2007

Use of bosentan, epoprostenol, iloprost, sildenafil and treprostinil in treatment of pulmonary arterial hypertension in Poland

Budget impact analysis

Medical University of Warsaw
December 2007

Authors:
Prof. Tomasz Hermanowski *(project manager)*
- Department of Pharmacoeconomics, Medical University of Warsaw
- School of Business, Warsaw University of Technology

Ewa Kowalik, MD, MSc *(model construction, cooperation with external institutions, preparation of the report)*
- Department of Congenital Heart Diseases, Institute of Cardiology, Warsaw

Dr. Michał Jakubczyk, PhD (Econ) *(construction of the model and calculation sheet, calculations, preparation of the report)*
- Department of Pharmacoeconomics, Medical University of Warsaw

Dr. Maciej Niewada, MD, PhD *(model construction, cooperation with external institutions, preparation of the report)*
- Department of Clinical and Experimental Pharmacology, Medical University of Warsaw

Contributors:
Lidia Becla, MSc *(internal verification of the report)*
- Agency for Health Technology Assessment in Poland

Anna Górska, MSc *(collection of cost data)*
- Department of Pharmacoeconomics, Medical University of Warsaw

Dr. Marcin Kurzyna, MD, PhD *(content-related consultations with respect to surveys and model construction, internal review)*
- Institute of Tuberculosis and Lung Diseases, Department of Chest Medicine

Kinga Malottki, MSc *(internal verification of the report)*
- Agency for Health Technology Assessment in Poland

Bogusława Osińska, MD *(internal verification of the report)*
- Agency for Health Technology Assessment in Poland

Address for correspondence:
Prof. Tomasz Hermanowski, PhD
Department of Pharmacoeconomics, Faculty of Pharmacy, Medical University of Warsaw
ul. Pawińskiego 3A, 02-106 Warszawa
e-mail: tomasz.hermanowski@am.edu.pl

Conflict of interest:
T. Hermanowski – no conflict of interest
E. Kowalik – no conflict of interest
M. Jakubczyk – no conflict of interest
M. Niewada – no conflict of interest
L. Becla – no conflict of interest
A. Górska – no conflict of interest
M. Kurzyna – conflict of interest did not result in the expert being excluded from work on the report
K. Malottki – no conflict of interest
B. Osińska – no conflict of interest

The report was commissioned by:
Agency for Health Technology Assessment in Poland, Al. Lotników 22, 02-668 Warszawa

Responsible representative of the commissioning party:
Iga Lipska, MD; e-mail: i.lipska@aotm.gov.pl

Peer Review: Department of Public Health & Epidemiology, University of Birmingham, Edgbaston, Birmingham, UK
Reviewers: Dr David Moore, Dr Yen-Fu Chen

Signatures of the authors:

.....	.....	.....	.....
T. Hermanowski	E. Kowalik	M. Jakubczyk	M. Niewada

Signatures of the contributors:

.....	.....	.....	.....	.....
L. Becla	A. Górska	M. Kurzyna	K. Malottki	B. Osińska

CONTENTS

KEYWORDS

pulmonary arterial hypertension, budget impact analysis, epoprostenol, iloprost, treprostinil, bosentan, sildenafil

EXECUTIVE SUMMARY

The aim of this study is to quantify the impact on the public payer's budget of reimbursement of the following medications: bosentan (Tracleer), epoprostenol (Flolan), iloprost (Ventavis), sildenafil (Revatio) and treprostinil (Remodulin) used in treatment of NYHA III/IV pulmonary arterial hypertension (PAH).

Two scenarios were compared – one describing existing practice and a new one, describing the anticipated situation after full reimbursement of the analysed medications has been introduced. A time horizon of five years was considered, within which the costs would be incurred and the effects achieved. Cost categories included costs of the analysed drugs, costs of the remaining drugs and costs of medical procedures (hospitalisations and outpatient visits). Costs of treatment of pulmonary arterial hypertension as well as costs associated with drug adverse effects were included. Clinical improvement defined as NYHA class decline rate was used to measure clinical outcomes.

Epidemiological data were based on published foreign studies (incidence) and a survey conducted in all identified Polish centres dealing with pulmonary hypertension management (prevalence). The survey results were used in order to determine current medical practice (use of drugs and other medical procedures) and anticipated treatment practice after reimbursement of the analysed drugs has been introduced (pattern of use of the analysed drugs, use of combination therapies). A systematic review was used as a source of data on: mortality rate, probabilities of change of therapy, probability of improvement according to the NYHA classification. Available information on costs generated by drugs imported and covered by the Ministry of Health was also used.

Current practice is characterized by the frequency of use of each drug/procedure. The new practice is defined as the Markov model, in which the patient can receive various therapies (including combination therapies) depending on various clinical events.

Four scenarios differing with respect to the target population size were analysed. The realistic scenario was based on point estimates of incidence rate and NYHA III/IV class proportion. The optimistic and pessimistic scenarios were based on upper and lower limits of 95% confidence intervals of the above parameters, respectively. In addition the fourth scenario, based on the pulmonary arterial hypertension prevalence estimated in France, was analysed.

Annual costs in the "current practice" scenario in the following five years amounted to (in consecutive years): 10.3 million PLN, 11.67 million PLN, 12.89 million PLN, 13.97 million PLN and 14.92 million PLN. For the new practice scenario respective costs increased to: 32.95 million PLN, 36.8 million PLN, 40.94 million PLN, 45.02 million PLN and 48.9 million PLN (incremental cost difference of 22.65 million PLN, 25.12 million PLN, 28.05 million PLN, 31.05 million PLN and 33.98 million PLN, respectively).

The main component of total costs in current practice were costs of the analysed drugs, representing 72.26% of all costs in the five-year time horizon. In the current practice scenario almost all of these costs were generated by two medications (imported and covered by the Ministry of Health): treprostinil and iloprost (71.46% and 24.04% of total drug costs, respectively). Reimbursement of analysed drugs would further increase the contribution of drug costs in total costs up to 91.31%. The cost distribution for analysed drugs was more balanced – bosentan (23.19%), epoprostenol (11.21%), iloprost (15.38%), sildenafil (16.21%), treprostinil (33.06% of total costs).

Proportional population changes resulted in almost proportional costs changes. For two scenarios, i.e. pessimistic and optimistic, the range of costs change resulting from reimbursement of analysed medications amounted to 21.87-23.52 million PLN and 28.72-39.91 million PLN in the first and the fifth year, respectively. In the prevalence-based scenario incremental costs amounted to 26.5 and 60.04 million PLN in the first and the fifth year, respectively. It should be stressed the last scenario was based on prevalence rate and morbidity more than twice exceeding the current number of patients treated.

Sensitivity analysis revealed that key variables influencing basic analysis results were: incidence rate (changing between scenarios), drug doses and administration, prices of the analysed drugs, especially bosentan, sildenafil and iloprost, and mean body weight.

Reimbursement of the analysed drugs and their unrestricted availability increased the number of patients with NYHA class reduction. Change from current practice to new practice would increase that number by 56% (from 326 to 510).

The most important limitations of this study were: lack of specific epidemiological data concerning incidence and prevalence rate of pulmonary arterial hypertension in Poland, specificity of the Polish market (i.e. common use of sildenafil generics, treatment provided within clinical trials) obscuring actual costs of current practice, lack of credible clinical evidence on the impact of analysed drugs on use of other procedures/drugs and associated savings.

These limitations could be eliminated with the national POLKARD registry of pulmonary hypertension patients in years 2007-2008. It is recommended to update the analysis based on data collected in the registry.

1 AIM OF THE REPORT

The aim of this study was the analysis of impact of reimbursement of the following drugs: bosentan (Tracleer), epoprostenol (Flolan), iloprost (Ventavis), sildenafil (Revatio) and treprostinil (Remodulin), used in treatment of NYHA III/IV pulmonary arterial hypertension in Poland, on the payer's budget.

2 INTRODUCTION

2.1 Definition and classification of pulmonary hypertension

Pulmonary circulation under normal circumstances is characterised by high flow rate and low pressure. The term "pulmonary hypertension" was first used in 1951 by Dresdale and Mitchom to designate a disease entity, whose characteristic feature was elevated pressure in the pulmonary artery. A diagnosis of pulmonary hypertension is established when mean pulmonary artery pressure exceeds 25 mmHg at rest or 30 mmHg during exercise. Depending on mean values of pulmonary artery pressure pulmonary hypertension is classified as: mild (26-35 mmHg), moderate (36-45 mmHg) or severe (> 46 mmHg) [25].

The first classification of pulmonary hypertension, proposed in 1956 by Wood, distinguished primary (i.e. of unknown aetiology) and secondary pulmonary hypertension (i.e. accompanying other diseases) [20]. In 1998 a new classification was introduced by the World Health Organization in order to define categories including disease entities characterised by similar pathophysiology, symptomatology and response to treatment. This classification was modified in 2003 [30].

According to the classification of the Third World Symposium on Pulmonary Hypertension (Venice, 2003) the following types of pulmonary arterial hypertension (PAH) are distinguished:

- idiopathic PAH;
- familial PAH;
- 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, hemoglobinopathies, myeloproliferative disorders, splenectomy);
- associated with significant venous or capillary involvement:
    - pulmonary veno-occlusive disease;
    - pulmonary capillary hemangiomatosis;

- persistent pulmonary hypertension of the newborn.

2.2 Epidemiology

There are no credible data concerning epidemiology of pulmonary arterial hypertension in Poland. A competition for the pulmonary arterial hypertension register to be kept in 2007-2008 was decided in May 2007 within the POLKARD program; its results may prove useful for this type of analyses in the future [22]. However, such data are not available at present; assessment of prevalence of pulmonary arterial hypertension in Poland was therefore based on a survey performed in all identified centres providing specialist care for this group of patients [14].

During review of the literature an additional obstacle was identified: the classification of pulmonary hypertension was changed in 2003. Earlier epidemiological data from Israel, the USA, Japan and other countries [2,16,18] present prevalence and incidence rates with respect to primary pulmonary hypertension. The only study identified by the authors as dealing with epidemiology of pulmonary arterial hypertension is a French report published in 2006 [15]. It was calculated from the register that prevalence rate in French population is 15 patients per million individuals, annual incidence rate 2.4 patients per million and annual survival rate for patients with pulmonary arterial hypertension – 88.4%. Patients in NYHA functional class III or IV comprised 75% of all patients diagnosed with pulmonary arterial hypertension.

2.3 Pathophysiology and clinical picture

Pathology of PAH is based on morphological lesions in vessel walls resulting in increased pulmonary vascular resistance. Proliferation of endothelial cells is observed, along with hyperplasia of fibroblasts and their transformation into myofibroblasts, proliferation of smooth muscle cells, thickening of the intima-media complex of pulmonary arteries as well as excessive synthesis and deployment of collagen in the vessel wall. Moreover, contraction of small pulmonary arteries and thrombosis of small vessels are found. Remodelling of the arterial wall and disturbed balance between vasoconstrictory and vasodilatory factors result in increased pulmonary vascular resistance, pulmonary hypertension and pressure overload of the right ventricle [31].

Symptoms of pulmonary hypertension include effort dyspnoea, fatigue, weakness, chest pain, and syncope. As the disease progresses, signs of right ventricular failure appear: hepatic enlargement, ascites, jugular venous distension, peripheral oedema and central cyanosis. Mortality in untreated PAH is high; median survival time from the moment of diagnosis does not exceed 3 years [8].

2.4 Treatment of pulmonary arterial hypertension

The following therapeutic options are used in treatment of PAH:

- non-pharmacological treatment, i.e. limitation of stay at high altitudes, prevention of infections, use of efficient contraceptive means, psychological support;
- pharmacological treatment, including so-called standard treatment and use of novel drugs acting in pulmonary vessels:
    - standard treatment is based on symptomatic treatment of right ventricular failure (diuretics, digitalis glycosides), use of pulmonary vasodilators (calcium channel blockers) in patients, in whom reactivity of pulmonary vessels was

confirmed, and use of anticoagulants and long-term oxygen therapy in patients with hypoxemia;

- in the 1990s new drugs for treatment of PAH were introduced:
  - synthetic prostacyclin and its analogues (epoprostenol, treprostinil, beraprost, iloprost);
  - endothelin-1 receptor antagonists (bosentan, sitaxsentan, ambrisentan);
  - type 5 phosphodiesterase inhibitors (sildenafil);

  According to current guidelines of the European Society of Cardiology concerning diagnostics and treatment of pulmonary hypertension these drugs are recommended in patients with NYHA class III and IV pulmonary arterial hypertension [11].

- in patients, in whom the disease progresses despite pharmacological treatment, atrial septostomy, pulmonary transplantation or cardiopulmonary transplantation may be considered [17].

3 METHODS OF THE ANALYSIS

3.1 Time horizon

The analysis was planned for five years: from January 1st, 2008 till December 31st, 2012. According to guidelines of the Agency for Health Technology Assessment in Poland [13] future costs and effects were not discounted.

The analysis was carried out at monthly steps (i.e. frequency of clinical events was calculated for each month); for simplification it was assumed that each moth lasts 30.5 days (approximation to 30 days would result in underestimation of the annual cost of treatment by ca. 1,37%). The results were summarised for each subsequent year.

3.2 Perspective of the analysis

This budget impact analysis was performed from the public healthcare payer perspective, i.e. that of the National Health Fund and the Ministry of Health (taking into account current practice, i.e. reimbursement of direct import of the analysed drugs).

3.3 Population

Patients with NYHA class III or IV pulmonary arterial hypertension constitute the analysed population.

Two subgroups of patients were analysed: the individuals diagnosed and treated before the beginning of the analysed period and new patients, who will join the analysed group during the whole period under consideration. The size of the first group reflects prevalence at the beginning of the analysed period, while the second one – incidence rate.

Prevalence was estimated directly from the results of the survey. It was assumed that the number of patients at the beginning of the analysed period will equal the total number of patients treated at all 6 institutions taking part in the survey (the questionnaire has been sent to all institutions currently providing treatment for pulmonary hypertension in Poland), including one paediatric centre, i.e. 188 patients in NYHA class III/IV from the whole population of 308 patients with pulmonary arterial hypertension.

Incidence rate was estimated according to the results reported by Humbert et al. [15] at 2.4 per million individuals annually. These results allowed also for calculation of the 95% confidence interval for incidence rate* being [1.97-2.83]. Incidence in the study was reported regardless of the NYHA class. In this analysis the percentage of patients in NYHA class III/IV was estimated from the survey results (61.04% of patients). The 95% interval for the percentage of patients in NYHA class III/IV was also calculated from the survey results at [55.59% - 66.49%].

Considering uncertainty of population size estimation, three scenarios have been analysed: realistic, optimistic and pessimistic, for different sizes of the target population (see section 3.4). For the pessimistic scenario lower limits of confidence intervals for incidence rate and the percentage of patients in NYHA class III/IV were taken into consideration, thus re-

* The calculation was based on the incidence rate (2.4) and the number of newly diagnosed patients (121) reported by Humbert et al. [15]. From this information size of the population and then classic 95% confidence interval were calculated.

ducing the size of the target population. In the optimistic scenario upper limits of these confidence intervals were used.

Incidence rate assumed in the realistic scenario is therefore 2.4 per million individuals, of whom 61.04% are patients in NYHA class III/IV; respective rates and percentages are 1.97 and 55.59% in the pessimistic and 2.83 and 66.49% in the optimistic scenario.

An additional, fourth (so-called prevalence-based) scenario was considered, in which data concerning prevalence rate reported in France were taken into account [15]. Based on those data, expected prevalence in Poland may be estimated at ca. 570 patients. In this scenario it was assumed that the number of patients diagnosed with pulmonary arterial hypertension will increase with time so that the number of patients treated in the last (fifth) year will reach 570. It wass therefore necessary to assume for this scenario an incidence rate of 5.4 per million individuals annually, i.e. more than twice higher than the basic value. Such prevalence-based approach is safe from the payer's budget point of view, with respect to increasing number of patients with diagnosed pulmonary hypertension. However, it should be stressed that present number of patients treated at specialist centres is significantly lower.

The number of patients treated in specific periods depends on prevalence and incidence rates and therefore is the same for both scenarios (based on current practice and the new one). This is due to the same mortality rate (see section 3.4.1.3) related to use of the analysed drugs.

Due to a small number of high referral level centres as well as a small number of patients no alternative scenarios, taking into account incomplete spreading of the new technology (and therefore incomplete replacement of the existing technology with the new one) or excessive use of the new technology, were considered. With respect to current legal regulations, full reimbursement (or full coverage of the drug costs within therapeutic programs) was taken into account. Possible patient's co-payment would generate very high costs for the patient (due to high prices of the analysed drugs) and make treatment practically impossible.

3.4 Current practice and the new scenario

The analysis includes:

- so-called "current practice" scenario, i.e. continuation of current clinical practice, being a natural reference for calculations concerning changes in budget impact;
- so-called "new scenario", i.e. new clinical practice after registration of the analysed drugs (bosentan, epoprostenol, iloprost, sildenafil and treprostinil) and introduction of their reimbursement by the payer.

3.4.1 Treatment methods

Procedures and drugs used in clinical management of the disease are described below. This list was prepared according to guidelines of the European Society of Cardiology and results of a survey performed among Polish clinicians treating patients with pulmonary arterial hypertension.

3.4.1.1 Procedures taken into account

In the analysis inpatient and outpatient procedures concerning diagnostics of pulmonary hypertension, periodic control of the patient's condition, treatment of exacerbations and additional procedures (oxygen therapy) were taken into account.

The list includes the following procedures:

- hospitalisations:

  - diagnostics of pulmonary hypertension (NHF procedure No. 5.06.00.0000827);
  - treatment of exacerbation of the disease (NHF procedure No. 5.06.00. 0001303);
  - periodic control of the patient's condition (NHF procedure No. 5.06.00.0001304);
  - atrial septostomy (surgical intervention) – contracted as an NHF procedure (No. 5.06.00.0000827);
- outpatient consultations:
  - pulmonary outpatient consultation (type I/II/III; NHF procedure No. 5.01.01.1272001, 5.01.01.1272002, 5.01.01.1272003);
  - cardiology outpatient consultation (type I/II/III; NHF procedure No. 5.01.01.1100001, 5.01.01.1100002, 5.01.01.1100003);
- other:
  - home oxygen therapy (NHF procedure No. 5.10.00.0000006);

Due to few pulmonary transplantations performed in patients with pulmonary arterial hypertension over the last years (in total, three patients after transplantation are treated at the surveyed institutions) and difficult assessment of perioperative risk as well as prognosis, costs of pulmonary transplantation and post-transplant care were not taken into account.[†]

3.4.1.2 Drugs taken into account

The following groups of drugs used in treatment of pulmonary arterial hypertension were taken into account in the analysis:

- analysed drugs:
  - bosentan;
  - epoprostenol;
  - iloprost;
  - sildenafil;
  - treprostinil;
- other (remaining) drugs:
  - anticoagulants:
    - acenocumarol;
  - heparins:
    - enoxaparin;
    - unfractionated heparin;
  - diuretics:
    - furosemide;
    - spironolactone;
    - hydrochlorothiazide;
    - torasemide;
    - chlortalidone;
    - amiloride + hydrochlorothiazide (brand name: Tialorid);
  - digitalis glycosides
  - calcium channel blockers:
    - diltiazem;
    - nifedipine;

[†] A workbook attached to this report makes it possible to take into account additional procedures parametrised by the user – see "Appendix – workbook description".

- amlodipine;
- verapamil;

- other drugs:
  - enalapril.

According to the above classification, terms: "analysed drugs" and "remaining drugs" are used in this analysis.

3.4.1.3 Mortality

According to the results of the study mentioned above [15] annual survival rate for patients with pulmonary arterial hypertension was assumed at 88.4%, regardless of the treatment applied (without the analysed drugs, with analysed drugs as monotherapy or in combination). A systematic review of short-term trials of the analysed drugs performed by the AHTAPol [6] demonstrated no statistically significant improvement in survival; therefore, it is not justified to assume any differences in prognosis of patients with pulmonary arterial hypertension depending on applied drug(s).

It was assumed that probability of death is constant in time. Based on these data one-month death probability of 1.02% was calculated for the model.[‡]

3.4.2 "Current practice" scenario

The "current practice" scenario was based on data accumulated in the survey of institutions providing care for patients with pulmonary arterial hypertension and represents actual current clinical practice.

Three subpopulations of patients may be considered in this scenario:

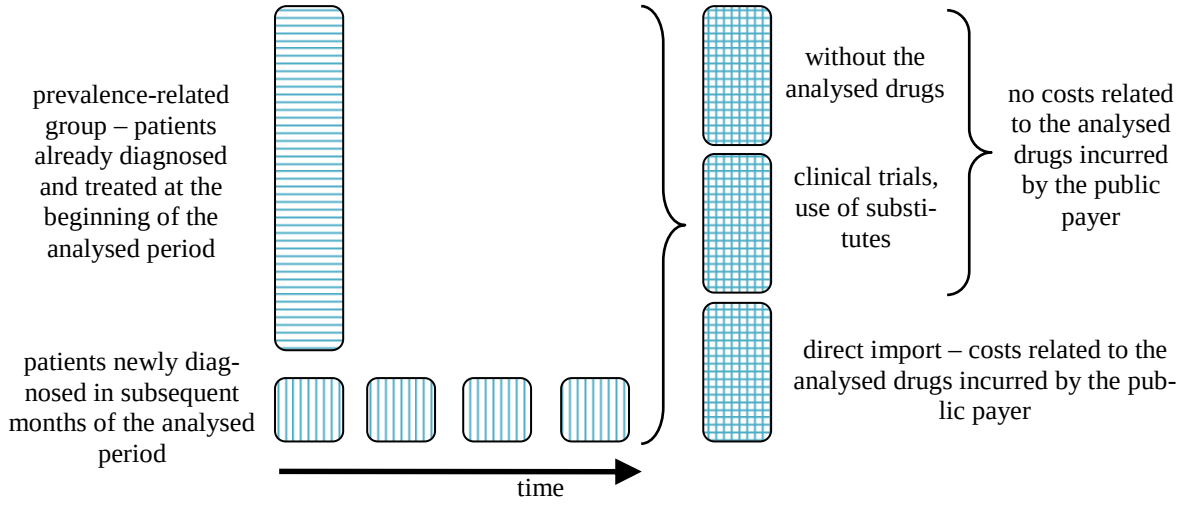
- the patients, who receive none of the 5 analysed drugs;
- the patients, who receive at least one of the 5 analysed drugs generating no costs for the payer (the NHF or the Ministry of Health), e.g. within clinical trials financed by pharmaceutical companies or at their own cost, or receiving another drug containing the same active agent (e.g. Viagra® or Maxigra® instead of Revatio®);
- the patients, who receive at least one of the 5 analysed drugs generating certain costs for the payer (the Ministry of Health) related to direct import of these pharmaceuticals.

In budget impact analysis it should be noted that for the public payer the first two subpopulations generate no costs related to the analysed drugs (although these subpopulations differ clinically with respect to applied pharmacotherapy). However, the size of the third subpopulation must be estimated in order to assess the percentage of patients receiving the analysed drugs financed by the public payer.

The classification described above includes both patients already diagnosed at the beginning of the analysed period and those newly diagnosed. For analysis of the current practice it was assumed that current methods of treatment financing will remain unchanged. All subgroups of patients in the whole target population are presented in Figure 1.

[‡] This probability was assumed in such a way that respective probability of survival of one year was the same as reported by Humbert et al.. [15] i. e. 88,4%. Thus, the following equation is true: $(1-P_{deathMonthly})^{12} = P_{survivalAnnual}$, where $P_{deathMonthly}$ – probability of death within one month, $P_{survivalAnnual}$ – probability of survival of one year.

Figure 1.
Treatment and costs incurred by the public payer in specific subgroups of patients – the "current practice" scenario.



Frequency of use of the analysed drugs financed by means of direct import was calculated from the number of consents for direct import of specific drugs issued by the Ministry of Health in 2006 (90 consents in total)[§], which, after conversion into patient-months of treatment, were applied to the number of patients estimated in the survey (it was assumed that prevalence in 2006 was equal to the number of currently treated patients), i.e. 188 patients. It was also assumed that all consents issued by the Ministry of Health concerned patients in NYHA class III/IV. Consents for direct import of epoprostenol were not taken into account in this analysis as this medication is used (mainly in pediatrics) for indications other than treatment of pulmonary arterial hypertension. Thus probability of receiving of at least one analysed drug could be estimated for the whole population – see Table 1.

Frequency of use of the remaining drugs and procedures (excepting hospitalization related to diagnostics of pulmonary arterial hypertension or atrial septostomy) was calculated from the survey results; on aggregation, data from specific centres were weighted with the number of patients in NYHA class III/IV. It was assumed that those frequency values were equal in all three subpopulations described above. This assumption had no effect on the results of calculations in the "current practice" scenario, but is important in construction of the new scenario (see section 3.4.3.1).

