	0.25 (0.04 to 1.57)	-
	Primary PAH	2	RCT	3	8-12 weeks	50	40	0.08 (0.01 to 0.47)	4 (3 to 10)
	PAH associated with other diseases	1	RCT	3	12 weeks	56	55	0.77 (0.14 to 3.81)	-
Iloprost	Total	1	RCT	2	12 weeks	101	102	0.24 (0.01 to 2.55)	-
	Primary PAH	1	RCT (subgroup)	2	12 weeks	51	51	0.49 (0.01 to 9.76)	-
	PAH associated with other diseases	1	RCT (subgroup)	2	12 weeks	50	51	0.25 (0.00 to 3.97)	-
Sildenafil	Total - adults	3	RCT	4	2-12 weeks	238	101	0.61 (0.09 to 4.36)**	-
	Primary PAH - adults	1	RCT	4	6 weeks	22	22	0.14 (0.00 to 6.82)	-
	Total – children and fetuses	2	RCT	4 - 5	4-42 hours	22	21	0.10 (0.01 to 0.89)	4 (3 to 13)
Treprostinil	Total	1	RCT	4	12 weeks	233	236	0.91 (0.32 to 2.54)	-
	PAH associated with other diseases	1	RCT (subgroup)	4	12 weeks	41	49	0.38 (0.01 to 5.04)	-
Quality of life									

Epoprostenol	Primary PAH	1	RCT	3	12 weeks	35-39	26-31	Chronic Heart Failure Questionnaire: Dyspnea: 7.0 (4.0 to 10.0) Fatigue: 5.0 (3.0 to 7.0) Emotional function: 7.0 (3.0 to 10.0) Control of the symptoms: 2.5 (1.0 to 4.0) Nottingham Health Profile: Emotional reaction: -14.7 (-24.5 to -4.9) Energy level: -36.8 (-60.8 to 0.0) Pain: 0.0 (-5.8 to 0.0) Physical abilities: -9.2 (-19.9 to 2.0) Sleep: -21.7 (-34.3 to -9.1) Social isolation: 0.0 (-20.1 to 0.0)	
Iloprost	Total	1	RCT	2	12 weeks	101	102	EuroQol: Questionnaire: 0.02 (-0.06 to 0.1) VAS: 5.4 (-0.14 to 10.94)	
Sildenafil	Primary PAH - adults	1	RCT	4	6 weeks	22	22	Chronic Heart Failure Questionnaire: Dyspnea: 4.33 (0.87 to 7.79) Fatigue: 1.66 (-1.3 to 4.62) Emotional function: 2.62 (-3.38 to 8.62)	
Treprostinil	Total	1	RCT	4	12 weeks	233	236	Minnesota Living with Heart Failure Questionnaire: Physical condition: nd (p = 0.0064) Total: nd (p = 0.17)	
Increase of exercise capacity by one WHO/NYHA functional class									
Bosentan	Total	3	RCT	3-4	16-28 weeks	149	138	2.25 (1.21 to 4.18)	7 (4 to 21)
Epoprostenol	Total	3	RCT	3	8-12 weeks	106	95	37.99 (8.43 to 171.22)	3 (2 to 4)
	Primary PAH	2	RCT	3	8-12 weeks	50	40	26.44 (4.49 to 155.81)	3 (2 to 4)
	PAH associated with other diseases	1	RCT	3	12 weeks	56	55	65.40 (5.69 to 2742.21)	3 (2 to 4)
Iloprost	Total	1	RCT	2	12 weeks	101	102	2.25 (1.02 to 5.13)	9 (5 to 79)
	Primary PAH	1	RCT (subgroup)	2	12 weeks	51	51	4.92 (1.19 to 28.66)	6 (4 to 24)
	PAH associated with other diseases	1	RCT (subgroup)	2	12 weeks	50	51	1.44 (0.51 to 4.14)	-
Sildenafil	Total	2	RCT	4	2-12 weeks	213	78	6.94 (2.78 to 17.31)	4 (3 to 6)
Increase of exercise capacity in the 6-minute walk test									
Bosentan	Total	4	RCT	3-5	16-28 weeks	292	159	43.33 m (27.55 to 59.12)	