It was assumed that hospitalisation related to diagnostics of pulmonary arterial hypertension takes place only once for each newly diagnosed patient.

Frequency of septostomy was assumed – after consultations with a clinician[**] – at 0.4% monthly (on average there were 3 interventions annually in a group of 63 patients treated at the Institute of Tuberculosis and Lung Diseases).

Doses of the analysed drugs and the remaining drugs were calculated from the survey results; confrontation of these doses with guidelines of the European Society of Cardiology demon-

[§] Consent of the Ministry of Health is issued for three months of therapy and a new decision must be issued after that time.

[**] Direct communication with dr. M. Kurzyna, MD, PhD, Institute of Tuberculosis and Lung Diseases, on August 26th, 2007.

strated no differences. Since Polish clinicians have no experience with epoprostenol, dosage of this drug was based on the results of the AHTAPol systematic review. For calculation of average doses related to the patient's body weight it was assumed that average body weight of an adult is 70 kg and that of a child – 37.16 kg.[††] Average doses for adults and children were calculated separately, from mean values reported by specific centres, weighted with the number of patients in NYHA class III/IV. Average dose for the whole population was then calculated by weighting of the average doses with the percentage of adults (96.81%) and children (3.19%) in the population estimated from the survey results. The results of these calculations are presented in the tables below.

Table 1.
Frequency of use and dosage of the analysed drugs – "current practice" scenario.

Drug	Daily dose	Patient-months of treatment (MH consents)	Probability of use in a specific month
bosentan	244.90 mg	3 (1 consent)	0.13%
epoprostenol	30 ng/kg/min	0 (0 consents)	0%
iloprost	6.15 vials	117 (39 consents)	5.19%
sildenafil	59.14 mg	0 (0 consents)	0%
treprostinil	22.82 ng/kg/min	150 (50 consents)	6.65%

In addition, in sensitivity analysis non-ideal confectioning, i.e. use of a part of a tablet/vial only resulting in increase of actual average doses, was taken into account. In this scenario average doses presented above were replaced with full available doses, i.e. the assumed daily dose was 250 mg for bosentan, 60 mg for sildenafil and 7 vials for iloprost.

Table 2.
Frequency of use and dosage of the remaining drugs – "current practice" scenario.

Drug	Daily dose	Frequency of use in the whole population
anticoagulants:		
acenocumarol	3.24 mg	62.18%
heparins:		
enoxaparin	65.75 mg	21.22%
unfractionated heparin	10,000 IU	0.43%
diuretics:		
furosemide	88.3 mg	60.60%
spironolactone	65.59 mg	66.84%
hydrochlorothiazide	25.16 mg	8.70%
torasemide	25 mg	10.96%
chlortalidone	38.74 mg	14.79%

[††] Based on information concerning patients remaining at present under care of the Child Health Centre – direct communication by e-mail with prof. W. Kawalec and dr. M. Żuk on August 23rd, 2007.

amiloride + hydrochlorothiazide (brand name: Tialorid)	25 mg	0.32%
digitalis glycosides:		
digoxin 0.25 mg	0.12 mg	23.94%
digoxin 0.1 mg	0.1 mg	0.32%
calcium channel blockers:		
diltiazem	211.68 mg	9.02%
nifedipine	60 mg	1.01%
amlodipine	7.5 mg	0.43%
verapamil	240 mg	28.24%
other:		
enalapril	13 mg	0.96%

Table 3.
Frequency of use of medical procedures – "current practice" scenario.

Procedure (NHF code)	**Average number of procedures per year**	**Monthly probability of the procedure**
hospitalisations:		
diagnostics of pulmonary hypertension (5.06.00.0000827)	once in each newly diagnosed patient	n.a.
treatment of exacerbation of the disease (5.06.00. 0001303)	1.68	14.01%
periodic control of the patient's condition (5.06.00.0001304)	1.47	12.28%
atrial septostomy (5.06.00.0000827)	0.05	0.4%
outpatient procedures:		
type I pulmonary consultation (5.01.01.1272001)	0.04	0.35%
type II pulmonary consultation (5.01.01.1272002)	0.09	0.71%
type III pulmonary consultation (5.01.01.1272003)	1.09	9.09%
type I cardiology consultation (5.01.01.1272001)	0.27	2.22%
type II cardiology consultation (5.01.01.1272002)	2.49	20.74%
type III cardiology consultation (5.01.01.1272003)	1.88	15.65%
other:		
home oxygen therapy (5.10.00.0000006)		34.98%

3.4.3 New scenario

In the new scenario reimbursement of the analysed drugs is assumed. The key element for construction of the new scenario is the distinction between patients already treated at the beginning of the analysed period (prevalence-related group) and the patients who join the analysed population with time as newly diagnosed cases (incidence-related group); see section 3.3. The subpopulations of patients defined according to this distinction and the differences in treatment at the beginning of the analysed period are defined below.

3.4.3.1 Different subpopulations of patients

In the new scenario two groups of patients are distinguished: those already diagnosed and treated at the beginning of the analysed period (the *prevalence-related group)* and those who will join the considered population, i.e. newly diagnosed patients (the *incidence-related group).*

It was assumed that the incidence-related group will be treated using a complex treatment protocol described below, including possibility of switching to another drug (due to adverse effects) and use of combination therapy (addition of another drug if monotherapy is inefficient).

The prevalence-related group may be further divided into two subgroups: patients already treated with the analysed drugs before the beginning of the analysed period (regardless of the financing: direct import, clinical trials, use of other drugs containing the same active agent) and patients who receive none of the analysed drugs. Percentage of patients in both subgroups was estimated from the survey results. For each centre the percentages of patients receiving specific analysed drugs were calculated; in order to take into account combination therapy (and avoid double counting), the percentage of patients receiving two of the analysed drugs at the same time was then subtracted from the sum of those percentages.[‡‡] Mean value weighted with the number of patients in NYHA class III/IV was then calculated. For the whole country the percentage of patients treated with the analysed drugs was 32.11%. Probability of use of specific drugs was calculated directly from the survey results; the values are presented in Table 4**Błąd! Nie można odnaleźć źródła odwołania.**. Dosage was calculated in the same way as for the current practice scenario.

Table 4.
Frequency of use and dosage of the analysed drugs within the new scenario in the subgroup of patients treated with at least one of the analysed drugs at the beginning of the analysed period.

Drug	Daily dose	Probability of use in a specific month of treatment
bosentan	244.90 mg	2.58%
epoprostenol	30 ng/kg/min	0%
iloprost	6.15 vials	23.96%
sildenafil	59.14 mg	58.96%
treprostinil	22.82 ng/kg/min	23.67%

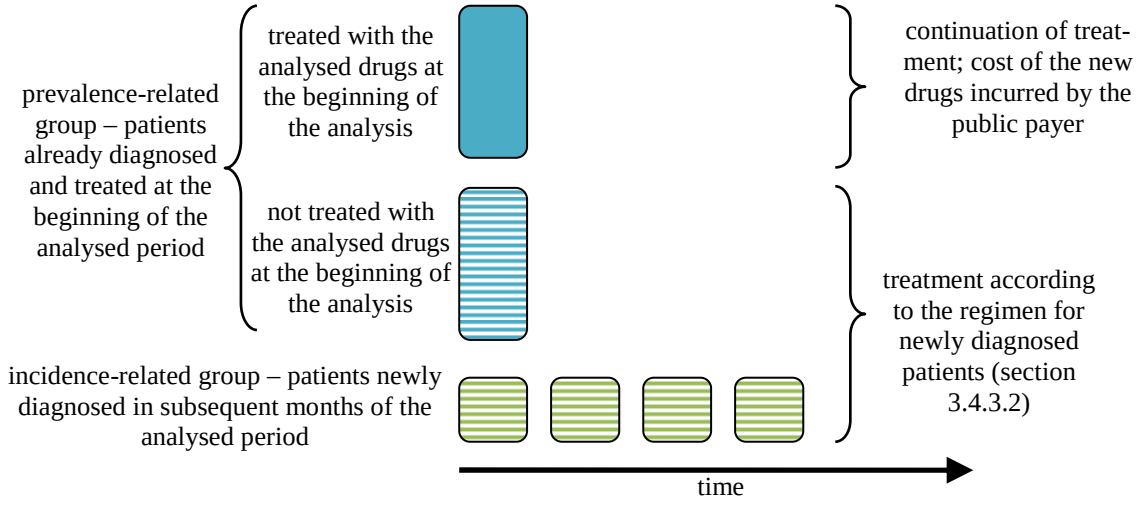
[‡‡] No cases of combination therapy with three or more of the analysed drugs were reported in the survey.

It was assumed in the analysis that the structure of use of the analysed drugs in patients in the first subgroup defined above, i.e. those already treated with the analysed drugs before the beginning of the analysed period (regardless of the financing), reached stationary condition (i.e. no changes of this structure due to changes in therapy or addition of new drugs should be expected). Methods of treatment used in this group of patients are therefore determined by the survey results and are the same as in the "current practice" scenario with respect to frequency of use of the remaining drugs and procedures. The obvious difference is financing of the analysed drugs by the public payer. In the analysis it was assumed that all patients in the prevalence-related group are treated with the analysed drugs (financed by the public payer) from the beginning of the analysed period.[§§] The patients treated with drugs sponsored by the manufacturer or financed by themselves will receive the same drugs reimbursed within public healthcare system.

It was further assumed in the analysis that the patients in the other subgroup, i.e. those not treated with the analysed drugs at the beginning of the analysed period, will from that moment be treated as newly diagnosed patients (the incidence-related group). This is due to the fact that in such patients therapy with the analysed drugs (commonly available within this scenario) will actually be introduced. Treatment regimens for patients, in whom the analysed drugs are newly introduced, are presented in section 3.4.3.2.

Figure 2 presents the patients' classification into subgroups.

Figure 2.
Introduction of the considered treatment methods within the new scenario - a diagram.



3.4.3.2 Treatment regimen for newly diagnosed patients

Treatment regimen for newly diagnosed patients with the assumption of unlimited availability of the analysed drugs was prepared according to results of the survey, in which Polish clinicians took part.

Assumed frequency of use of medical procedures and the remaining drugs was the same as in the "current practice" scenario.

[§§] In the workbook attached to this report it is possible to prolong the period of introduction of the analysed drugs to 12 months. The remaining patients are then treated in the same way as in the „current practice" scenario, i.e. at no cost for the public payer, until they have been included in the treated group.

Use of the analysed drugs was modelled using a Markov model, in which specific states reflect the analysed drugs or combination therapies, initial probability of a specific state reflects the structure of actually used first-line therapies and transition probabilities are related to probabilities of clinical decisions concerning treatment adjustment (due to adverse effects or ineffectiveness of monotherapy).

According to the survey results it was assumed that in first-line treatment the analysed drugs will be used in monotherapy only. Frequency of use of specific drugs calculated from the survey results is presented in Table 5.

Table 5.
Frequency of use and dosage of the analysed drugs in first-line treatment.

Drug	Daily dose	Frequency of use (% of patients)
bosentan	244.90 mg	25.07%
epoprostenol	30 ng/kg/min	5.46%
iloprost	6.15 vials	6.58%
sildenafil	59.14 mg	57.43%
treprostinil	22.82 ng/kg/min	5.46%

It was assumed that treatment may be adjusted for one of the two reasons:

- occurrence of adverse effects;
- ineffectiveness of treatment.

In case of adverse effects it was assumed that the drug would be substituted by another analysed drug belonging to another pharmacological group; e.g. instead of bosentan sildenafil or any drug from the group including prostacyclin and its analogues might be introduced, while epoprostenol might be replaced with bosentan or sildenafil. The probabilities of switching to specific therapy were not based on survey results as it would be very difficult for clinicians to reliably assess the subsequent steps of therapy in case of adverse effects. Instead relative frequency of switch to epoprostenol, iloprost or treprostinil (i.e. relative frequency of their use in the expected final structure of use of the analysed drugs) was estimated from the survey results. Switch rates to bosentan and sildenafil were set to 50% based on clinical expert opinion. Probabilities of specific changes in case of adverse effects are presented in Table 6.

Table 6.
Probabilities of specific changes in case of adverse effects.

From:	To:				
	bosentan	**epoprostenol**	**iloprost**	**sildenafil**	**treprostinil**
Bosentan		4.65%	24.67%	50%	20.68%
epoprostenol	50%			50%	
iloprost	50%			50%	
sildenafil	50%	4.65%	24.67%		20.69%
treprostinil	50%			50%	

Probabilities of adverse events resulting in treatment adjustment were obtained from the systematic review performed by the AHTAPol. For all trials identified within the review monthly

probabilities of the patient's withdrawal from the study due to adverse effects were calculated (equal distribution of probability in time was assumed).[***] If more than one trial was identified for a specific drug, mean probability (weighted with the number of participating patients) was calculated. It was assumed that 4.33 weeks of treatment represent one month. The results are presented in Table 7.

Table 7.
Monthly probabilities of adverse events resulting in treatment adjustment.

Drug	Trial(s)	Percentage of patients, in whom adverse effects were observed, n/N; %	Duration of trial(s) (range)	Calculated monthly probability
bosentan	[7,26,4,9],	17/262; 6.49%	16-28 weeks	1.74%
epoprostenol	[5]	2/41; 4.88%	12 weeks	1.79%
iloprost	[24]	4/101; 3.96%	12 weeks	1.45%
sildenafil	[9][†††]	2/207; 0.97%	12 weeks	0.35%
treprostinil	[29]	18/233; 7.73%	12 weeks	2.86%

In case of inefficient treatment it was assumed that another drug will be introduced (combination therapy). Three combination therapy regimens (combining drugs from two different pharmacological groups, according to the survey results) were considered: sildenafil + bosentan, sildenafil + iloprost, sildenafil + treprostinil.[‡‡‡] Relative frequency of change from epoprostenol or sildenafil in monotherapy to combination therapy was estimated from the survey results (as relative frequency of their use in relation to all reported combination therapy regimens). Probabilities of change from monotherapy (due to its ineffectiveness) to combination therapy are presented in Table 8.

Table 8.
Probabilities of change from monotherapy (due to its ineffectiveness) to combination therapy.

From:	To combination therapy:		
	sildenafil+bosentan	sildenafil+iloprost	sildenafil+treprostinil
bosentan	100%		
epoprostenol	5.42%	39.35%	55.23%
iloprost		100%	
sildenafil	5.42%	39.35%	55.23%
treprostinil			100%

[***] If p is probability of withdrawal in a period of n months, then probability of withdrawal within one month (p*) may be calculated from the following equation: $(1-p^*)^n=1-p$.

[†††] Since published information was not precise, it was assumed that a half of the reported adverse events was observed in the sildenafil group.

[‡‡‡] Polish experts reported no other drug combinations.

Probabilities of treatment ineffectiveness resulting in introduction of combination therapy were obtained from the AHTAPol systematic review. It was assumed that combination therapy is introduced after occurrence of the following study endpoints: exacerbation of symptoms of the disease (in case of iloprost) or worsening of the patient's condition (for bosentan, sildenafil or treprostinil). As these data were not available for epoprostenol, decrease of exercise capacity according to the NYHA classification was used as a measure of decreased treatment effectiveness. For all trials identified within the review monthly probabilities of occurrence of treatment ineffectiveness were calculated (equal distribution of probability in time was assumed). If more than one trial was identified for a specific drug, mean probability (weighted with the number of participating patients) was calculated. The results are presented in Table 9.

Table 9.
Monthly probabilities of occurrence of treatment ineffectiveness resulting in introduction of combination therapy.

Drug	Trial(s)	Percentage of patients, in whom treatment ineffectiveness was observed, n/N; %	Duration of trial(s) (range)	Calculated monthly probability
bosentan	[7,26]	4/134; 2.99%	16-18 weeks	0.77%
epoprostenol*	[5]	5/40; 12.5%	12 weeks	4.7%
iloprost	[24]	5/101; 4.95%	12 weeks	1.82%
sildenafil	[10]	3/207; 1.45%	12 weeks	0.53%
treprostinil	[29]	6/233; 2.58%	12 weeks	0.94%
* in case of epoprostenol ineffectiveness of treatment was defined as reclassification of a patient into a higher NYHA class				

3.5 Costs taken into account

3.5.1 Drug prices

Prices of all the analysed drugs were obtained by the AHTAPol from the manufacturers. In case of drugs administered in outpatient settings (bosentan, sildenafil, iloprost) gross prices (i.e. including wholesale and retail margins) were assumed. In case of drugs administered in hospital settings (epoprostenol, treprostinil) only wholesale margin was taken into account.[§§§]

Calculations were based on mean prices per one milligram.

In case of treprostinil the manufacturer proposed so-called *price volume agreement* (PVA) in order to limit the risk for the public payer of substantial costs of treatment of one patient to be incurred in a specific year. Within this agreement annual treatment costs exceeding 380,000 PLN would be fully covered by the manufacturer. In this analysis the PVA was not directly taken into account; instead of that baseline drug price has been appropriately adjusted. The adjustment was calculated in the following way. A hypothetical group of 244 patients (see section 4.1), in whom treatment was introduced during one year, was considered. This group included patients already treated at the beginning of the year (and there-

[§§§] The VAT (7%) and wholesale margin (8.91%), calculated in relation to the price with wholesale margin, were taken into account.

fore treated for 12 months) and those, in whom treatment was introduced in subsequent months (and therefore treated for 11.5 months, 10.5 months, …, 0.5 months on average). Mean costs of treatment of one patient with or without the PVA in specific subgroups (patients who joined the group in subsequent months) were calculated by means of simulation (repeated 1,000 times). Mean costs were calculated assuming constant dose of the drug per kilogram of body weight (see Table 1, section 3.4.1.1) and different body weight of specific patients. Assumed mean body weight was 68.95 kg (see section 3.4.2, page **Błąd! Nie zdefiniowano zakładki.**) with a standard deviation of 10 kg, according to the results of clinical trials [1,12,21,32]. Mean cost of treatment of the whole group of patients included during the year with and without the PVA was then calculated. The results suggested that introduction of the PVA will reduce the total cost by 11.8%. This value was applied to baseline drug price and the price thus reduced was used in the analysis in order to take the PVA into account.

Prices of the analysed drugs are presented in Table 10. Prices of the remaining drugs are presented in Table 11.

Table 10.
Drug prices used in the analysis – the analysed drugs.

Drug	Formulation	Price (PLN)
bosentan	125 mg x 56 tablets	13,630
epoprostenol	0.5 mg x 12 vials 1.5 mg x 12 vials mean price per 1 mg	5,638.38 12,122.52 806.6
iloprost	30 vials	2,204.4
sildenafil	20 mg x 90 tablets	2,899.32
treprostinil	1 mg/ml x 20 ml 2.5 mg/ml x 20 ml 5 mg/ml x 20 ml mean price per 1 mg price per 1 mg (PVA)	13,548.03 23,586.67 40,185.98 516 456

Table 11.
Drug prices used in the analysis – the remaining drugs.

Drug	Formulation	Reimbursement (PLN)
acenocumarol	4 mg, 60 tablets	7.52
enoxaparin	60 mg per vial, 2 vials	29.45
unfractionated heparin	5,000 IU/0.2 ml, 10 vials	15.67
furosemide	40 mg, 30 tablets	0.54
spironolactone	25 mg, 100 tablets	8.71
hydrochlorothiazide	25 mg, 30 tablets	0
torasemide	10 mg, 30 tablets	0
chlortalidone	50 mg, 20 tablets	0

amiloride + hydrochlorothiazide (brand name: Tialorid)	55 mg	3.99
digoxin	0.25 mg, 30 tablets	0
metyldigoxin (brand name: Bemecor)	0.1 mg, 30 tablets	0
diltiazem	60 mg, 100 tablets	11.1
nifedipine	10 mg, 50 tablets	0
amlodipine	10 mg, 30 tablets	9.04
verapamil	120 mg, 40 tablets	3.42
enalapril	10 mg, 30 tablets	0

3.5.2 Costs of outpatient visits and hospitalizations

Costs related to both hospitalizations and outpatient treatment were taken into account in the analysis. These were obtained from the contracts between the NHF and specific institutions; mean costs of particular procedures (weighted with the number of patients treated at specific institutions) were calculated.

For each institution the cost was calculated as the product of the number of points multiplied by the value of one point (appropriately increased in order to take into account additional means transferred to service providers by the NHF in effect of the act of Parliament from July 22nd, 2006 concerning transfer of additional means for salary increase). For this adjustment it was assumed that the total additional sum was distributed between all procedures contracted in a specific institution proportionally to total values of these procedures. Data for specific procedures are presented in Table 12.

It should be noted that due to proposed changes in the rules of medical procedures contracting in 2008 (a proposal of the President of the NHF regarding specification of rules of contracting and realization of hospitalization and related services [23]) prices of certain services may change in comparison to 2007 and therefore appropriate adjustment of the calculations presented here may be needed.

Table 12.
Prices of the procedures in specific institutions.

Name of the procedure	NHF code	Number of points	Basic price for one point (PLN)	Adjust-ment	Adjusted price for one point (PLN)	Cost of the procedure (PLN)
J. Babiński District Hospital, Wrocław						
pulmonary arterial / thromboembolic hypertension – diagnostics	5.06.00.0000827	500	11	49.69%	16.47	8,232.93
pulmonary arterial / thromboembolic hypertension – treatment of exacerba-tion	5.06.00.0001303	300	11	49.69%	16.47	4,939.76
pulmonary arterial / thromboembolic hypertension – periodic assessment of progress of the disease	5.06.00.0001304	220	11	49.69%	16.47	3,622.49
Child Health Centre, Warszawa						
pulmonary arterial / thromboembolic hypertension – diagnostics	5.06.00.0000827	500	11	16.75%	12.84	6,421.03
type I cardiology outpatient consultation	5.01.01.1101001	2.1	8.8	18.07%	10.39	21.82
type II cardiology outpatient consultation	5.01.01.1101002	4.2	8.8	18.07%	10.39	43.64
type III cardiology outpatient consultation	5.01.01.1101003	7.35	8.8	18.07%	10.39	76.37
University Hospital, Kraków						
pulmonary arterial / thromboembolic hypertension – diagnostics	5.06.00.0000827	500	11	17.06%	12.88	6,438.15
pulmonary arterial / thromboembolic hypertension – treatment of exacerba-tion	5.06.00.0001303	300	11	17.06%	12.88	3,862.89
pulmonary arterial / thromboembolic hypertension – periodic assessment of progress of the disease	5.06.00.0001304	220	11	17.06%	12.88	2,832.79
type I cardiology outpatient consultation	5.01.01.1101001	2.1	7.8	15.59%	9.02	18.93
type II cardiology outpatient consultation	5.01.01.1101002	4.2	7.8	15.59%	9.02	37.87
type III cardiology outpatient consultation	5.01.01.1101003	7.35	7.8	15.59%	9.02	66.27
Silesian Centre of Heart Diseases, Zabrze						
pulmonary arterial / thromboembolic hypertension – diagnostics	5.06.00.0000827	500	10	15.9%	11.59	5,794.87
pulmonary arterial / thromboembolic hypertension – treatment of exacerba-tion	5.06.00.0001303	300	10	15.9%	11.59	3,476.92

Name of the procedure	NHF code	Number of points	Basic price for one point (PLN)	Adjust-ment	Adjusted price for one point (PLN)	Cost of the procedure (PLN)
pulmonary arterial / thromboembolic hypertension – periodic assessment of progress of the disease	5.06.00.0001304	220	10	15.9%	11.59	2,549.74
type I cardiology outpatient consultation	5.01.01.1101001	2.1	7.49	16.93%	8.76	18.39
type II cardiology outpatient consultation	5.01.01.1101002	4.2	7.49	16.93%	8.76	36.78
type III cardiology outpatient consultation	5.01.01.1101003	7.35	7.49	16.93%	8.76	64.37
SP ZOZ Specialist Hospital, Zabrze						
pulmonary arterial / thromboembolic hypertension – diagnostics	5.06.00.0000827	500	10	16.54%	11.65	5,827.25
pulmonary arterial / thromboembolic hypertension – treatment of exacerba-tion	5.06.00.0001303	300	10	16.54%	11.65	3,496.35
pulmonary arterial / thromboembolic hypertension – periodic assessment of progress of the disease	5.06.00.0001304	220	10	16.54%	11.65	2,563.99
type I cardiology outpatient consultation	5.01.01.1101001	2.1	7.02	17.7%	8.26	17.35
type II cardiology outpatient consultation	5.01.01.1101002	4.2	7.02	17.7%	8.26	34.7
type III cardiology outpatient consultation	5.01.01.1101003	7.35	7.02	17.7%	8.26	60.73
Institute of Tuberculosis and Lung Diseases, Warszawa						
pulmonary arterial / thromboembolic hypertension – diagnostics	5.06.00.0000827	500	11	15.99%	12.76	6,379.33
pulmonary arterial / thromboembolic hypertension – treatment of exacerba-tion	5.06.00.0001303	300	11	15.99%	12.76	3,827.60
pulmonary arterial / thromboembolic hypertension – periodic assessment of progress of the disease	5.06.00.0001304	220	11	15.99%	12.76	2,806.91
type I pulmonary outpatient consultation	5.01.01.1240001	2.28	8.8	15.41%	10.16	23.15
type II pulmonary outpatient consultation	5.01.01.1240002	4.56	8.8	15.41%	10.16	46.31
type III pulmonary outpatient consultation	5.01.01.1240003	7.98	8.8	15.41%	10.16	81.04
atrial septostomy	5.06.00.0000827	500	11	15.99%	12.76	6,379.33
home oxygen therapy (monthly)	5.10.00.0000006	32	8.5	8.75%	9.24	295.81

Aggregated data are presented in Table 13.

Table 13.
Prices of the procedures used in the analysis.

Code of the procedure	Description of the procedure	Cost of the procedure (PLN)
5.10.00.0000006	home oxygen therapy (monthly)	295.81
5.06.00.0000827	pulmonary arterial / thromboembolic hypertension – diagnostics	6,325.83
5.06.00.0001303	pulmonary arterial / thromboembolic hypertension – treatment of exacerbation	3,793.61
5.06.00.0001304	pulmonary arterial / thromboembolic hypertension – periodic assessment of progress of the disease	2,781.98
	Septostomy	6,379.33
5.01.01.1272001	type I pulmonary outpatient consultation	23.15
5.01.01.1272002	type II pulmonary outpatient consultation	46.31
5.01.01.1272003	type III pulmonary outpatient consultation	81.04
5.01.01.1100001	type I cardiology outpatient consultation	18.73
5.01.01.1100002	type II cardiology outpatient consultation	37.47
5.01.01.1100003	type III cardiology outpatient consultation	65.58

3.5.3 Costs of adverse effects

In the survey conducted in institutions treating pulmonary arterial hypertension in Poland practically no adverse effects generating additional costs for the public payer have been reported in patients treated so far. Most of the reported adverse effects, such as cough, dry mouth or skin flushes, caused discomfort to the patients but generated no additional costs (although they sometimes resulted in discontinuation of the drug or dose reduction). Both these events are taken into account in the model as possibility of change of treatment due to adverse effects and assumption of doses based on actual reports of the clinicians.

Nevertheless, data presented in the AHTAPol systematic review and EMEA and FDA documents concerning the analysed drugs suggest that some of the reported adverse effects may generate additional costs for the payer. These include: pneumonia,[****] sepsis and pneumothorax (hospital procedures) as well as gastritis, pruritus and rash (use of reimbursed drugs).

Frequency of adverse events is presented in Table 16. In the calculations equal distribution of probability of an adverse event (i.e. occurrence of an adverse effect) in time was assumed and monthly probabilities were calculated from probabilities estimated in the whole follow-up period of a trial. It was assumed that one month represents 4.33 weeks.

Costs of hospital treatment of sepsis, pneumothorax and pneumonia were calculated from the contracts between NHF and the Institute of Tuberculosis and Lung Diseases (pneumothorax and pneumonia) and the Hospital for Infectious Diseases in Warsaw (sepsis). Costs of treatment are presented in Table 14.

[****] It was assumed in the analysis that pneumonia in patients with PAH (i.e. high risk patients) is treated in hospital settings.

Table 14.
Costs of treatment of adverse effects.

Name of the procedure	NHF code	Number of points	Basic price for one point (PLN)	Adjustment	Adjusted price for one point (PLN)	Cost of the procedure (PLN)
Hospital for Infectious Diseases, Warszawa						
Sepsis	5.06.00.0001287	450	10.5	16.29%	12.21	5,494.68
Institute of Tuberculosis and Lung Diseases, Warszawa						
Pneumothorax – conservative treatment	5.06.00.0001297	120	11	15.99%	12.76	1,531.04
Uncomplicated pneumonia	5.06.00.0001180	140	11	15.99%	12.76	1,786.21

Costs of treatment of pruritus, rash and gastritis were calculated from prices of reimbursed drugs used in those conditions. Details are presented in Table 15.

Table 15.
Costs of treatment of adverse effects.

Adverse effect	Drug	Dose, duration of treatment	NHF cost per package (PLN)	Cost of treatment (PLN)
Pruritus	Cetirizine	1 tablet daily for 7 days	30 tablets x 10 mg, 7.28 PLN	1.7 PLN
Rash	Cetirizine	1 tablet daily for 7 days	30 tablets x 10 mg, 7.28 PLN	1.7 PLN
Gastritis	Omeprazole	1 tablet daily for 4 weeks	28 tablets x 20 mg, 23.1 PLN	23.1 PLN

Frequency of occurrence and costs related to adverse effects observed in the group of patients receiving placebo were not taken into consideration in this analysis.

Table 16.
Frequency of adverse events.

Drug	bosentan	epoprostenol	iloprost	sildenafil	treprostinil
Source	EMEA	FDA, AHTAPol	EMEA	FDA	FDA
Duration of follow-up	16 weeks	12 weeks	12 weeks	12 weeks	12 weeks
Event: n/N; % during follow-up; % monthly					
Pneumonia	5/165; 3.03%; 0.83%		2/101; 1.98%; 0.72%		
Gastritis				2/69; 2.9%; 1.06%	
Pruritus	6/165; 3.64%; 1%				…/236; 8%*; 2.69%
Rash					…/236; 14%*; 5.3%
Sepsis		2/52; 3.85%; 1.41%			
Pneumothorax		2/52; 3.85%; 1.41%			

* no data allowing for unequivocal calculation of the numbers and percentages

3.6 Analysis of health-related effects

Clinical trials identified in the systematic review performed by the AHTAPol do not allow for credible evaluation of the effect of treatment on mortality in pulmonary arterial hypertension due to short follow-up. The analysis of health-related effects was therefore based on the results of this systematic review concerning effects of used drugs on clinical improvement, defined as improvement of exercise capacity according to the NYHA classification (reclassification into a lower NYHA functional class). As this endpoint was not assessed in any of the clinical trials for treprostinil, mean value was calculated for the two other drugs in the same therapeutic group (i.e. epoprostenol and iloprost) and assumed for treprostinil.

Monthly probability of achieving of this clinical outcome was calculated separately for each of the analysed drugs and standard treatment (without any of the analysed drugs) from the results of trials. As the trials differed with respect to duration of treatment and follow-up, monthly probabilities of achieving of clinical improvement were calculated assuming equal distribution of probability in time. If more than one trial was available for a specific drug (or standard treatment), monthly probability was calculated for each trial; from these values mean probability (weighted with the number of patients participating in specific trials) was calculated. The results are presented in Table 17.

In case of combination therapy the assumed outcome measure was mean efficacy of used drugs.

It was assumed that clinical improvement may be achieved only once for each patient treated with a specific drug. Achievement of clinical improvement is possible again only if the therapy has been changed (i.e. a drug has been added or changed). It was also assumed in the analysis that achievement of clinical improvement does not influence mortality or probability of treatment change.

A summary measure for health-related effects of the treatment methods under consideration (i.e. the "current practice" scenario and the new scenario) is the number of patients, in whom clinical improvement was achieved within the time horizon of the analysis.

Table 17.
Monthly probability of achievement of clinical improvement.

Drug	Trial(s)	Percentage of patients, in whom clinical improvement was achieved (for all trials combined): n/N; %	Duration of trial(s) (range)	Calculated monthly probability
bosentan	[7,9,26]	48/126; 38.1%	16-28 weeks	11.23%
epoprostenol	[3,5,27]	47/106; 44.34%	8-12 weeks	24.03%
iloprost	[24]	25/101; 24.75%	12 weeks	9.75%
sildenafil	[10,28]	74/213; 34.74%	2-12 weeks	15.7%
treprostinil	None			16.89% – mean value for epoprostenol and iloprost
standard treatment	[3,4,5,7,9,10,24,26,27,28]	48/430; 11.16%	2-28 weeks	3.71%

3.7 Validation of the model

Internal validation of the budget impact model was successfully carried out. The results obtained were checked for specific values of particular parameters (zero values, parameters changed by 10%; see section 4.5.1).

3.8 Sensitivity analysis

Additional sensitivity analysis (for the population size estimated in the realistic scenario) was carried out, including:

- analysis of key parameters – effect of change of selected, key parameters by 10% (an arbitrarily selected value – the aim of this analysis was to compare the strength of influence of specific parameters) on the final results;
- analysis of non-ideal confectioning of the drugs, i.e. utilisation of only a part of a tablet/vial; doses presented in Table 1 were substituted with doses representing whole tablets/vials – the assumed dose was 250 mg for bosentan, 60 mg for sildenafil and 7 vials for iloprost.

Changes of the following elements of the model were evaluated within the analysis of key parameters:

- body weight;
- percentage of adults;
- prevalence rate;
- frequency of use and costs of the procedures;
- doses of the analysed drugs;
- prices of the analysed drugs;
- frequency of use of oxygen therapy among patients treated with new drugs.

4 BUDGET IMPACT ANALYSIS

4.1 Analysis of the realistic scenario

4.1.1 Current practice costs

Current practice costs and the population size are presented in details in Table 18; various combinations of their specific components are presented in Figure 4,-Figure 9 and Figure 22.

Large number of patients included during the first year is due to the fact that the patients already diagnosed and treated at the beginning of the analysed period are taken into account.

Mean cost of one patient-month of treatment in the "current practice" scenario is ca. 4,120.57 PLN. Annual costs within the time horizon of five years increase from 10.3 to 14.92 million PLN (the values in subsequent years are: 10.3, 11.67, 12.89, 13.97 and 14.92 million PLN).

Drug costs represent the dominant component (72.26% of total costs); among them, treprostinil and iloprost generate the highest costs (71.46% and 24.04% of total drug costs, respectively). Costs of medical procedures are mostly related to hospitalisations (97.71%).

Figure 3.
The number of patients newly diagnosed and treated in subsequent years.

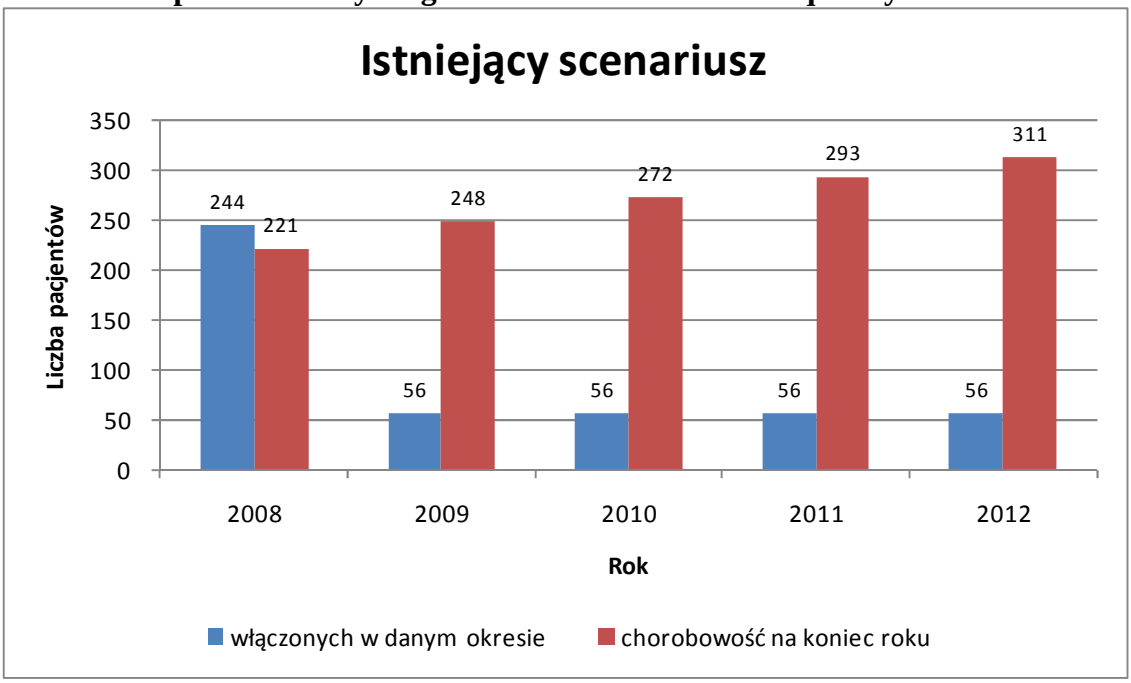


Figure 4.
Cost structure.

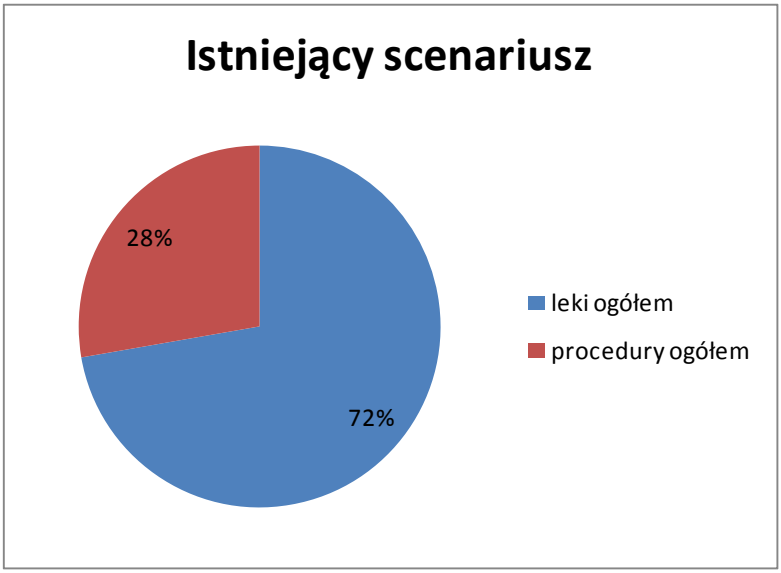


Figure 5.
Cost structure of the analysed drugs.

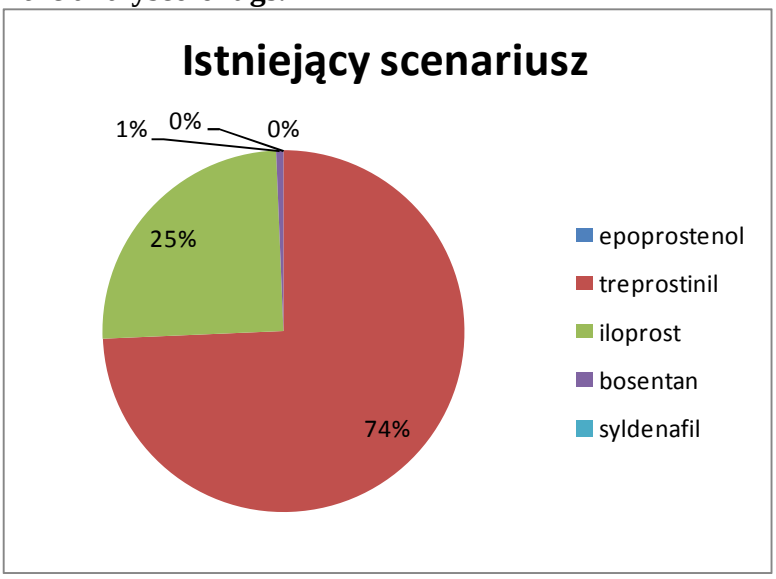


Figure 6.
Change of costs of the analysed drugs.

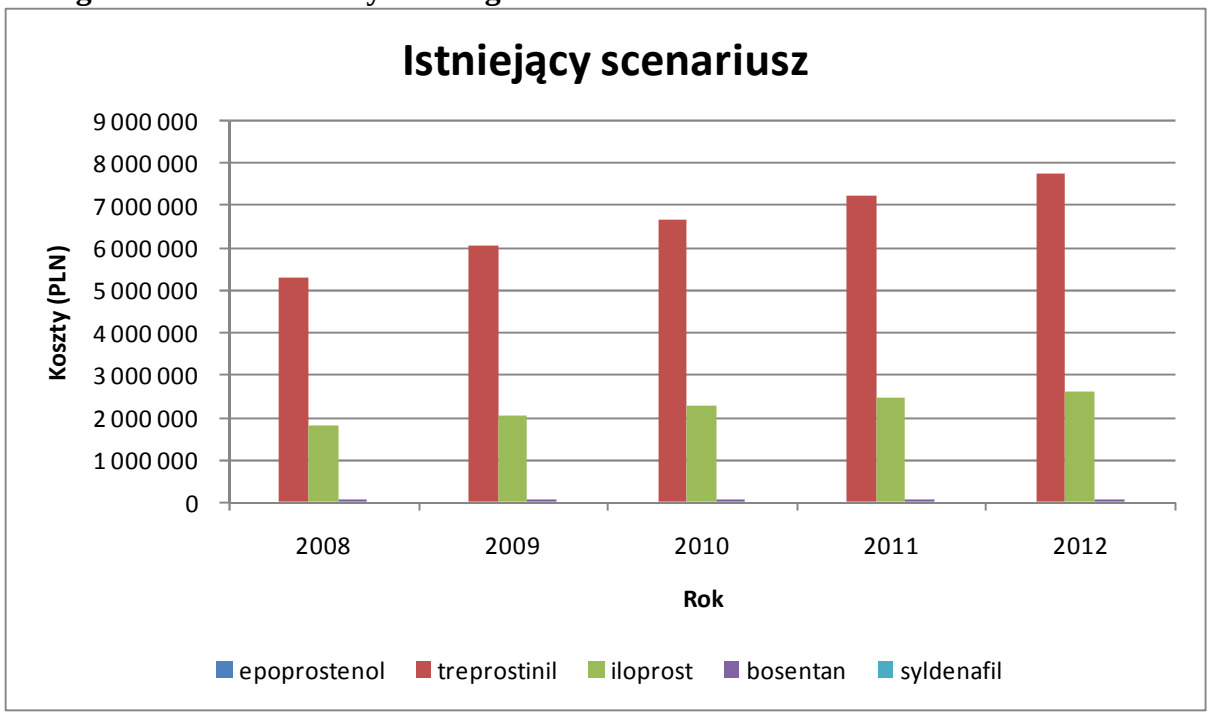


Figure 7.
Change of costs of all drugs.

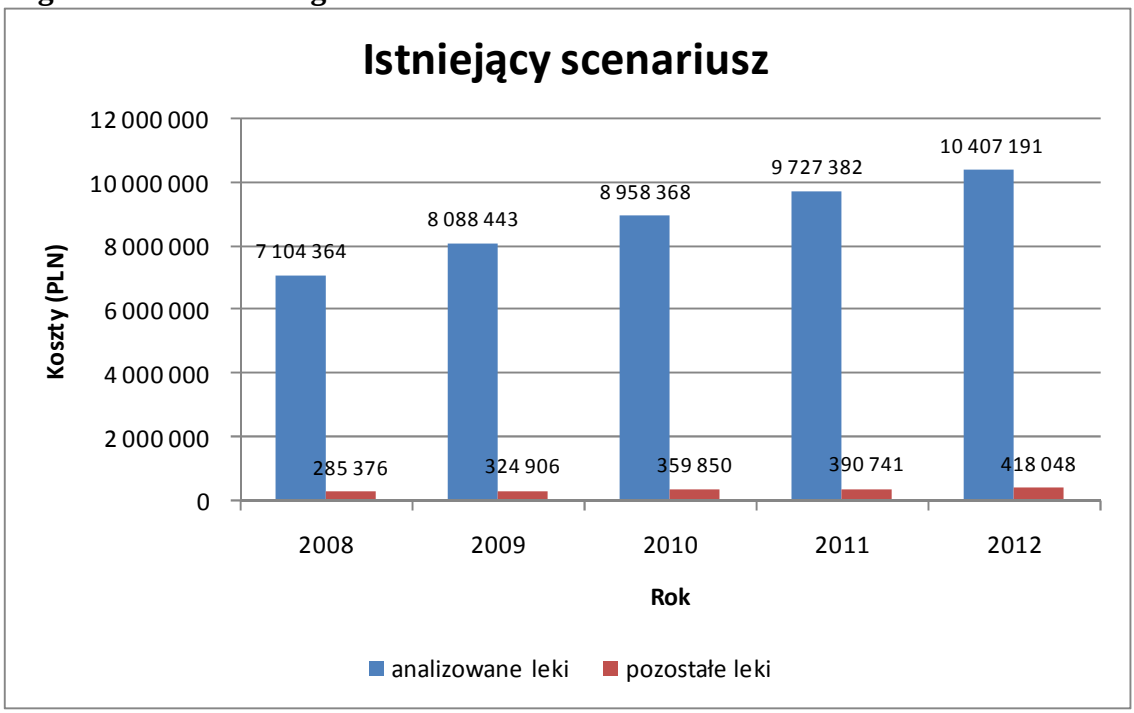


Figure 8.
Change of costs of drugs and procedures.

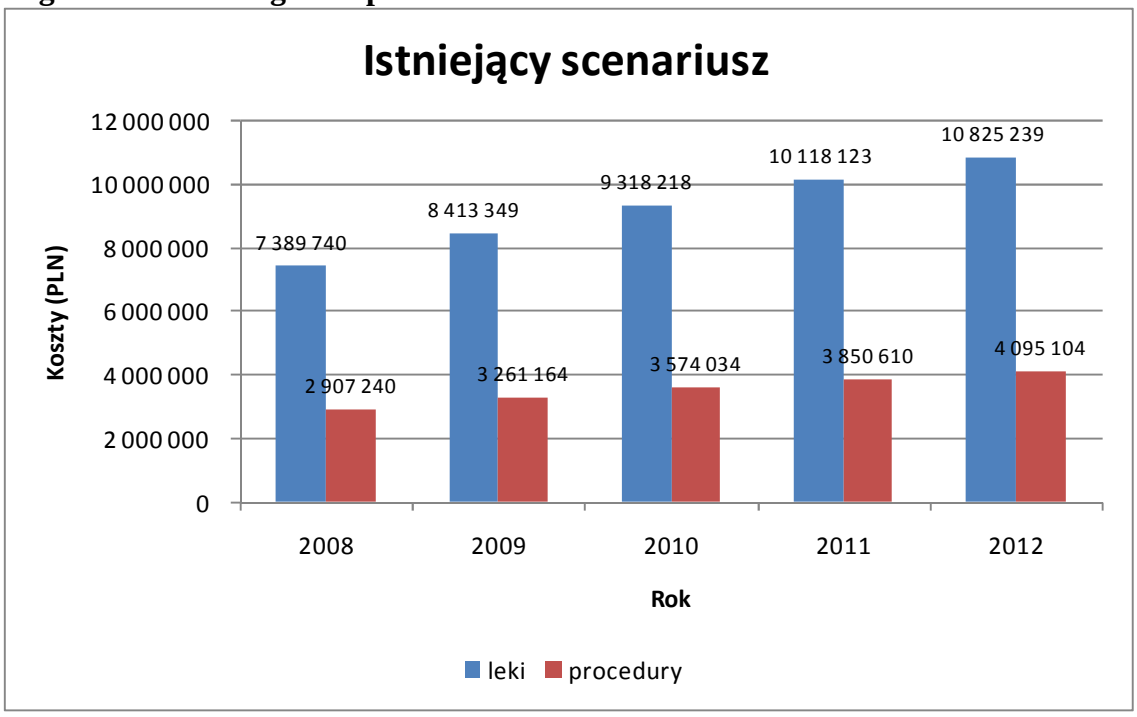


Figure 9.
Change of costs of the procedures used.

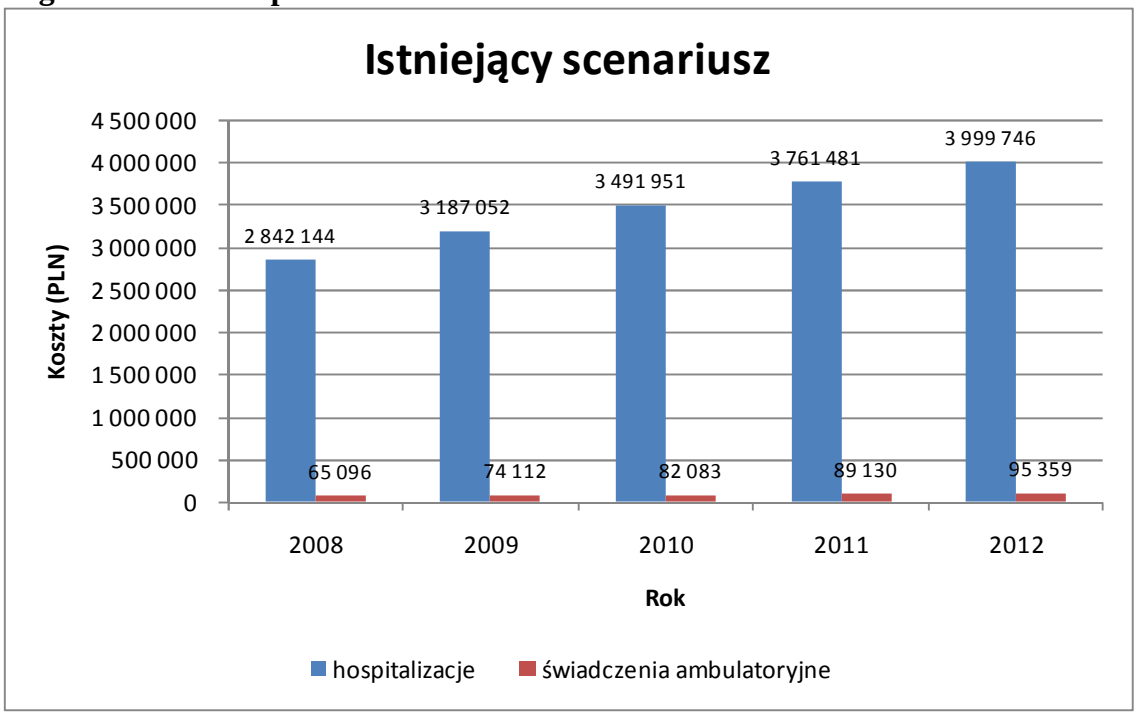


Table 18.
Costs in the "current practice" scenario.