Epoprostenol	Primary PAH	2	RCT	3	8-12 weeks	51	49	46.90 m (17.60 to 76.19)	
	PAH associated with other diseases	1	RCT	3	12 weeks	56	55	99.5 m (nd)	
Iloprost	Total	1	RCT	2	12 weeks	101	102	36.4 m (p = 0.004)	
	Primary PAH	1	RCT (subgroup)	2	12 weeks	51	51	58.8 m (NS)	
	PAH associated with other diseases	1	RCT (subgroup)	2	12 weeks	50	51	12.0 m (NS)	
Sildenafil	Total	3	RCT	3-4	2-12 weeks	236	99	55.82 m (38.03 to 73.61)	
Treprostinil	Total	1	RCT	4	12 weeks	233	236	16 m (4.4 to 27.6)	
	Primary PAH	1	RCT	3	8 weeks	15	9	43 (-17.3 to 103.3)	
	PAH associated with other diseases	1	RCT (subgroup)	4	12 weeks	41	49	21 (-6.49 to 48.49)	
Dyspnea									
Bosentan	Total	1	RCT	3	16 weeks	74	69	Borg Dyspnea Score: -0.4 (-0.95 to 0.15)	
Epoprostenol	Total	2	RCT	3	12 weeks	97	86	Dyspnea – Fatigue Rating: 2.00 (1.55 to 2.45)	
	Primary PAH	1	RCT	3	12 weeks	41	31	Dyspnea – Fatigue Rating: 2.00 (1.00 to 3.00)	
	PAH associated with other diseases	1	RCT	3	12 weeks	56	55	Dyspnea – Fatigue Rating: 2.00 (2.00 to 3.00) Borg Dyspnea Score: -2.5 (-3.5 to -1.5)	
Iloprost	Total	1	RCT	2	12 weeks	101	102	Mahler Dyspnea Index: 1.12 (0.43 to 1.81)	
Sildenafil	Total	2	RCT	4	2-12 weeks	216	79	Borg Dyspnea Score: -1.23 (p < 0.01) – *Bharani 2003* -0.68 (n.s.)– SUPER-1	
Treprostinil	Total	2	RCT	3-4	8-12 weeks	248	245	Dyspnea – Fatigue Rating: 1.3 (p = 0.0001) Borg Dyspnea Score: -0.91 (-1.34 to -0.48)	
	Primary PAH	1	RCT	3	8 weeks	15	9	Dyspnea – Fatigue Rating: 1.5 (n.s.) Borg Dyspnea Score: -1.0 (-2.57 to 0.57)	
	PAH associated with other diseases	1	RCT	4	12 weeks	41	49	Dyspnea – Fatigue Rating: 0.9 (0.16 to 1.64) Borg Dyspnea Score: -0.8 (-2.2 to 0.6)	
Adverse events (all)									
Bosentan	Total	2	RCT	3-4	18-28 weeks	81	73	0.64 (0.26 to 1.59)	-
Iloprost	Total	1	RCT	2	12 weeks	101	101	1.11 (0.41; 3.08)	-
Serious adverse events									