	Year					Total
	2008	**2009**	**2010**	**2011**	**2012**	
Number of patients included	244	56	56	56	56	**466**
Patient-months of treatment in a specific year	2,482	2,826	3,130	3,398	3,636	**15,472**
Number of patients at the end of the year	221	248	272	293	311	**n.a.**
Drug costs (PLN):						
epoprostenol	0.00	0.00	0.00	0.00	0.00	**0.00**
treprostinil	5,280,986.13	6,012,495.08	6,659,148.98	7,230,791.04	7,736,122.62	**32,919,543.85**
iloprost	1,776,450.42	2 022 519.87	2,240,045.27	2,432,337.72	2,602,324.25	**11,073,677.53**
bosentan	46,927.36	53,427.62	59,173.85	64,253.52	68,743.94	**292,526.29**
sildenafil	0.00	0.00	0.00	0.00	0.00	**0.00**
Total costs of the analysed drugs	7,104,363.91	8,088,442.57	8,958,368.10	9,727,382.28	10,407,190.81	**44,285,747.66**
Costs of the remaining drugs	285,376.41	324,906.04	359,850.23	390,740.89	418,048.23	**1,778,921.80**
Total costs of pharmacotherapy	7,389,740.32	8,413,348.60	9,318,218.33	10,118,123.17	10,825,239.04	**46,064,669.46**
Procedure costs (PLN):						
hospitalizations	2,842,144.21	3,187,052.05	3,491,950.58	3,761,480.88	3,999,745.67	**17,282,373.39**
outpatient services	65,095.54	74,112.41	82,083.32	89,129.61	95,358.53	**405,779.42**
total	2,907,239.75	3,261,164.46	3,574,033.91	3,850,610.49	4,095,104.20	**17,688,152.81**
Total costs (PLN):						
Total costs	**10,296,980.07**	**11,674,513.06**	**12,892,252.23**	**13,968,733.66**	**14,920,343.24**	**63,752,822.27**

4.1.2 Costs in the new scenario.

Costs calculated for the new scenario are presented in details in Table 19; various combinations of their specific components are presented in Figures 10-15 below and Figure 22. Size of the target population and its dynamics are the same as for the "current practice" scenario.

Mean cost of one patient-month of treatment in the new scenario is ca. 13,224.32 PLN. Annual costs within the time horizon of five years increase from 32.95 to 48.9 million PLN (the values in subsequent years are: 32.95, 36.8, 40.94, 45.02 and 48.9 million PLN).

Drug costs represent the dominant component (91.31% of total costs); the percentages of costs related to specific drugs are as follows: bosentan (23.19%), epoprostenol (11.21%), iloprost (15.38%), sildenafil (16.21%), treprostinil (33.06%). Costs of medical procedures are mostly related to hospitalisations (97,72%).

Figure 10.
Cost structure.

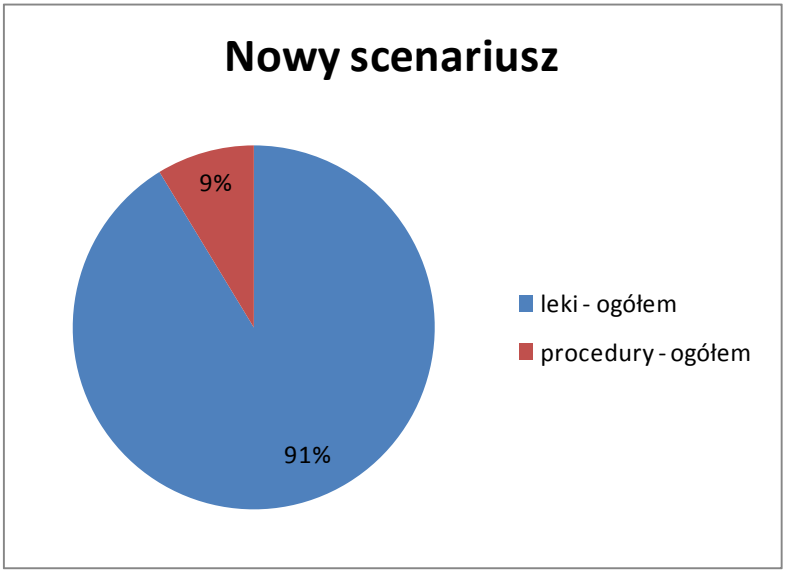


Figure 11.
Cost structure of the analysed drugs.

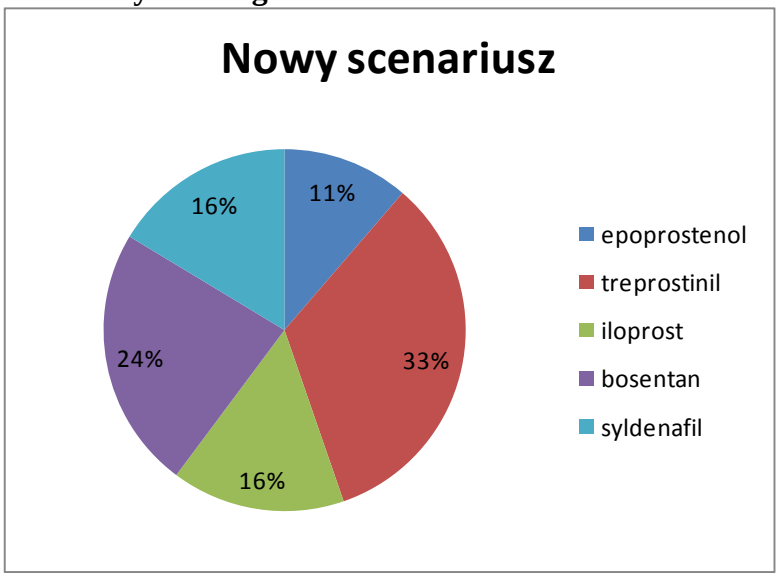


Figure 12.
Change of costs of the analysed drugs.

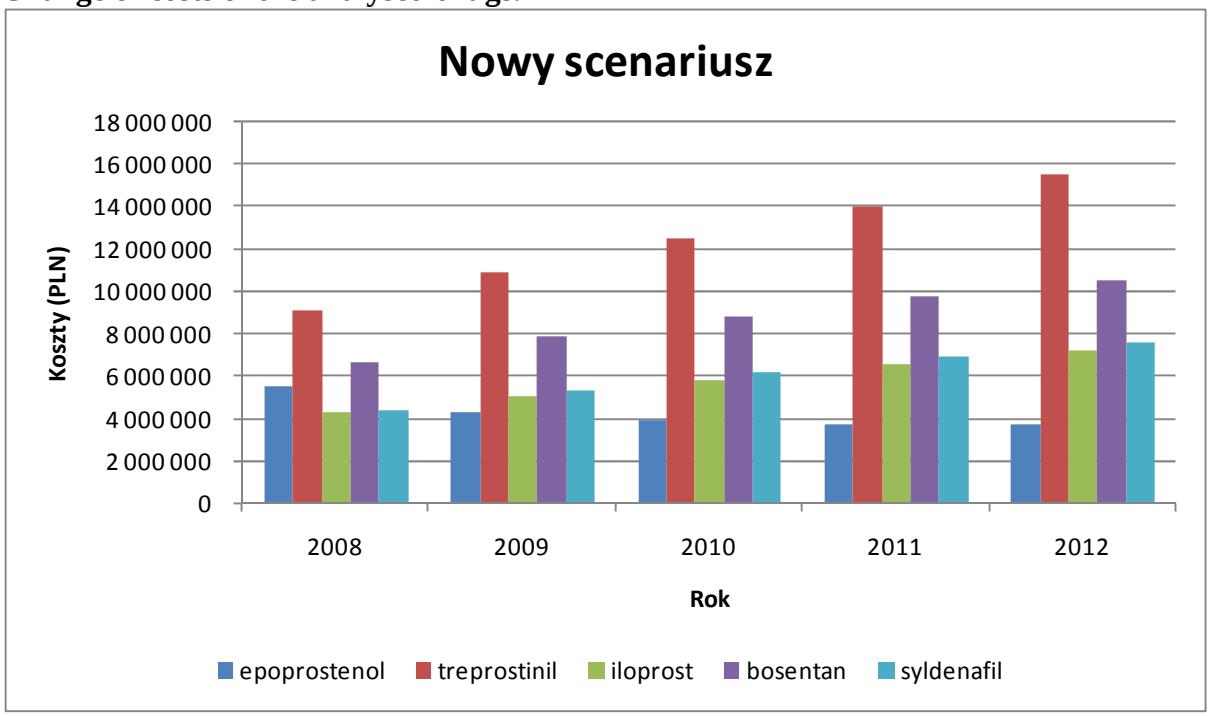


Figure 13.
Change of costs of all drugs.

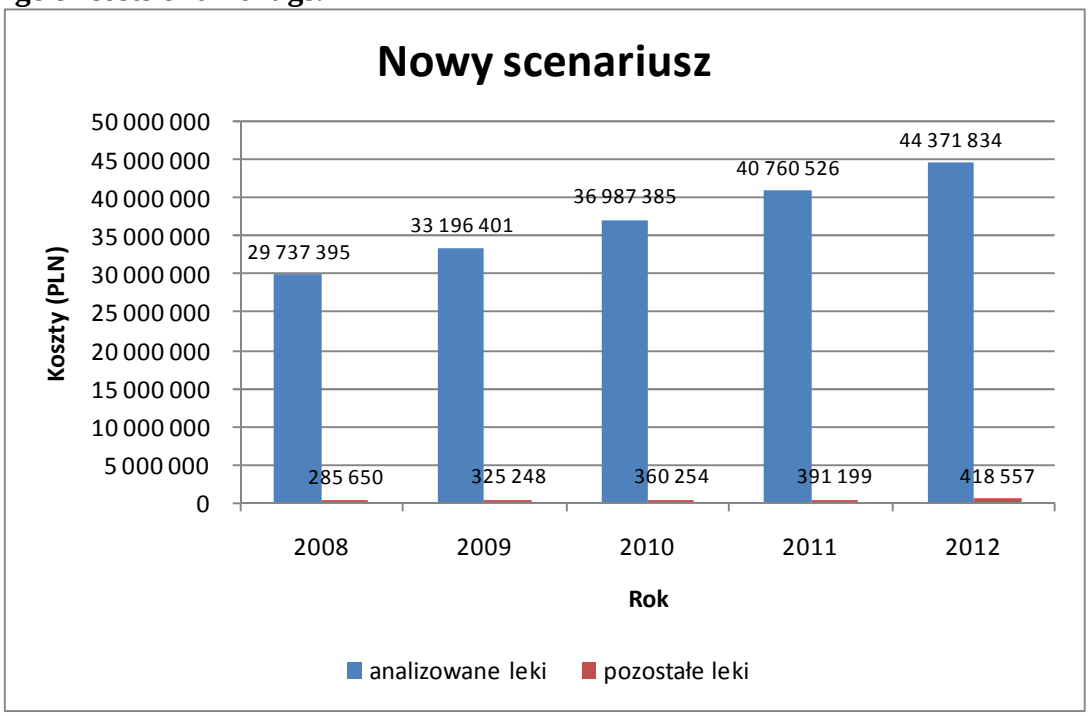


Figure 14.
Change of costs of drugs and procedures.

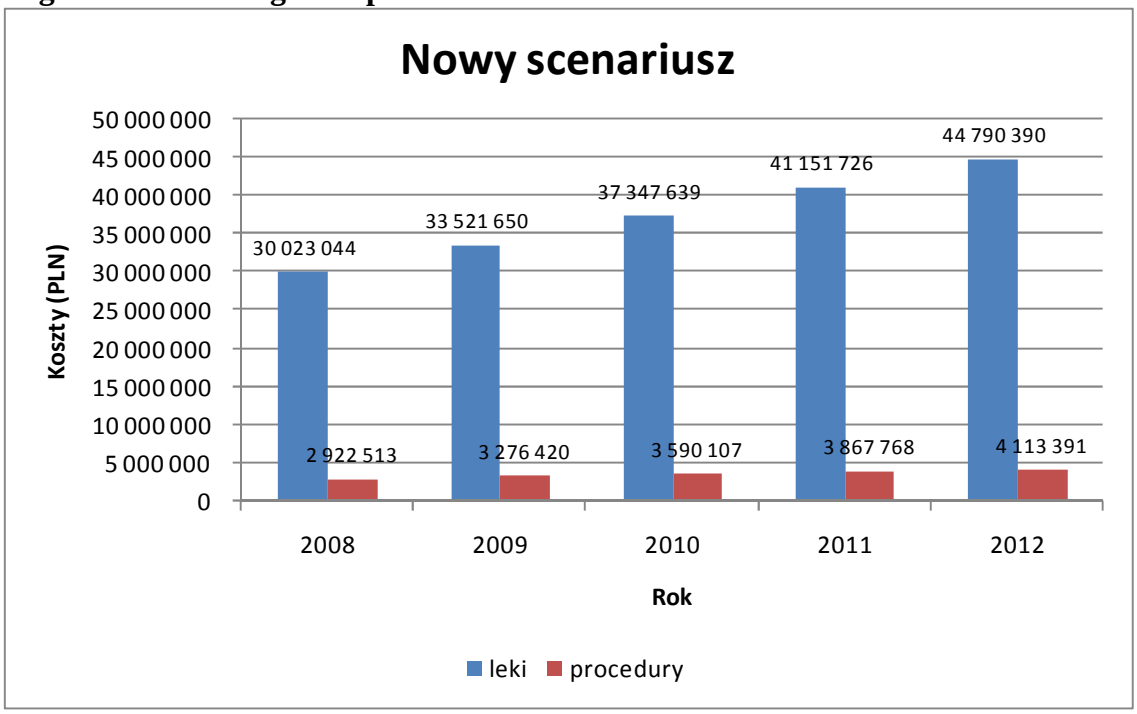


Figure 15.
Change of costs of the procedures used.

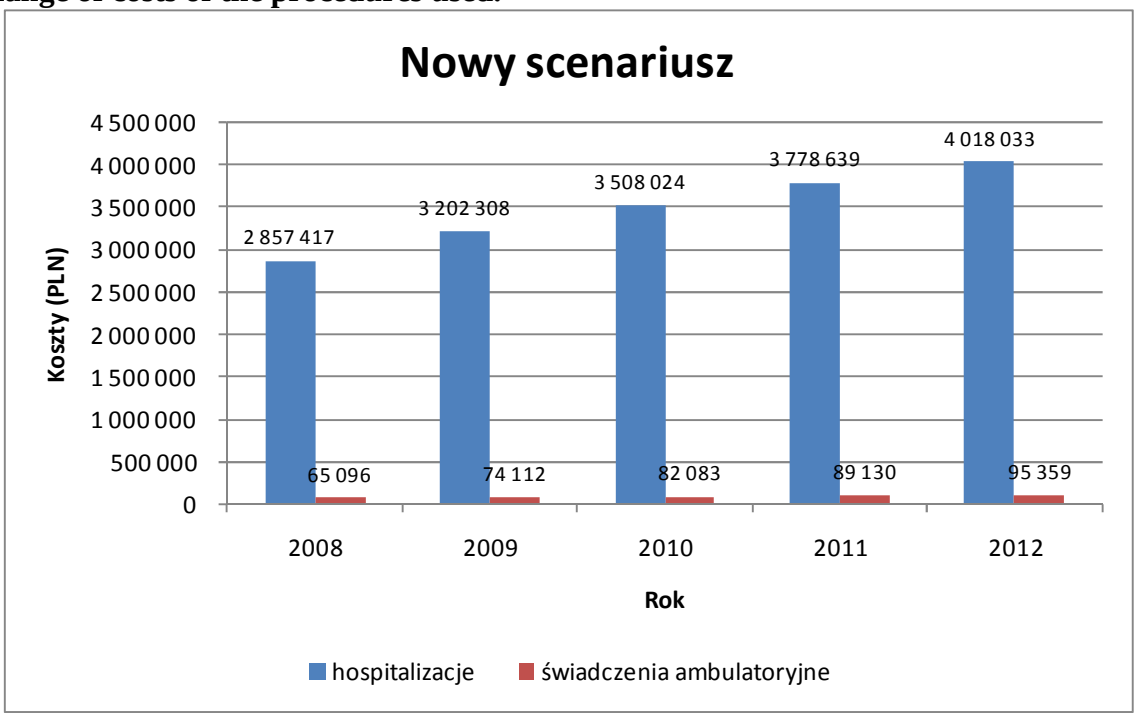


Table 19.
Costs in the new scenario.

	Year					Total
	2008	**2009**	**2010**	**2011**	**2012**	
Number of patients included	244	56	56	56	56	**466**
Patient-months of treatment in a specific year	2,482	2,826	3,130	3,398	3,636	**15,472**
Number of patients at the end of the year	221	248	272	293	311	**n.a.**
Drug costs (PLN):						
epoprostenol	5,421,040.44	4,270,989.71	3,850,992.50	3,712,558.21	3,680,069.64	**20,935,650.50**
treprostinil	9,088,323.38	10,796,429.61	12,415,970.17	13,981,155.62	15,491,873.62	**61,773,752.40**
iloprost	4,221,383.69	5,024,813.13	5,783,642.19	6,508,175.96	7,198,452.11	**28,736,467.08**
bosentan	6,641,647.35	7,790,051.14	8,786,646.07	9,664,567.49	10,443,092.71	**43,326,004.75**
sildenafil	4,364,999.72	5,314,117.73	6,150,134.09	6,894,069.17	7,558,345.50	**30,281,666.20**
Total costs of the analysed drugs	29,737,394.58	33,196,401.32	36,987,385.01	40,760,526.44	44,371,833.58	**185,053,540.93**
Costs of the remaining drugs	285,649.57	325,248.24	360,253.65	391,199.40	418,556.56	**1,780,907.42**
Total costs of pharmacotherapy	30,023,044.15	33,521,649.55	37,347,638.66	41,151,725.85	44,790,390.13	**186,834,448.35**
Procedure costs (PLN):						
hospitalisations	2,857,417.19	3,202,307.73	3,508,023.88	3,778,638.71	4,018,032.65	**17,364,420.15**
outpatient services	65,095.54	74,112.41	82,083.32	89,129.61	95,358.53	**405,779.42**
total	2,922,512.73	3,276,420.14	3,590,107.21	3,867,768.32	4,113,391.18	**17,770,199.57**
Total costs (PLN):						
Total costs	**32,945,556.88**	**36,798,069.69**	**40,937,745.87**	**45,019,494.17**	**48,903,781.31**	**204,604,647.92**

4.1.3 Incremental analysis

Change from the "current practice" scenario to the new scenario would result in increase of mean monthly cost of treatment by 9,103.75 PLN. The target population would not change (neither with respect to incidence nor prevalence rates). Annual costs within the time horizon of five years would increase from 22.65 to 33.98 million PLN (the values in subsequent years would be: 22.65, 25.12, 28.05, 31.05 and 33.98 million PLN).

Nearly all this increase would be the result of increased costs of the analysed drugs (99.94%). The percentages of cost increase related to specific drugs would be as follows: bosentan (30,57%), epoprostenol (14,87%), iloprost (12,55%), sildenafil (21,51%), treprostinil (20,5%).

Costs related to outpatient procedures do not change in the considered model.

Comparison of both scenarios with respect to specific cost categories is presented in the figures and the table below.

Figure 16.
Change of costs of the analysed drugs.

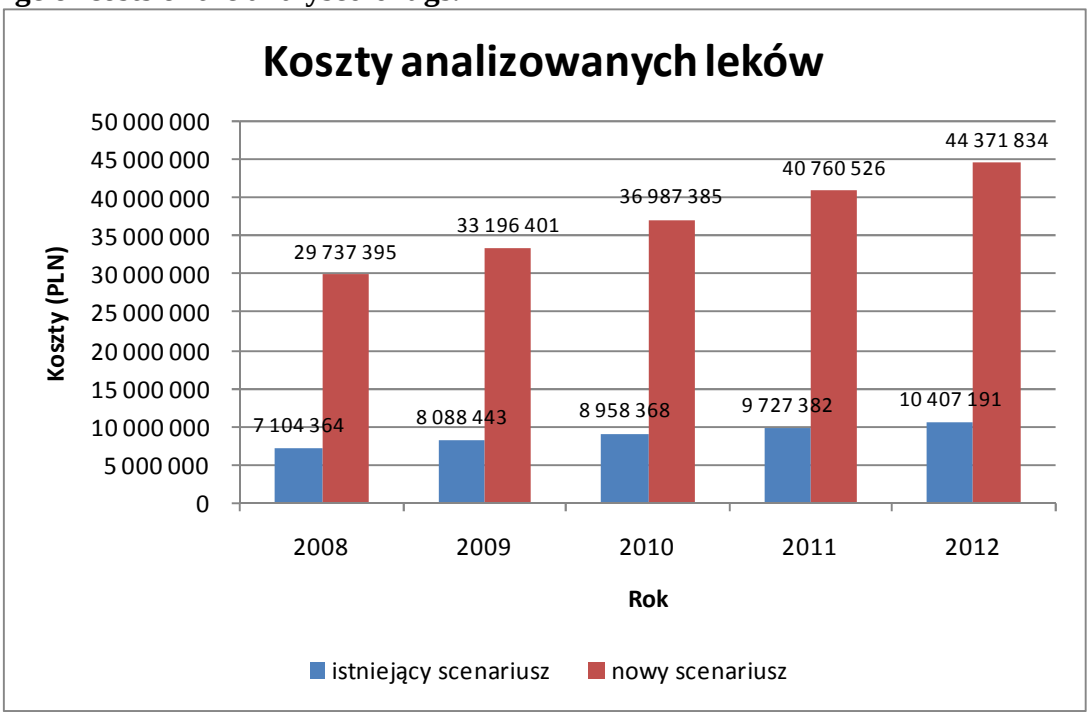


Figure 17.
Change of costs of the remaining drugs.

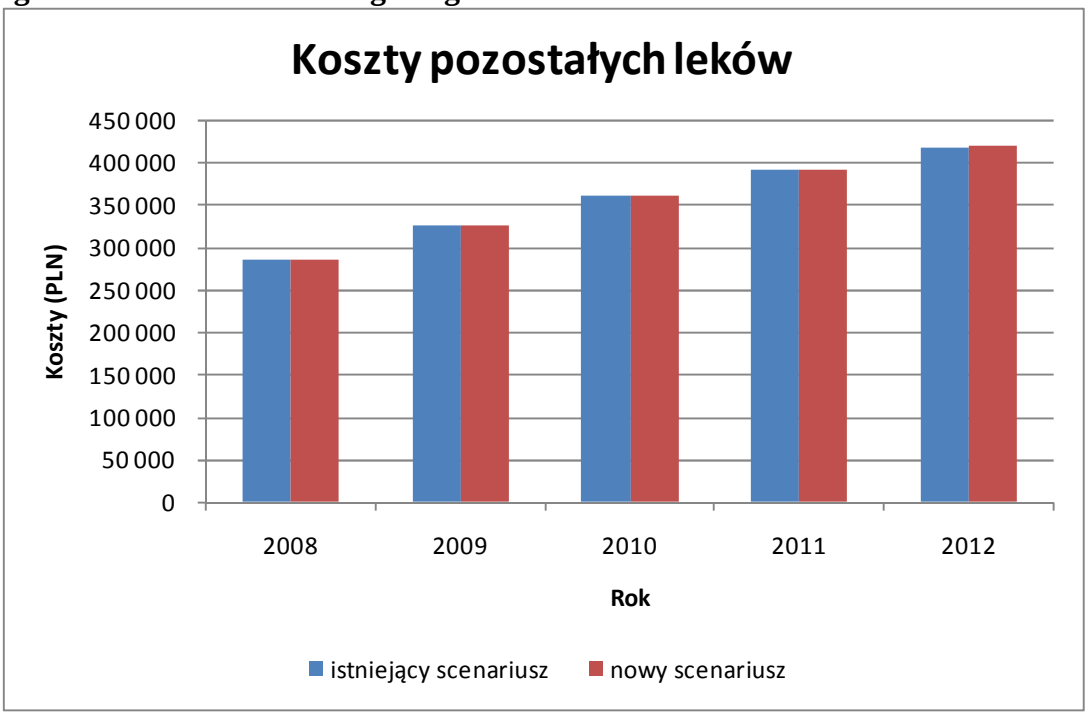


Figure 18.
Change of costs of all drugs.

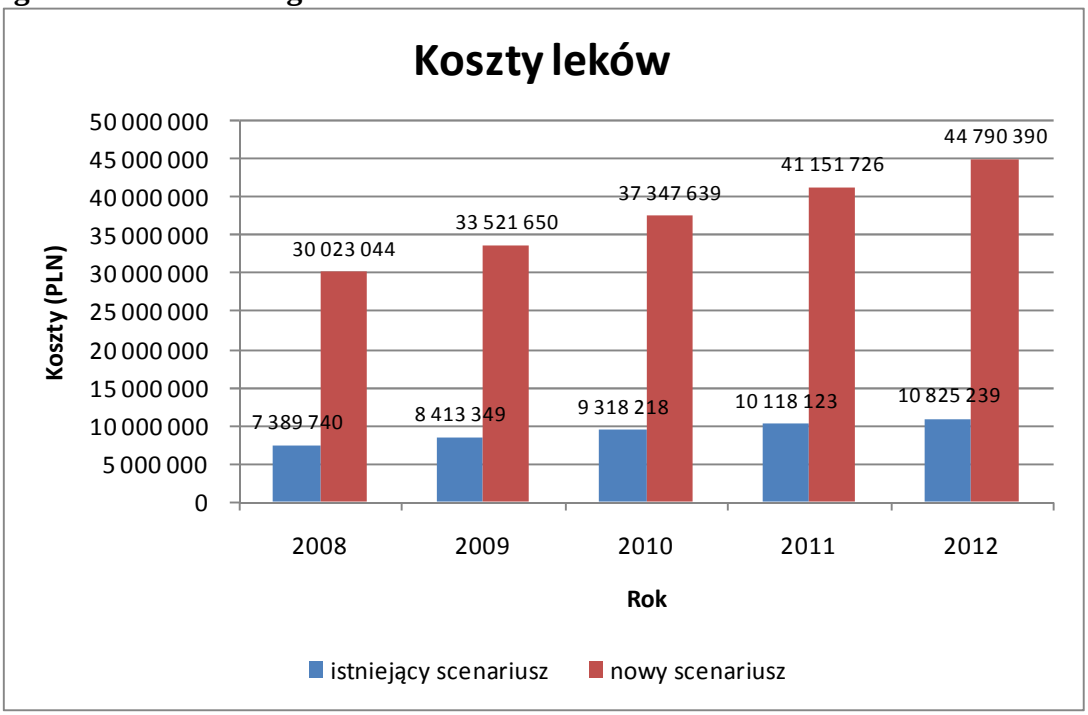


Figure 19.
Change of costs of medical procedures.

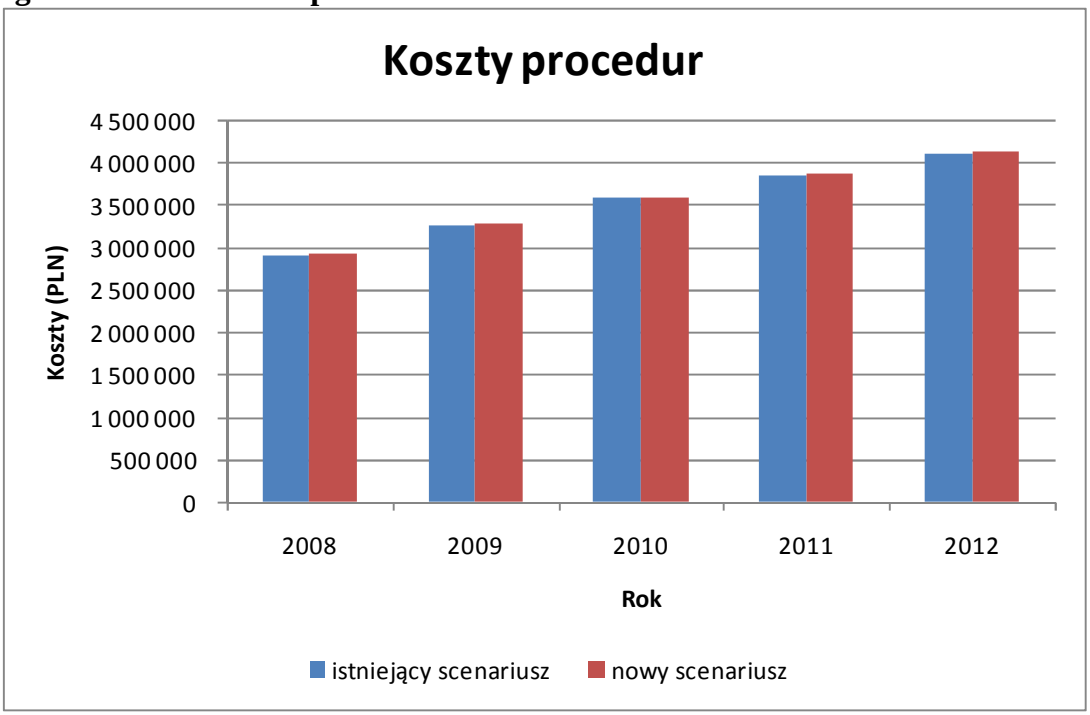


Figure 20.
Change of costs of hospitalisations.

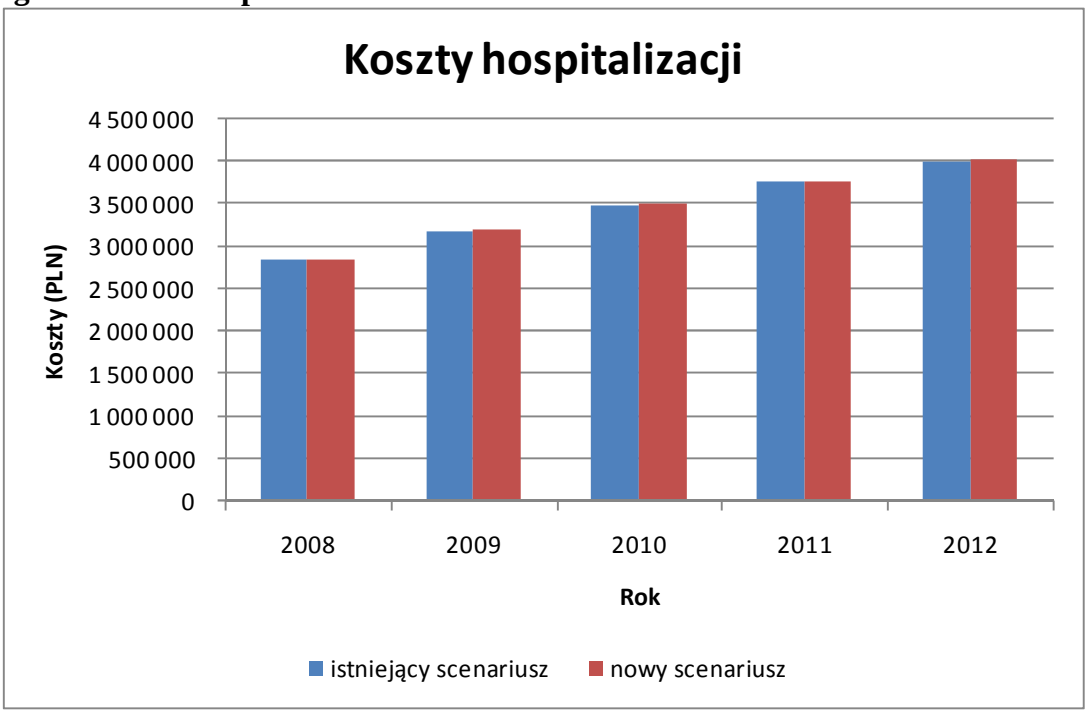


Figure 21.
Change of costs of outpatient services.

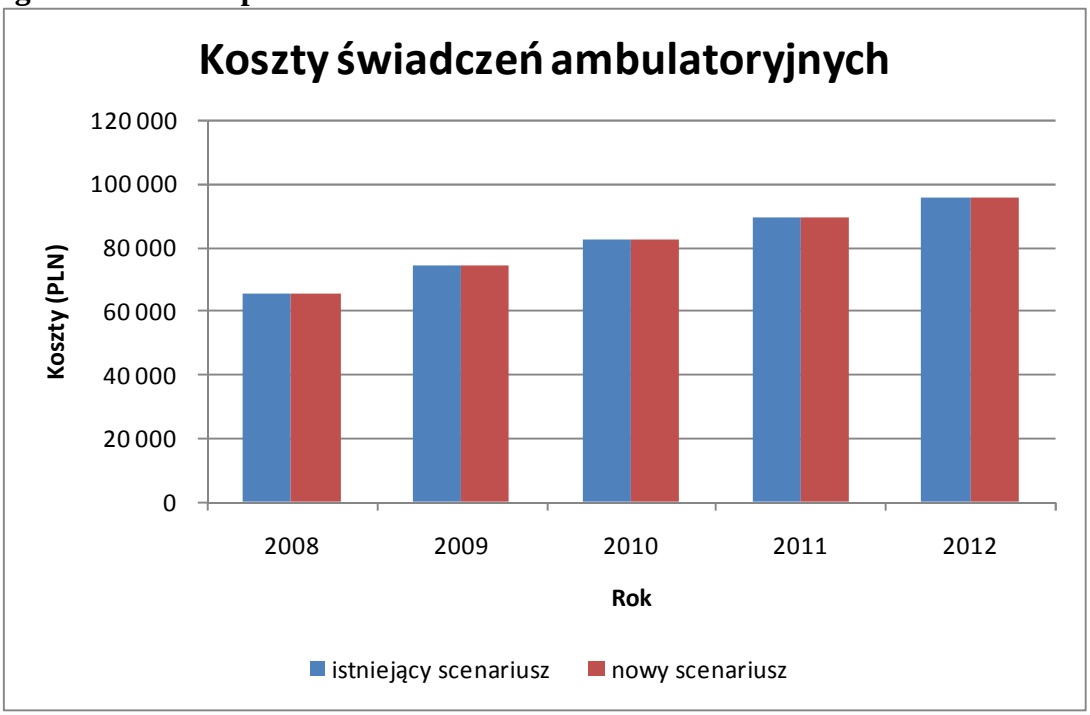


Figure 22.
Change of total costs.

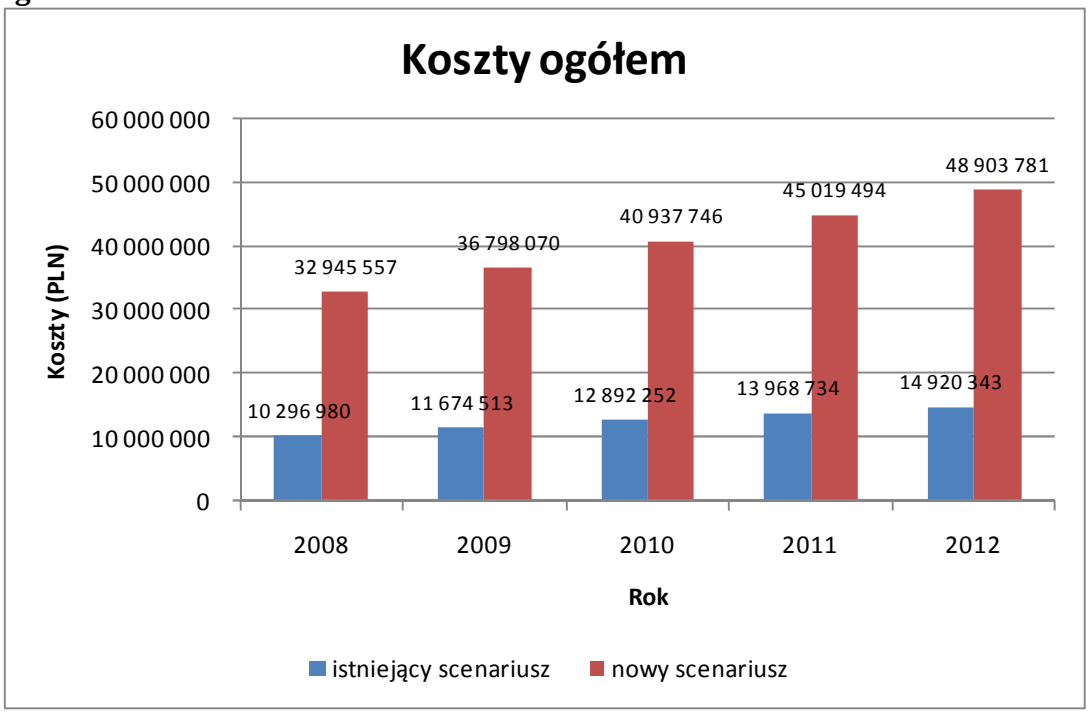


Table 20.
Results of incremental analysis.

	Year					Total
	2008	**2009**	**2010**	**2011**	**2012**	
Number of patients included						
Patient-months of treatment in a specific year	5,421,040.44	4,270,989.71	3,850,992.50	3,712,558.21	3,680,069.64	**20,935,650.50**
Number of patients at the end of the year	3,807,337.26	4,783,934.53	5,756,821.18	6,750,364.58	7,755,751.00	**28,854,208.55**
Drug costs (PLN)	2,444,933.27	3,002,293.26	3,543,596.92	4,075,838.24	4,596,127.86	**17,662,789.55**
epoprostenol	6,594,719.99	7,736,623.52	8,727,472.22	9,600,313.97	10,374,348.76	**43,033,478.46**
treprostinil	4,364,999.72	5,314,117.73	6,150,134.09	6,894,069.17	7,558,345.50	**30,281,666.20**
iloprost	22,633,030.67	25,107,958.75	28,029,016.91	31,033,144.17	33,964,642.77	**140,767,793.27**
bosentan	273.16	342.20	403.42	458.52	508.32	**1,985.61**
sildenafil	22,633,303.83	25,108,300.95	28,029,420.33	31,033,602.68	33,965,151.09	**140,769,778.89**
Total costs of the analysed drugs						
Costs of the remaining drugs	15,272.98	15,255.68	16,073.30	17,157.83	18,286.98	**82,046.77**
Total costs of pharmacotherapy	0.00	0.00	0.00	0.00	0.00	**0.00**
Procedure costs (PLN):	15,272.98	15,255.68	16,073.30	17,157.83	18,286.98	**82,046.77**
hospitalisations						
outpatient consultations	**22,648,576.81**	**25,123,556.63**	**28,045,493.64**	**31,050,760.51**	**33,983,438.07**	**140,851,825.65**

4.2 Analysis of the pessimistic scenario

The pessimistic scenario differs from the realistic one with respect to the method of the target population size estimation. In the pessimistic scenario lower incidence rate – 1.97 (instead of 2.4) – and lower percentage of patients in NYHA class III/IV – 55.59% (instead of 61.04%) – were assumed. The difference between the realistic and pessimistic scenario lies therefore in proportional rescaling of the number of patients. This will not result in proportional rescaling of costs due to the fact that the model includes costs of initial diagnostics, which apply to the newly diagnosed patients only and not the patients previously diagnosed and treated at the beginning of the analysed period.

4.2.1 Current practice analysis

Mean cost of one patient-month of treatment in the "current practice" scenario is ca. 4,102.82 PLN. Annual costs within the time horizon of five years increase from 9.86 to 12.47 million PLN (the values in subsequent years are: 9.86, 10.63, 11.32, 11.93 and 12.47 million PLN).

The cost structure is similar to that in the realistic scenario. Drug costs represent the dominant component (72.57% of total costs); among them, treprostinil and iloprost generate the highest costs (71.46% and 24.04% of total drug costs, respectively). Costs of medical procedures are mostly related to hospitalisations (97.67%).

Figure 23.
The number of patients newly diagnosed and treated in subsequent years.

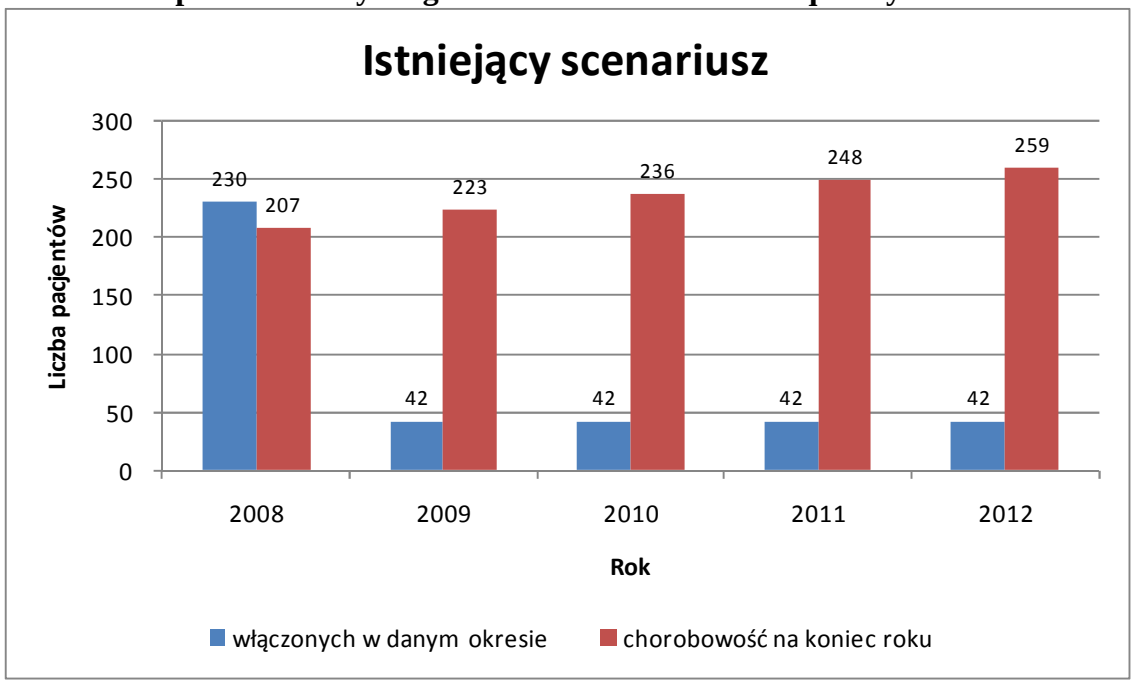


Figure 24.
Cost structure.

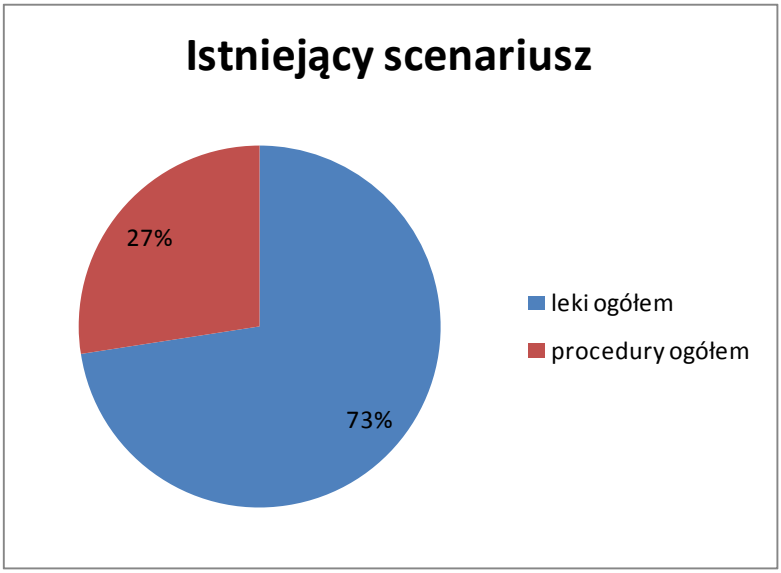


Figure 25.
Cost structure of the analysed drugs.

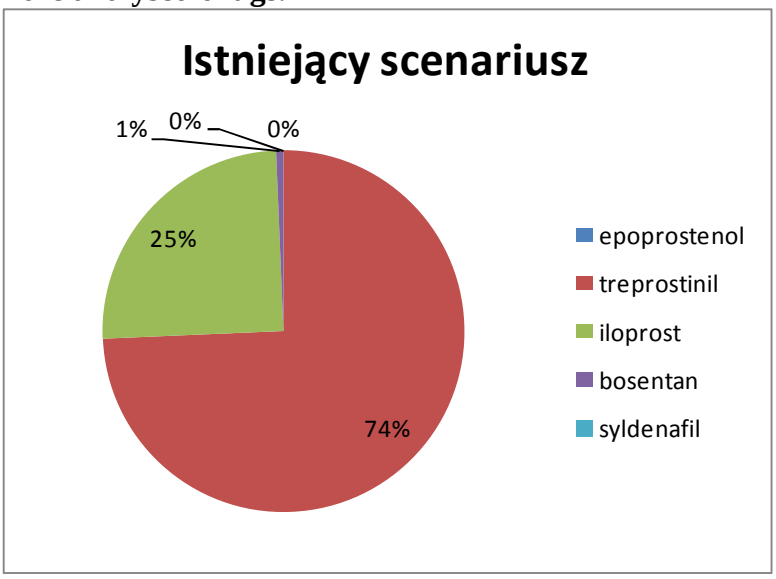


Figure 26.
Change of costs of the analysed drugs.

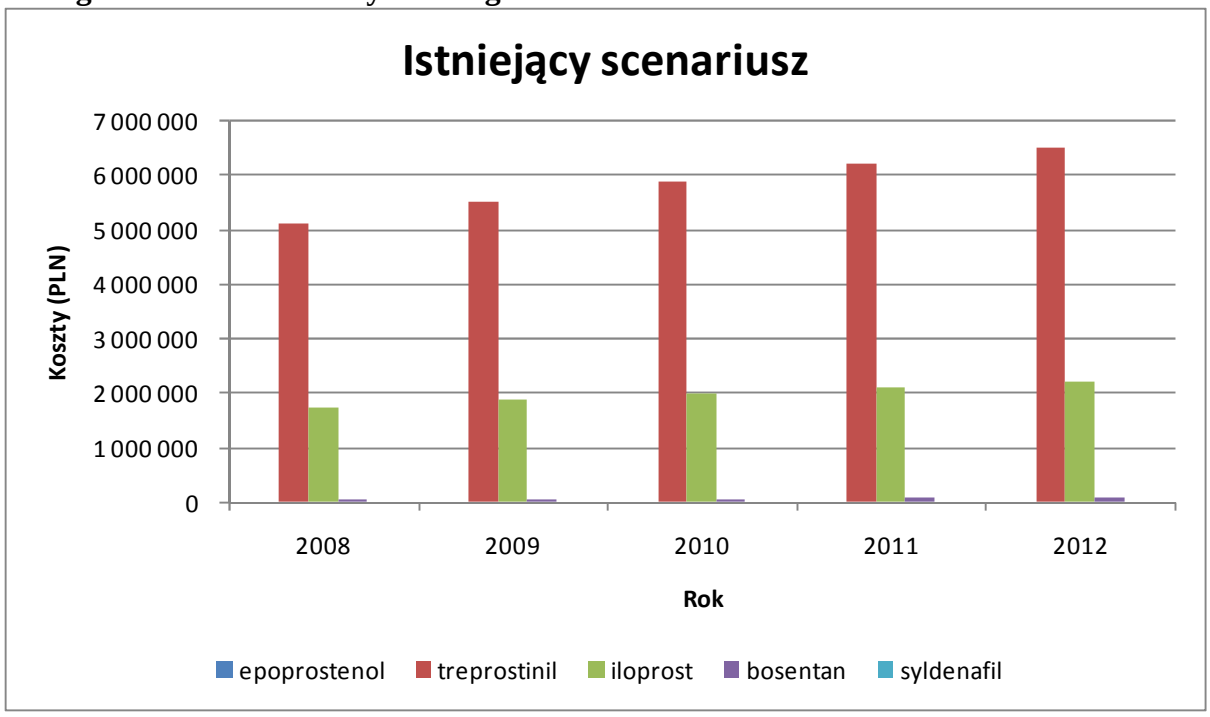


Figure 27.
Change of costs of all drugs.