Bosentan	Total	1	RCT	5	16 weeks	37	17	0.73 (0.12 to 5.38)	-
Iloprost	Total	1	RCT	2	12 weeks	101	102	1.18 (0.60 to 2.33)	-
Syncope									
Bosentan	Total	1	RCT	3	16 weeks	74	69	1.43 (0.32 to 7.22)	-
Epoprostenol	Total	1	RCT	3	12 weeks	56	55	0.31 (0.07 to 1.14)	-
Iloprost	Total	1	RCT	2	12 weeks	101	102	Syncope: 1.65 (0.46 to 6.64) Serious syncope: 7.77 (1.32 to 45.66)	- 23 (10 to 83)
Sildenafil	Total	1	RCT	4	6 weeks	22	22	0.49 (0.00 to 8.51)	-
Treprostinil	Total	1	RCT	3	8 weeks	17	9	0.13 (0.002 to 2.8)	-
Nausea									
Bosentan	Total	1	RCT	3	18 weeks	60	62	0.13 (0.02 to 0.97)	16 (7 to 28547)
Epoprostenol	Total	1	RCT	3	12 weeks	56	55	3.56 (1.36 to 9.83)	5 (3 to 13)
Iloprost	Total	1	RCT	2	12 weeks	101	101	1.72 (0.62 to 5.01)	-
Sildenafil	Total	1	RCT	4	6 weeks	22	22	Nausea and vomiting: 0.16 (0.00 to1.71)	-
Treprostinil	Total	1	RCT	4	12 weeks	233	236	1.37 (0.84 to 2.22)	-
Diarrhea									
Epoprostenol	Total	1	RCT	3	12 weeks	56	55	17.33 (4.61 to 94.37)	3 (2 to 4)
Iloprost	Total	1	RCT	2	12 weeks	101	101	0.80 (0.28 to 2.24)	-
Sildenafil	Total	1	RCT	4	12 weeks	207	70	1.86 (0.60 to 7.72)	-
Treprostinil	Total	1	RCT	4	12 weeks	233	236	1.84 (1.13 to 5.67)	11 (6 to 42)
Jaw pain									
Epoprostenol	Total	1	RCT	3	12 weeks	56	55	327.00 (27.58 to 11155.05)	2 (2 to 2)
Iloprost	Total	1	RCT	2	12 weeks	101	101	4.40 (1.13 to 24.94)	12 (6 to 54)
Treprostinil	Total	1	RCT	4	12 weeks	233	236	3.14 (1.49 to 7.09)	12 (8 to 28)

Flushing									
Bosentan	Total	1	RCT	3	16 weeks	74	69	2.30 (0.50 to 14.28)	-
Iloprost	Total	1	RCT	2	12 weeks	101	101	3.73 (1.57 to 9.53)	6 (4 do14)
Sildenafil	Total	1	RCT	4	12 weeks	207	70	2.93 (0.84 to 15.64)	-
Edema									
Treprostinil	Total	1	RCT	4	12 weeks	233	236	3.80 (1.44 to 11.69)	16 (9 to 42)
Pain at the injection site									
Treprostinil	Total	2	RCT	3-4	8-12 weeks	249	245	17.65 (11.14 to 27.96)	2 (2 to 2)
Reaction at the injection site									
Treprostinil	Total	1	RCT	4	12 weeks	233	236	14.87 (9.21 to 24.11)	2 (2 to 2)
Hematoma or induration of the injection site									
Treprostinil	Total	1	RCT	3	8 weeks	17	9	56.00 (3.31 to 2670.59)	2 (2 to 3)
Sudden vasodilation									
Treprostinil	Total	1	RCT	4	12 weeks	249	245	2.46 (1.13 to 5.67)	17 (9 to 77)

* OR calculated from the results of a single study (74 patients in the BOS group and 69 in the PL group), in 3 other clinical trials no case of death was observed in the analyzed observation period

** OR calculated from the results of two studies (229 patients in the SIL group and 92 in the PL group), in 1 study no case of death was observed in the analyzed observation period

† For dichotomic parameters OR and NNT/NNH were calculated; for continuous parameters – WMD

8.9. Final review of the report (17.12.2008)

“Clinical effectiveness analysis of bosentan, epoprostenol, iloprost, sildenafil and treprostinil in treatment of pulmonary arterial hypertension. Systematic review of randomised controlled trials”

Reviewers: Dr Yen-Fu Chen and Dr David Moore

The report is clearly written, well structured and the findings of the review readily accessible. Considering when this review was undertaken, no relevant but available studies appear to have been omitted and comprehensive analyses of all relevant data have been undertaken. The authors have appropriately addressed our comments in the final version where comments were related to the remit of the report.

This is a complex and detailed topic, with limited availability of data and what data is accessible is often difficult to interpret due to multiple factors relating to heterogeneous patient populations, outcome measures and the design and conduct of studies. We wish to congratulate the authors for undertaking a thorough review in the face of such complexity.

9. TABLES

10. FIGURES