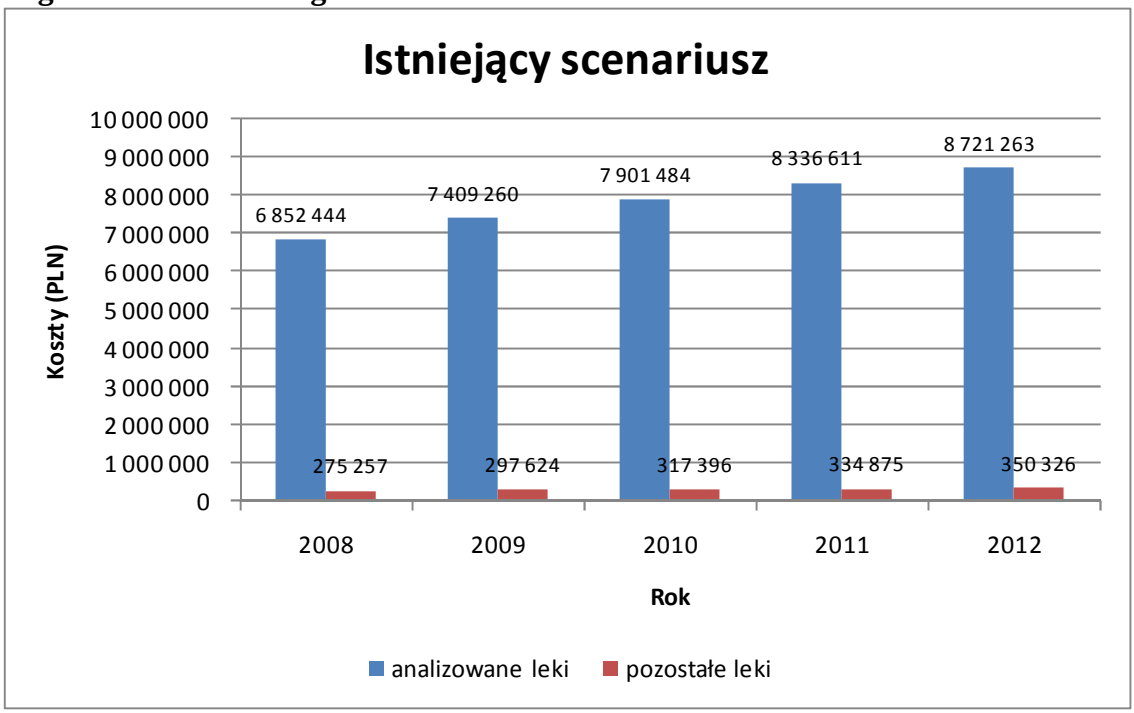


Figure 28.
Change of costs of drugs and procedures.

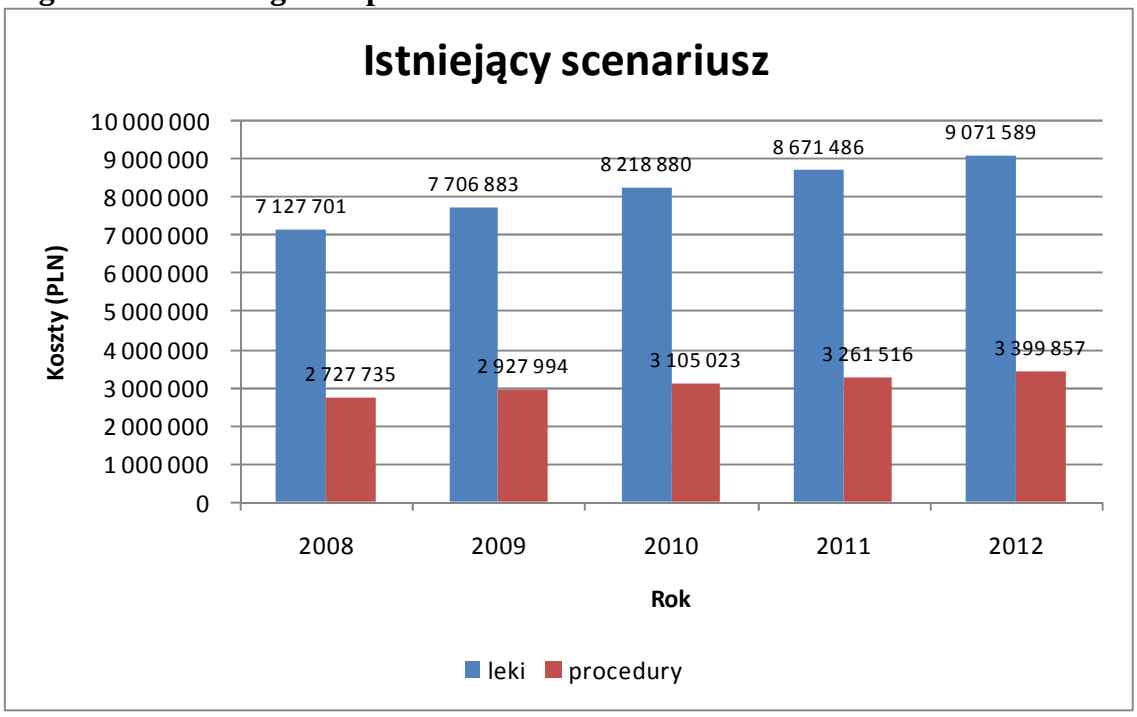


Figure 29.
Change of costs of the procedures used.

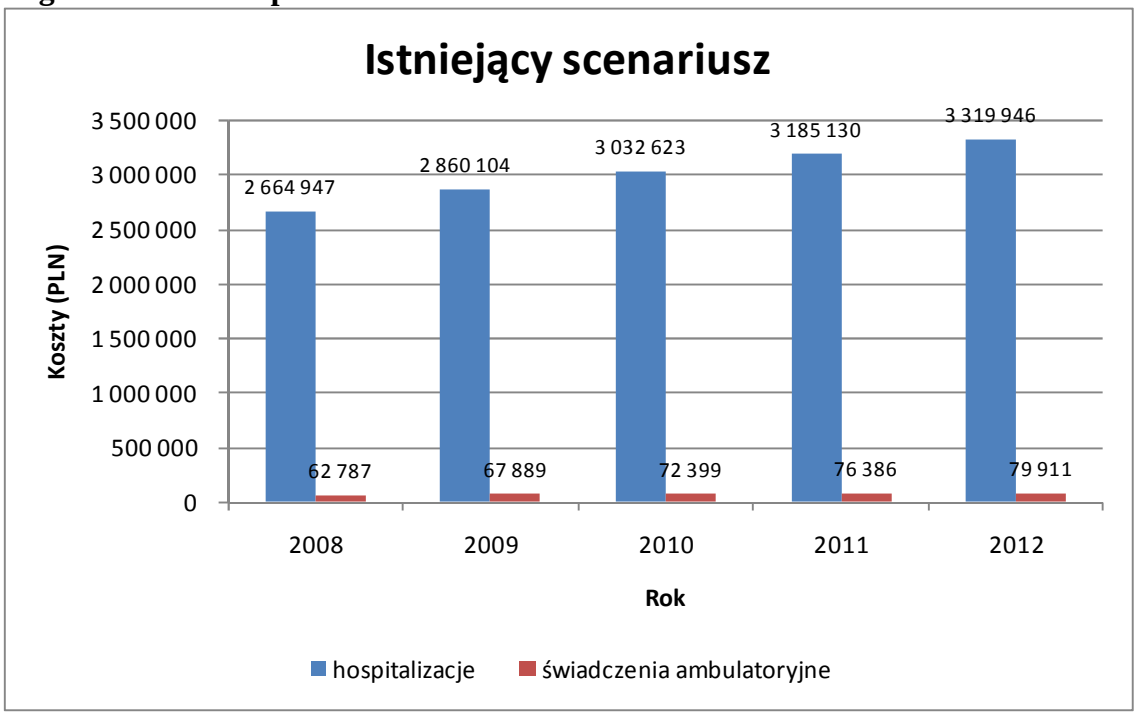


Table 21.
Costs in the "current practice" scenario.

	Year					Total
	2008	**2009**	**2010**	**2011**	**2012**	
Number of patients included	230	42	42	42	42	**396**
Patient-months of treatment in a specific year	2,394	2,589	2,760	2,913	3,047	**13,702**
Number of patients at the end of the year	207	223	236	248	259	**n.a.**
Drug costs (PLN):						
epoprostenol	0.00	0.00	0.00	0.00	0.00	**0.00**
treprostinil	5,093,723.07	5,507,628.44	5,873,520.79	6,196,969.63	6,482,898.40	**29,154,740.33**
iloprost	1,713,457.72	1,852,689.75	1,975,770.85	2,084,574.55	2,180,757.02	**9,807,249.89**
bosentan	45,263.32	48,941.33	52,192.68	55,066.88	57,607.67	**259,071.87**
sildenafil	0.00	0.00	0.00	0.00	0.00	**0.00**
Total costs of the analysed drugs	6,852,444.11	7,409,259.51	7,901,484.32	8,336,611.06	8,721,263.09	**39,221,062.10**
Costs of the remaining drugs	275,257.00	297,623.82	317,396.08	334,874.76	350,325.91	**1,575,477.58**
Total costs of pharmacotherapy	7,127,701.12	7,706,883.33	8,218,880.40	8,671,485.82	9,071,589.01	**40,796,539.67**
Procedure costs (PLN):						
hospitalisations	2,664,947.34	2,860,104.50	3,032,623.43	3,185,130.16	3,319,946.11	**15,062,751.53**
outpatient services	62,787.26	67,889.22	72,399.36	76,386.32	79,910.79	**359,372.95**
total	2,727,734.60	2,927,993.72	3,105,022.78	3,261,516.48	3,399,856.90	**15,422,124.48**
Total costs (PLN):						
Total costs	**9,855,435.71**	**10,634,877.05**	**11,323,903.19**	**11,933,002.30**	**12,471,445.91**	**56,218,664.16**

4.2.2 Costs in the new scenario.

Mean cost of one patient-month of treatment in the new scenario is ca. 13,248.07 PLN. Annual costs within the time horizon of five years increase from 31.73 to 41.19 million PLN (the values in subsequent years are: 31.73, 33.71, 36.18, 38.73 and 41.19 million PLN).

Drug costs represent the dominant component (91.47% of total costs); the percentages of costs related to specific drugs are as follows: bosentan (22.51%), epoprostenol (10.62%), iloprost (15.76%), sildenafil (16.15%), treprostinil (34.01%). Costs of medical procedures are mostly related to hospitalisations (97.68%).

Figure 30.
Cost structure.

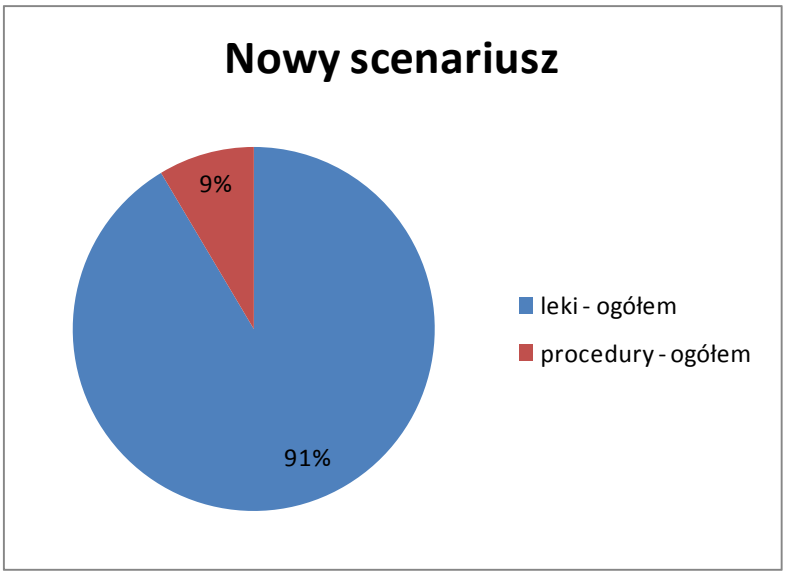


Figure 31.
Cost structure of the analysed drugs.

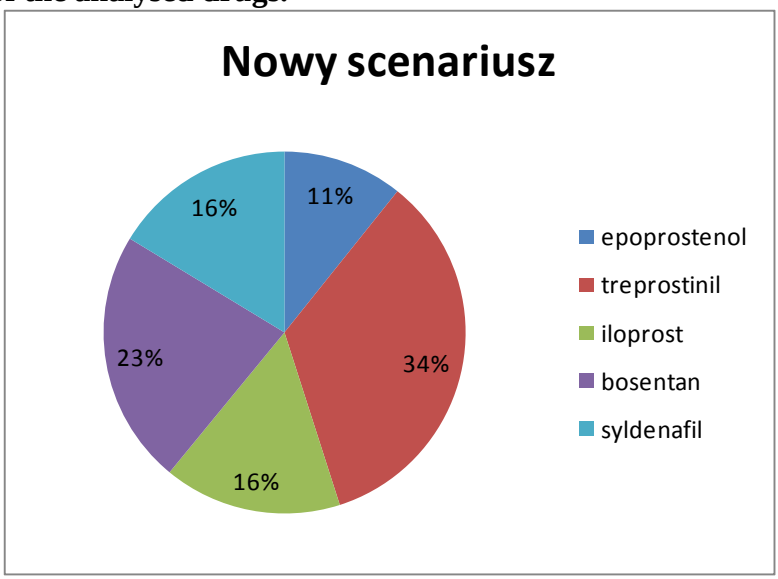


Figure 32.
Change of costs of the analysed drugs.

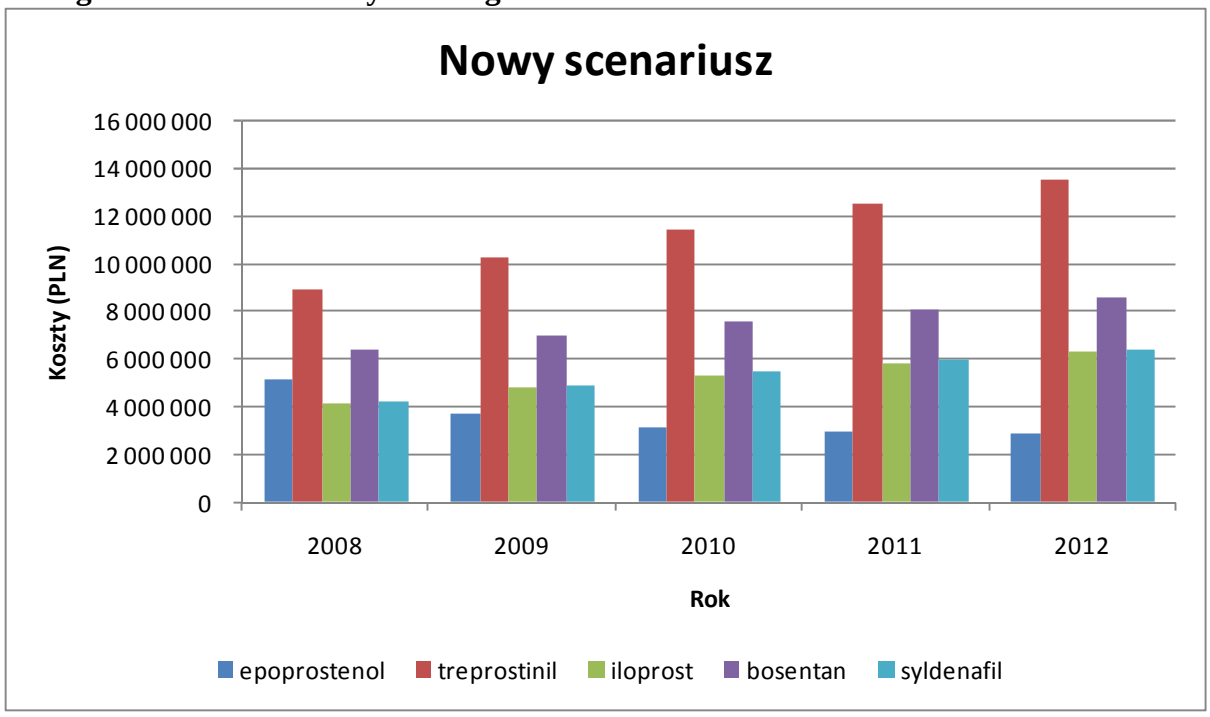


Figure 33.
Change of costs of all drugs.

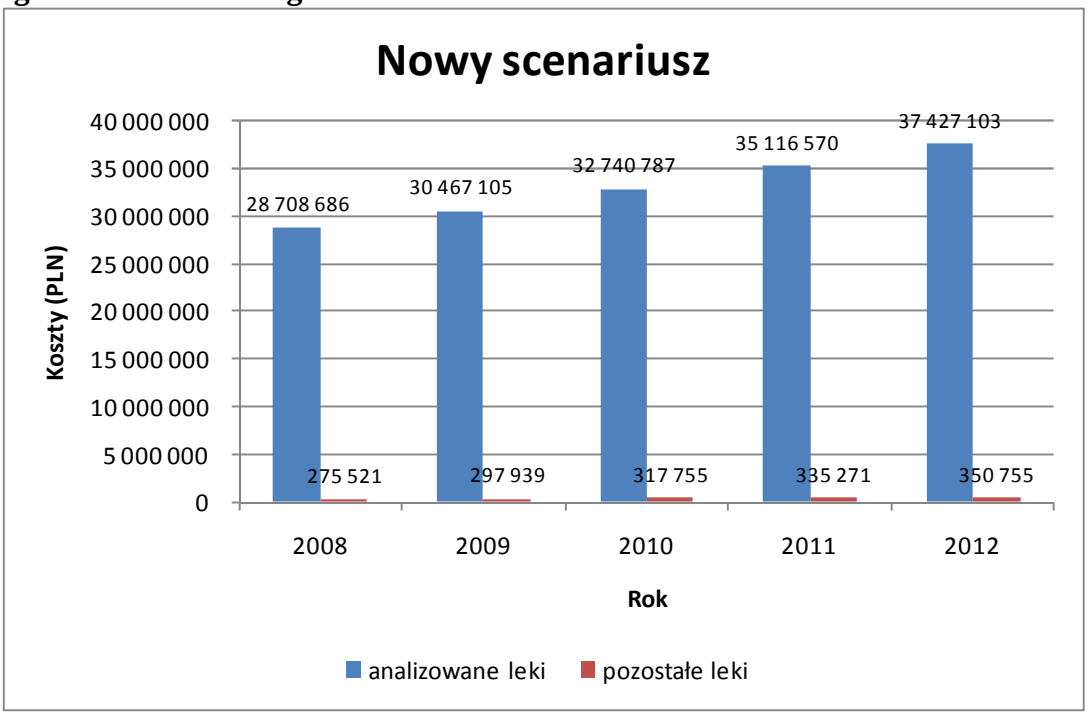


Figure 34.
Change of costs of drugs and procedures.

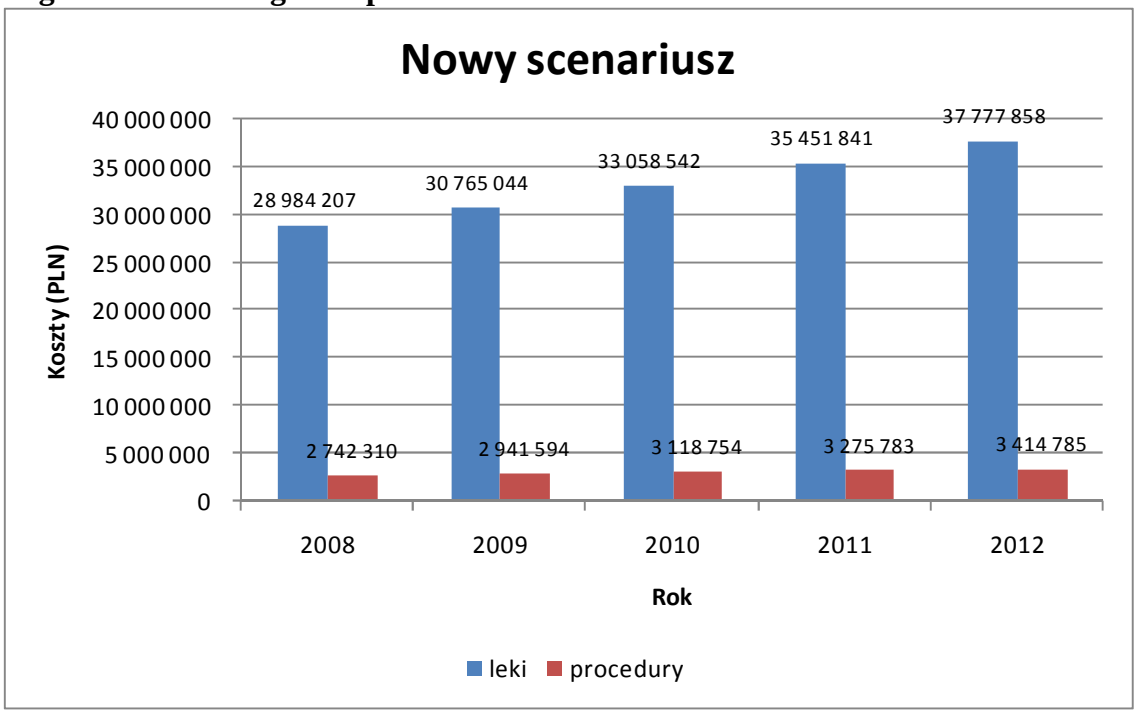


Figure 35.
Change of costs of the procedures used.

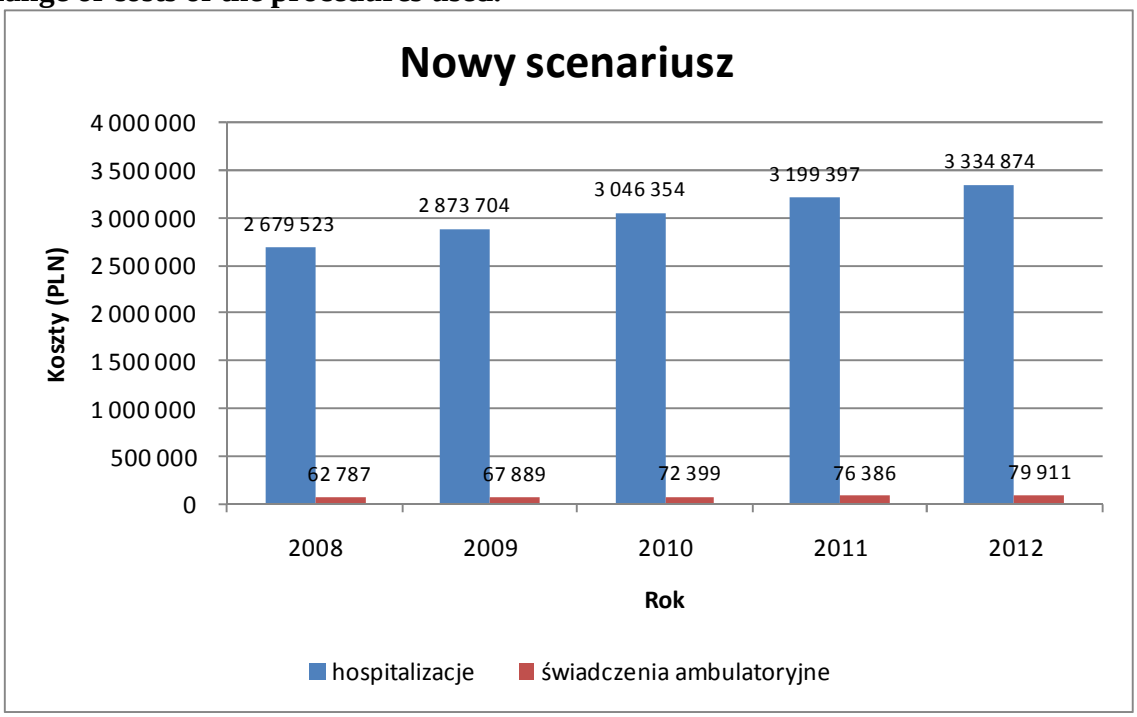


Table 22.
Costs in the new scenario.

	Year					Total
	2008	**2009**	**2010**	**2011**	**2012**	
Number of patients included	230	42	42	42	42	**396**
Patient-months of treatment in a specific year	2,394	2,589	2,760	2,913	3,047	**13,702**
Number of patients at the end of the year	207	223	236	248	259	**n.a.**
Drug costs (PLN):						
epoprostenol	5,133,299.37	3,672,872.69	3,109,947.30	2,899,154.60	2,825,584.35	**17,640,858.31**
treprostinil	8,907,572.73	10,216,861.02	11,381,919.11	12,467,735.14	13,492,592.34	**56,466,680.34**
iloprost	4,129,929.13	4,738,247.79	5,280,155.80	5,779,335.91	6,243,950.56	**26,171,619.21**
bosentan	6,326,621.22	6,962,052.90	7,528,978.26	8,043,316.32	8,510,966.17	**37,371,934.86**
sildenafil	4,211,263.48	4,877,070.67	5,439,786.47	5,927,028.36	6,354,009.30	**26,809,158.28**
Total costs of the analysed drugs	28,708,685.92	30,467,105.07	32,740,786.94	35,116,570.33	37,427,102.73	**164,460,250.99**
Costs of the remaining drugs	275,521.07	297,939.24	317,754.76	335,271.07	350,755.47	**1,577,241.61**
Total costs of pharmacotherapy	28,984,206.99	30,765,044.31	33,058,541.70	35,451,841.40	37,777,858.19	**166,037,492.60**
Procedure costs (PLN):						
hospitalisations	2,679,522.87	2,873,704.40	3,046,354.30	3,199,396.76	3,334,873.74	**15,133,852.06**
outpatient services	62,787.26	67,889.22	72,399.36	76,386.32	79,910.79	**359,372.95**
total	2,742,310.13	2,941,593.62	3,118,753.65	3,275,783.08	3,414,784.53	**15,493,225.01**
Total costs (PLN):						
Total costs	**31,726,517.12**	**33,706,637.93**	**36,177,295.35**	**38,727,624.48**	**41,192,642.72**	**181,530,717.61**

4.2.3 Incremental analysis

Change from the "current practice" scenario to the new scenario would result in increase of mean monthly cost of treatment by 9,145.24 PLN. The target population would not change (neither with respect to incidence nor prevalence rates). Increase (in absolute numbers) of annual costs within the time horizon of five years would be (in subsequent years): 21.87, 23.07, 24.85, 26.79 and 28.72 million PLN.

Nearly all this increase would be the result of increased costs of the analysed drugs (99.94%). The percentages of cost increase related to specific drugs would be as follows: bosentan (29.63%), epoprostenol (14.09%), iloprost (13.07%), sildenafil (21.41%), treprostinil (21.81%).

Costs related to outpatient procedures do not change in the considered model.

Comparison of both scenarios with respect to specific cost categories is presented in the figures and the table below.

Figure 36.
Change of costs of the analysed drugs.

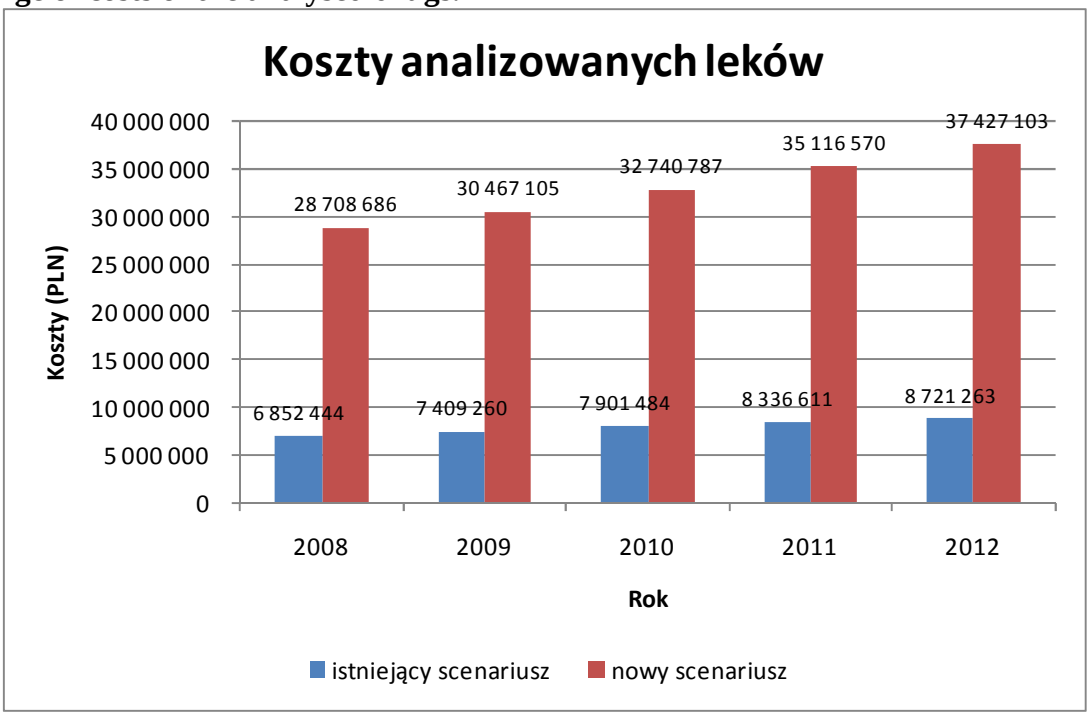


Figure 37.
Change of costs of the remaining drugs.

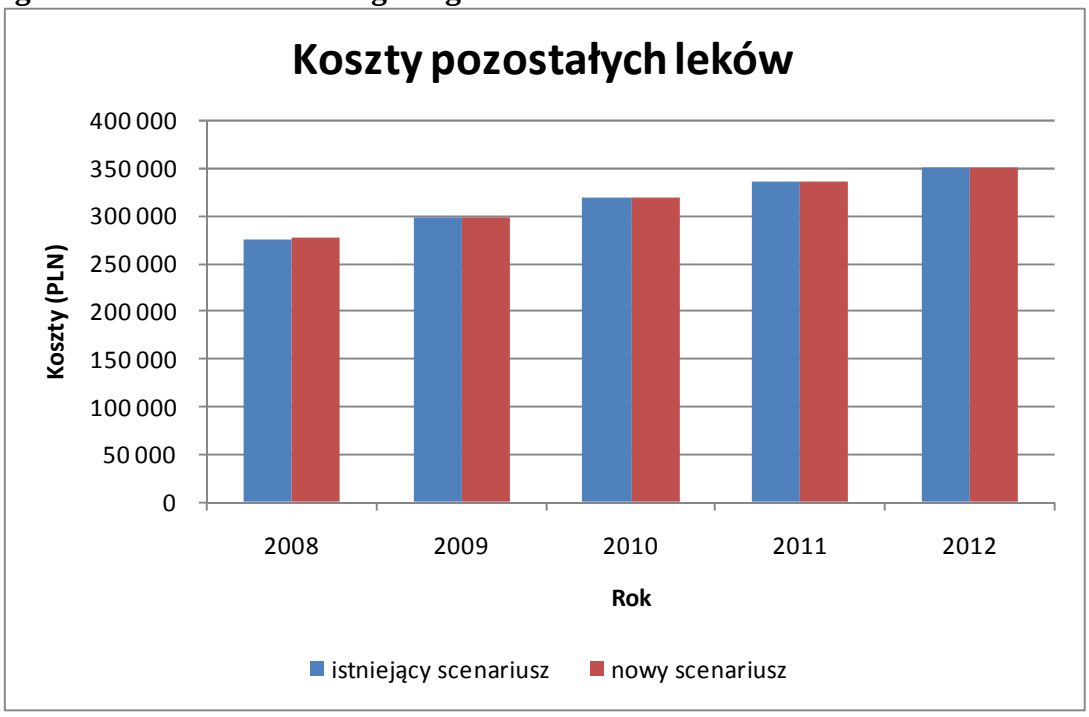


Figure 38.
Change of costs of all drugs.

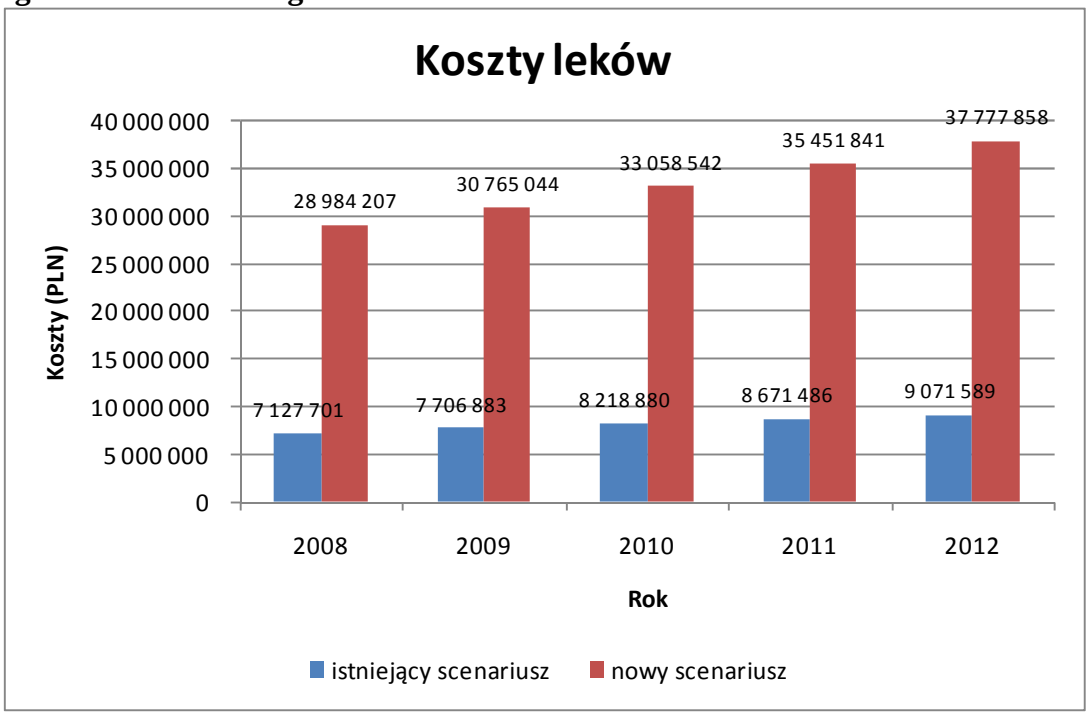


Figure 39.
Change of costs of medical procedures.

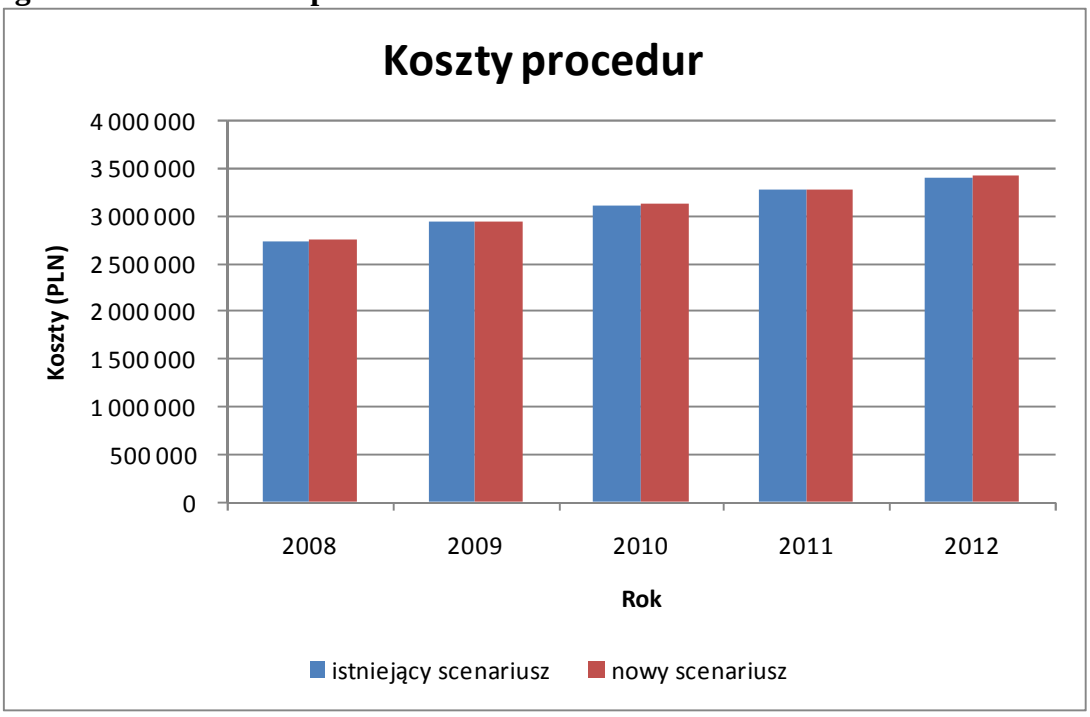


Figure 40.
Change of costs of hospitalisations.

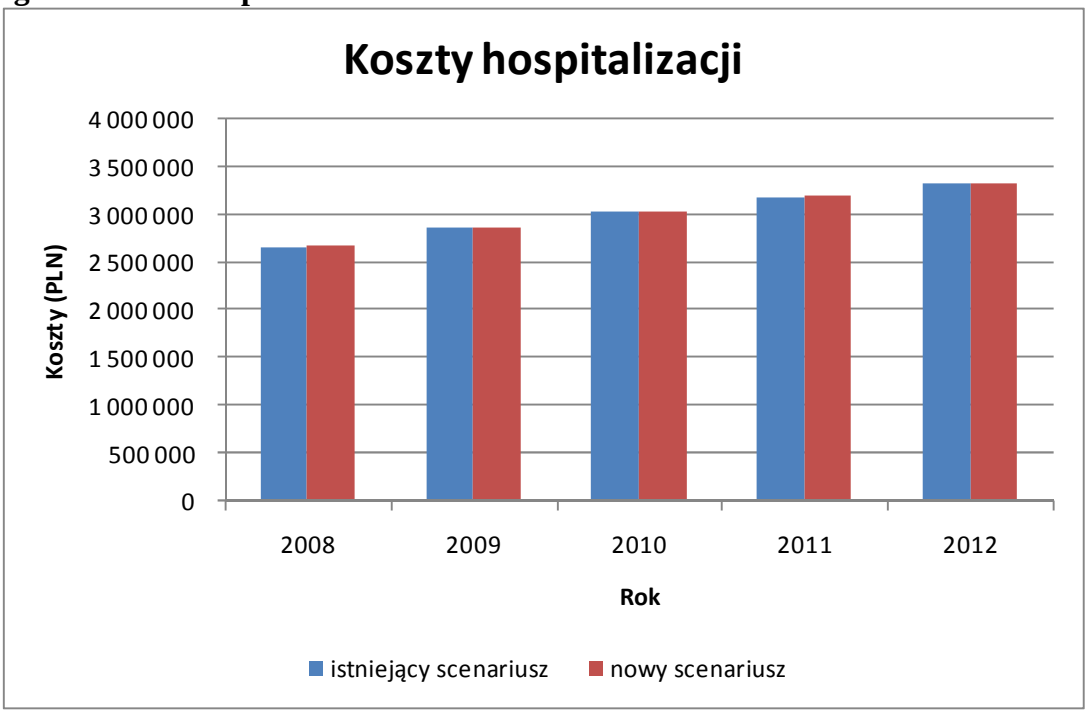


Figure 41.
Change of costs of outpatient services.

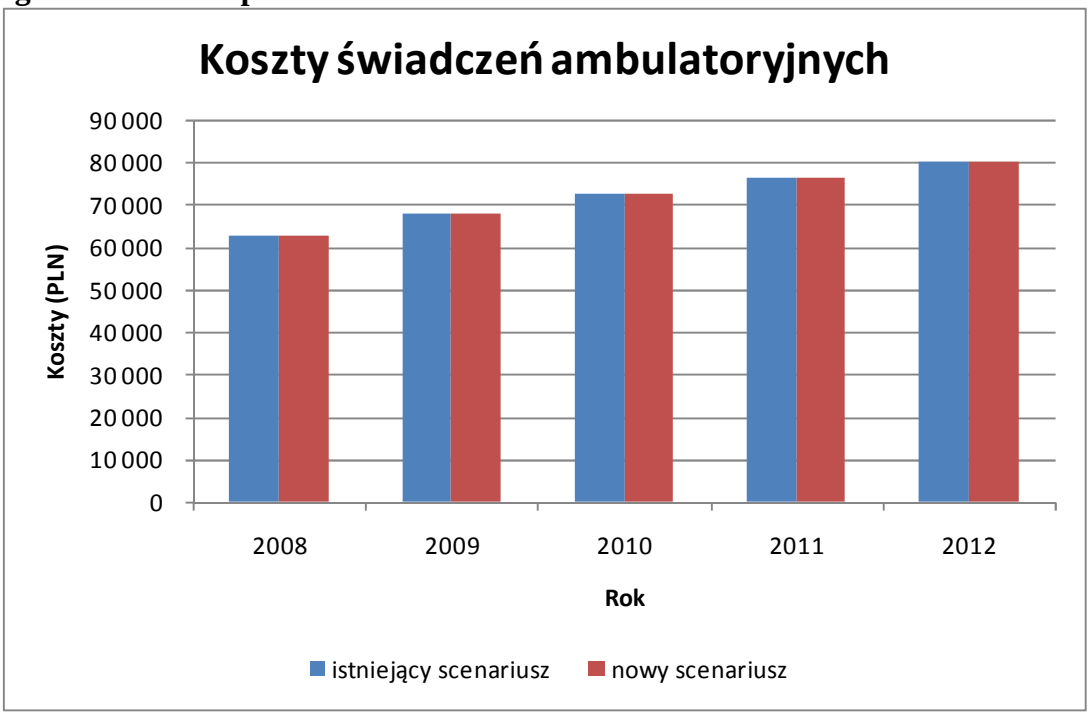


Figure 42.
Change of total costs.

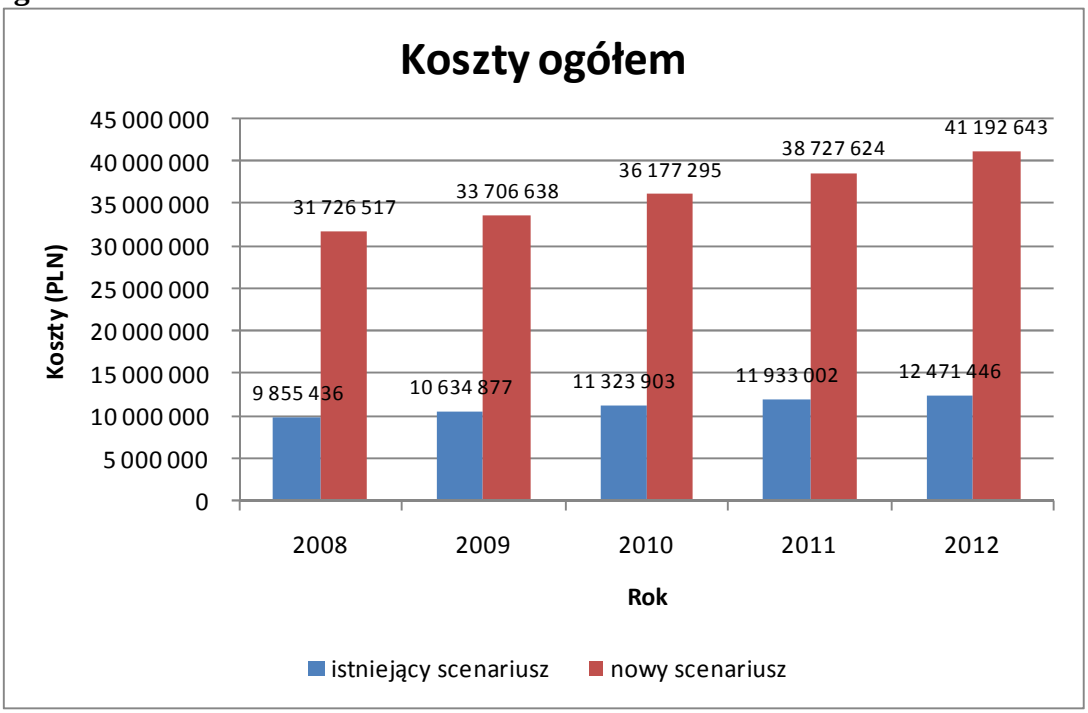


Table 23.
Results of incremental analysis.

	Year					Total
	2008	**2009**	**2010**	**2011**	**2012**	
Drug costs (PLN):						
epoprostenol	5,133,299.37	3,672,872.69	3,109,947.30	2,899,154.60	2,825,584.35	**17,640,858.31**
treprostinil	3,813,849.66	4,709,232.57	5,508,398.32	6,270,765.51	7,009,693.94	**27,311,940.01**
iloprost	2,416,471.41	2,885,558.05	3,304,384.95	3,694,761.36	4,063,193.54	**16,364,369.31**
bosentan	6,281,357.89	6,913,111.57	7,476,785.58	7,988,249.44	8,453,358.50	**37,112,862.98**
sildenafil	4,211,263.48	4,877,070.67	5,439,786.47	5,927,028.36	6,354,009.30	**26,809,158.28**
Total costs of the analysed drugs	21,856,241.81	23,057,845.56	24,839,302.62	26,779,959.27	28,705,839.64	**125,239,188.89**
Costs of the remaining drugs	264.07	315.42	358.68	396.31	429.55	**1,764.03**
Total costs of pharmacotherapy	21,856,505.87	23,058,160.98	24,839,661.30	26,780,355.58	28,706,269.19	**125,240,952.92**
Procedure costs (PLN):						
hospitalisations	14,575.53	13,599.90	13,730.87	14,266.60	14,927.62	**71,100.53**
outpatient consultations	0.00	0.00	0.00	0.00	0.00	**0.00**
total	14,575.53	13,599.90	13,730.87	14,266.60	14,927.62	**71,100.53**
Total costs (PLN):						
Total costs	**21,871,081.41**	**23,071,760.88**	**24,853,392.16**	**26,794,622.18**	**28,721,196.81**	**125,312,053.45**

4.3 Analysis of the optimistic scenario

The optimistic scenario differs from the realistic one with respect to the method of the target population size estimation. In the optimistic scenario higher incidence rate – 2.83 (instead of 2.4) – and higher percentage of patients in NYHA class III/IV – 66.49% (instead of 61.04%) – were assumed. The difference between the realistic and optimistic scenario lies therefore in proportional rescaling of the number of patients. This will not result in proportional rescaling of costs due to the fact that the model includes costs of initial diagnostics, which apply to the newly diagnosed patients only and not the patients previously diagnosed and treated at the beginning of the analysed period.

4.3.1 Current practice analysis

Mean cost of one patient-month of treatment in the "current practice" scenario is ca. 4,136.25 PLN and is equal to mean cost in the realistic scenario. Annual costs within the time horizon of five years increase from 10.79 to 17.68 million PLN (the values in subsequent years are: 10.79, 12.85, 14.66, 16.26 and 17.68 million PLN).

The cost structure is similar to that in the realistic scenario. Drug costs represent the dominant component (71.98% of total costs); among them, treprostinil and iloprost generate the highest costs (71.46% and 24.04% of total drug costs, respectively). Costs of medical procedures are mostly related to hospitalisations (97.74%).

Figure 43.
The number of patients newly diagnosed and treated in subsequent years.

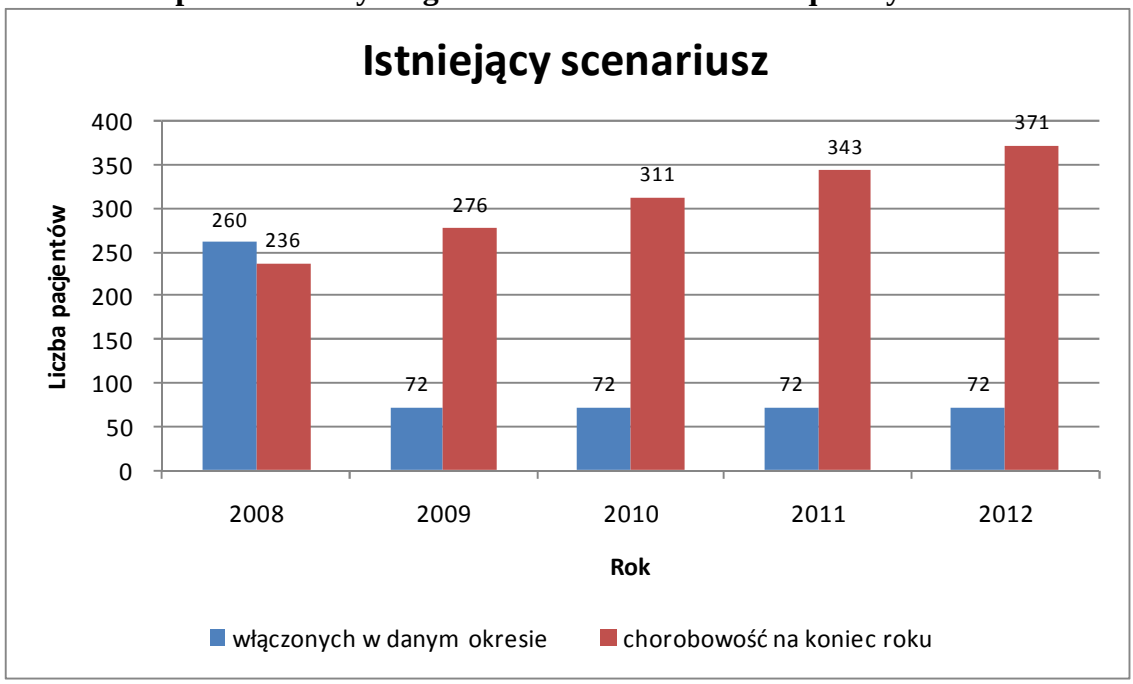


Figure 44.
Cost structure.

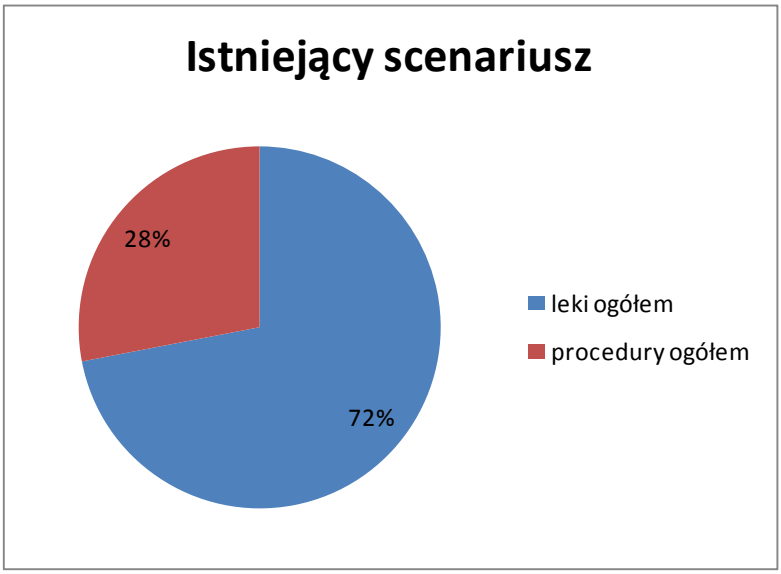


Figure 45.
Cost structure of the analysed drugs.

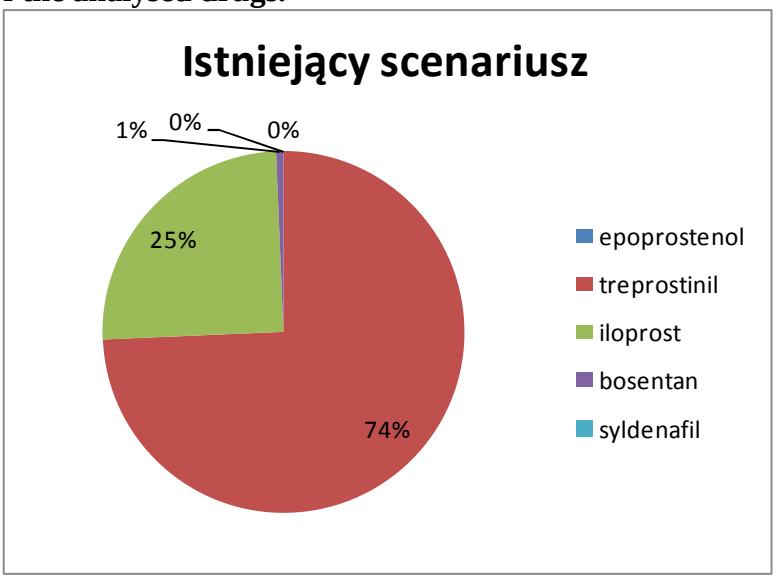


Figure 46.
Change of costs of the analysed drugs.

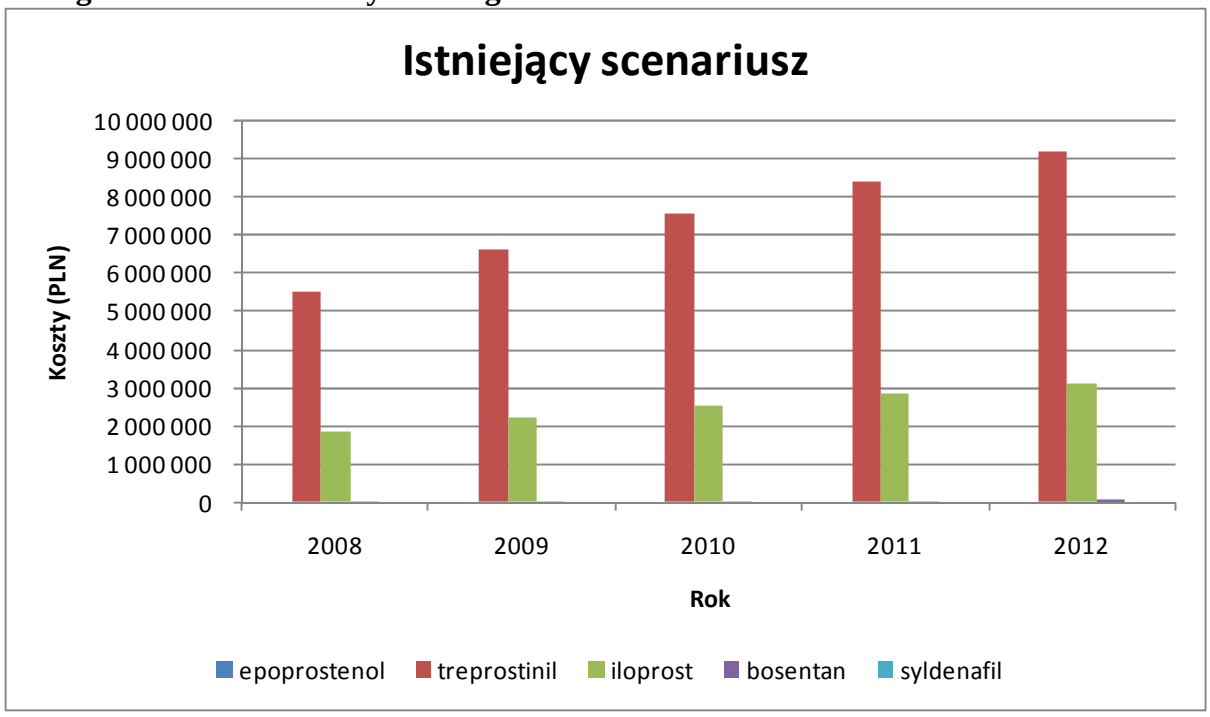


Figure 47.
Change of costs of all drugs.

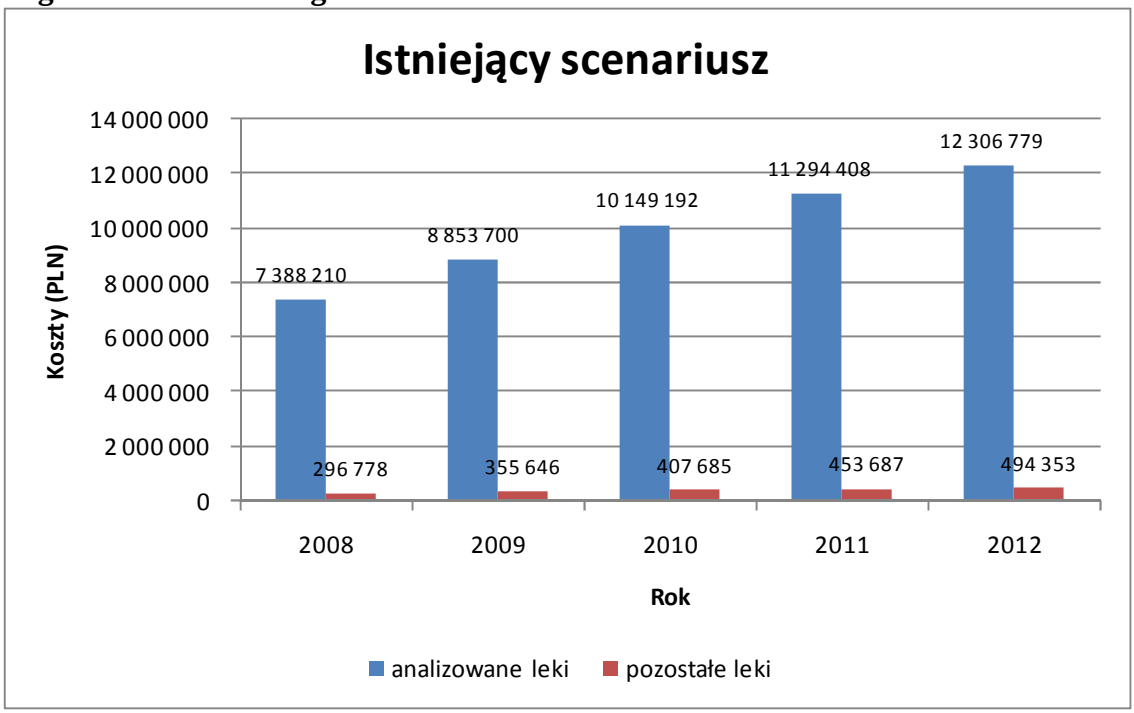


Figure 48.
Change of costs of drugs and procedures.

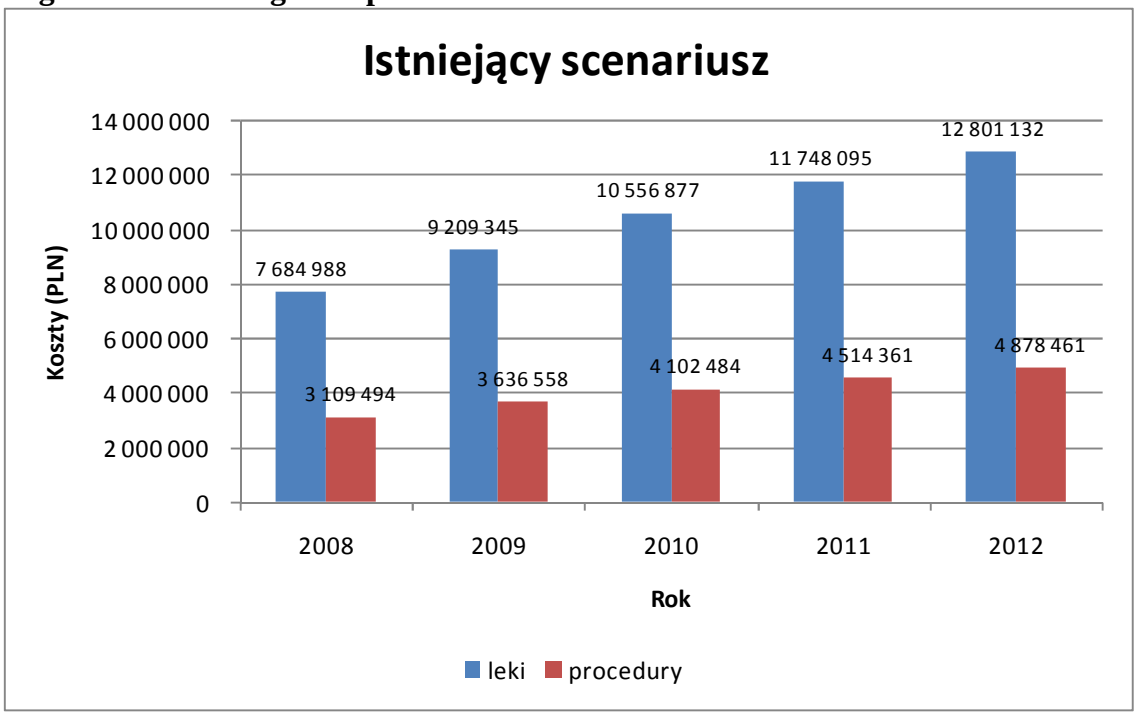


Figure 49.
Change of costs of the procedures used.

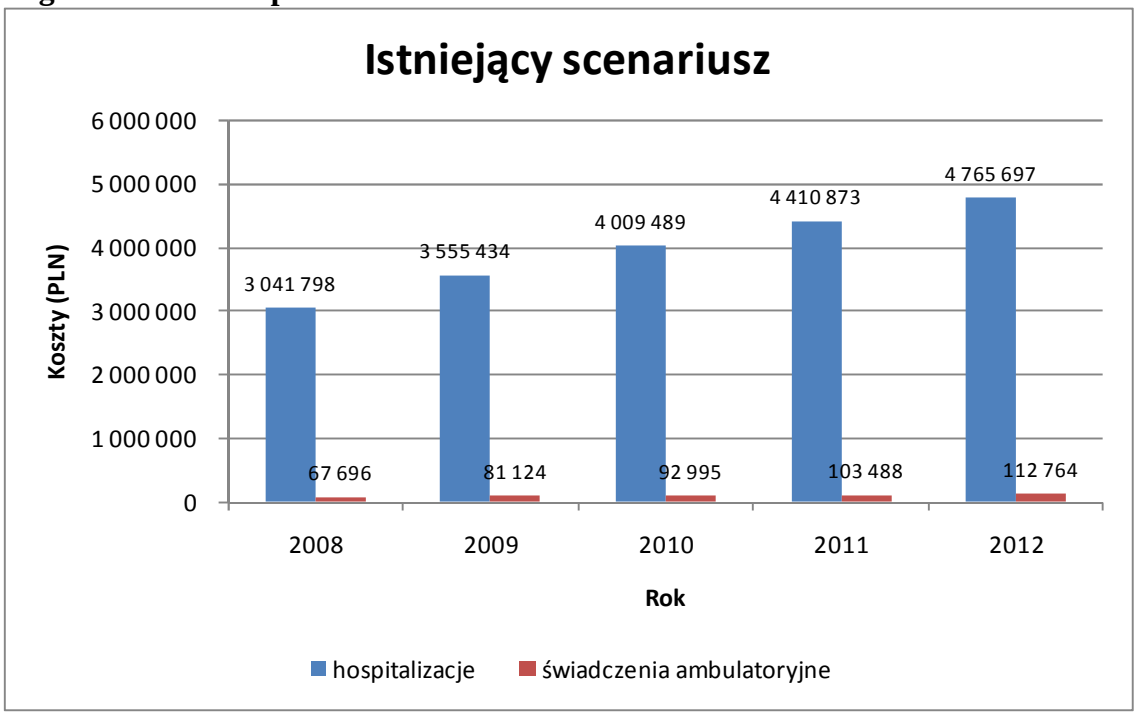


Table 24.
Costs in the "current practice" scenario.

	Year					Total
	2008	**2009**	**2010**	**2011**	**2012**	
Number of patients included	260	72	72	72	72	**546**
Patient-months of treatment in a specific year	2,581	3,093	3,546	3,946	4,300	**17,466**
Number of patients at the end of the year	236	276	311	343	371	**n.a.**
Drug costs (PLN):						
epoprostenol	0.00	0.00	0.00	0.00	0.00	**0.00**
treprostinil	5,491,981.32	6,581,344.22	7,544,341.02	8,395,630.19	9,148,169.82	**37,161,466.58**
iloprost	1,847,426.27	2,213,872.83	2,537,811.58	2,824,173.44	3,077,317.32	**12,500,601.44**
bosentan	48,802.28	58,482.47	67,039.75	74,604.39	81,291.53	**330,220.43**
sildenafil	0.00	0.00	0.00	0.00	0.00	**0.00**
Total costs of the analysed drugs	7,388,209.87	8,853,699.51	10,149,192.35	11,294,408.03	12,306,778.68	**49,992,288.45**
Costs of the remaining drugs	296,778.27	355,645.78	407,684.65	453,687.02	494,353.11	**2,008,148.82**
Total costs of pharmacotherapy	7,684,988.14	9,209,345.29	10,556,877.00	11,748,095.04	12,801,131.79	**52,000,437.27**
Procedure costs (PLN):						
hospitalisations	3,041,797.51	3,555,434.16	4,009,488.96	4,410,873.40	4,765,697.25	**19,783,291.27**
outpatient consultations	67,696.35	81,124.27	92,994.55	103,487.88	112,763.99	**458,067.05**
Total	3,109,493.86	3,636,558.43	4,102,483.51	4,514,361.28	4,878,461.23	**20,241,358.32**
Total costs (PLN):						
Total costs	**10,794,482.00**	**12,845,903.72**	**14,659,360.52**	**16,262,456.33**	**17,679,593.02**	**72,241,795.58**

4.3.2 Costs in the new scenario.

Mean cost of one patient-month of treatment in the "current practice" scenario is ca. 13,203.32 PLN and is equal to mean cost in the realistic scenario. Annual costs within the time horizon of five years would increase from 34.32 to 57.59 million PLN (the values in subsequent years would be: 34.32, 40.28, 46.3, 52.11 and 57.59 million PLN.

Drug costs represent the dominant component (91.18% of total costs); the percentages of costs related to specific drugs are as follows: bosentan (23.8%), epoprostenol (11.72%), iloprost (15.04%), sildenafil (16.26%), treprostinil (32.22%). Costs of medical procedures are mostly related to hospitalisations (97.75%).

Figure 50.
Cost structure.

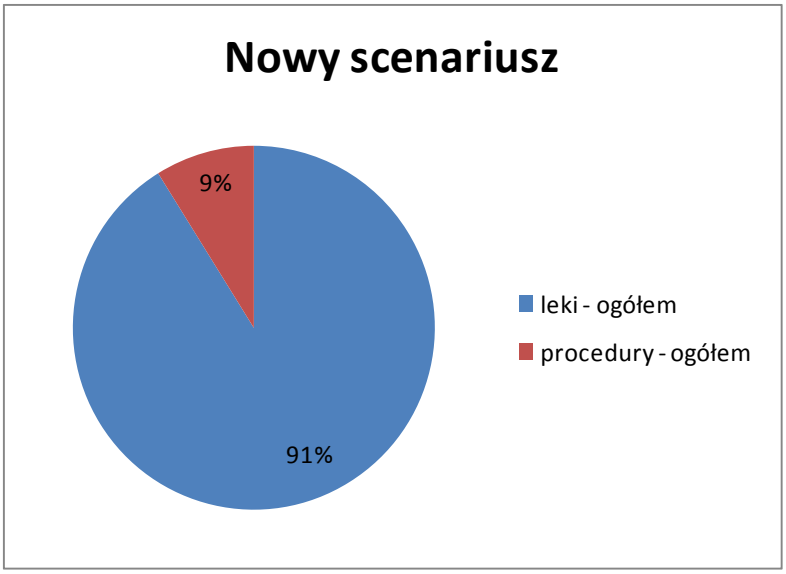


Figure 51.
Cost structure of the analysed drugs.

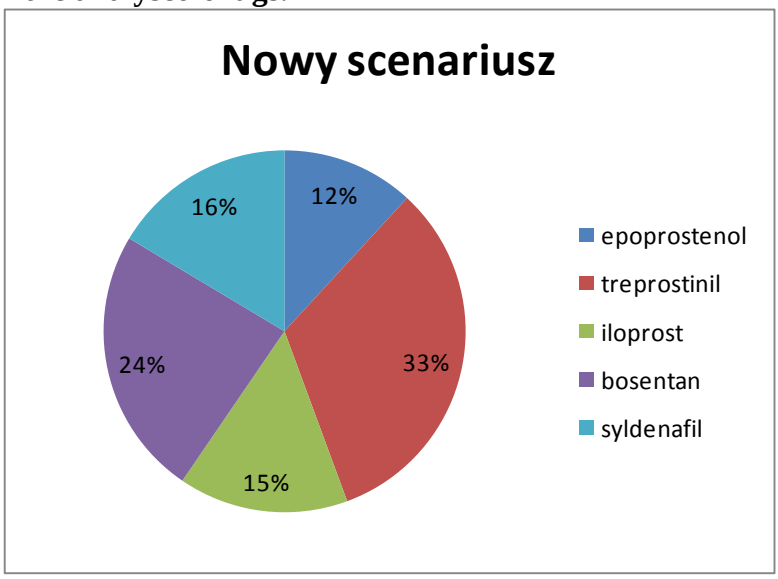


Figure 52.
Change of costs of the analysed drugs.

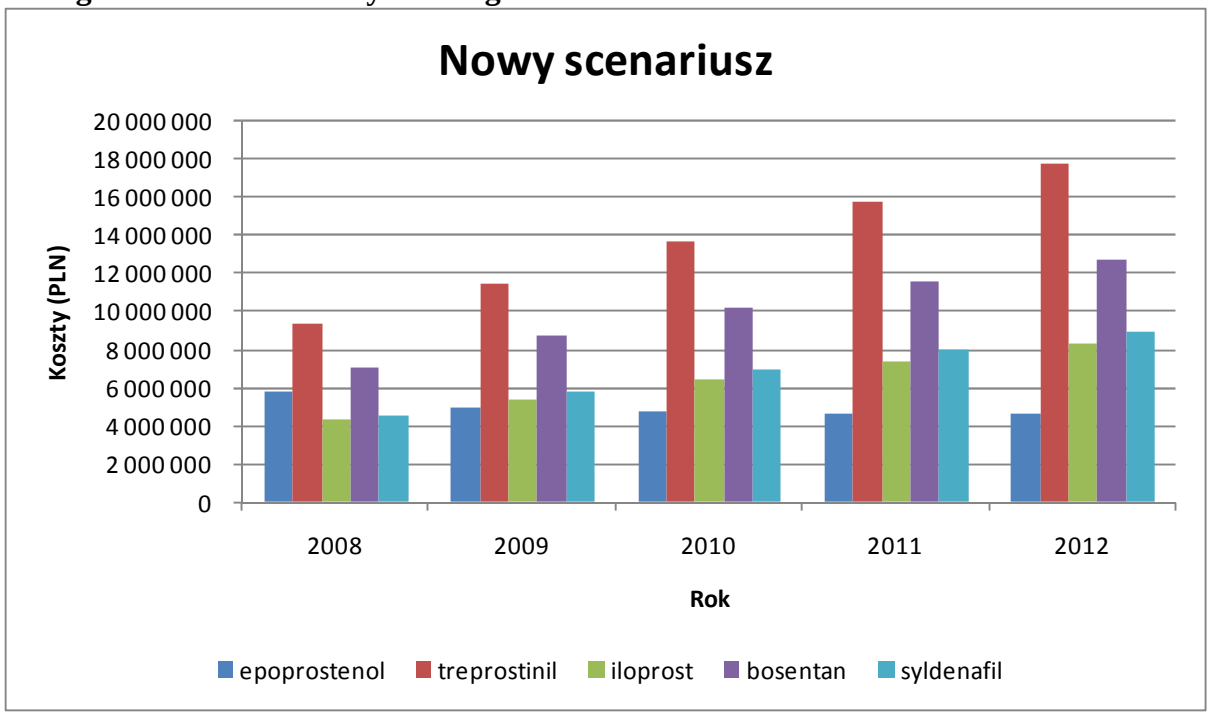


Figure 53.
Change of costs of all drugs.

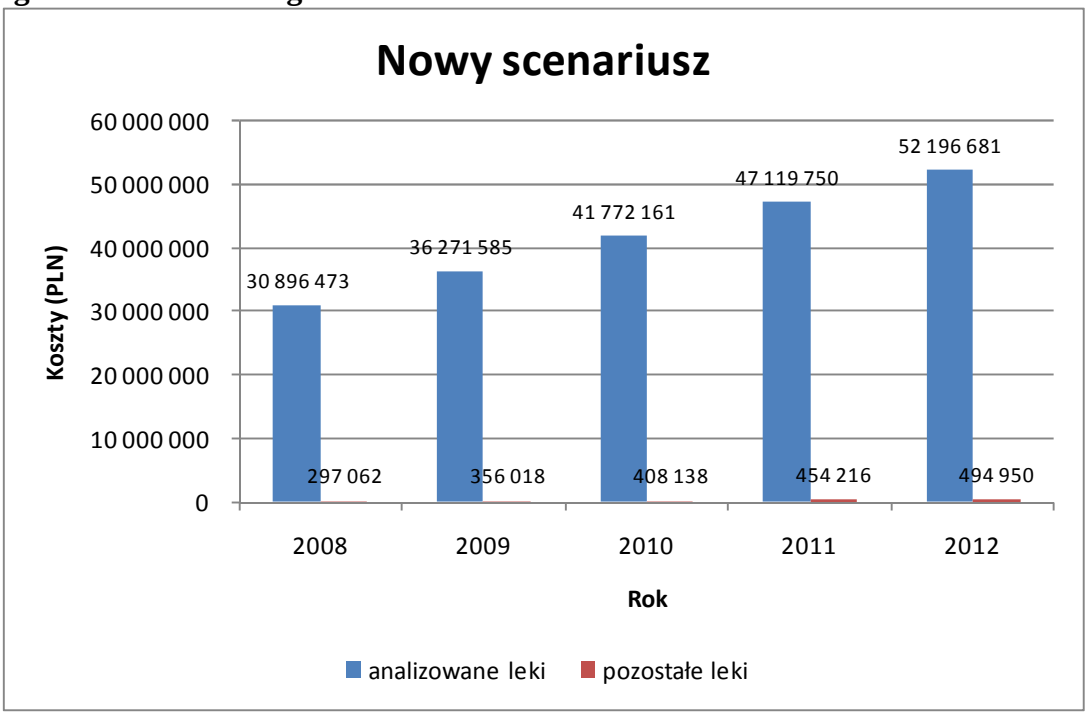


Figure 54.
Change of costs of drugs and procedures.

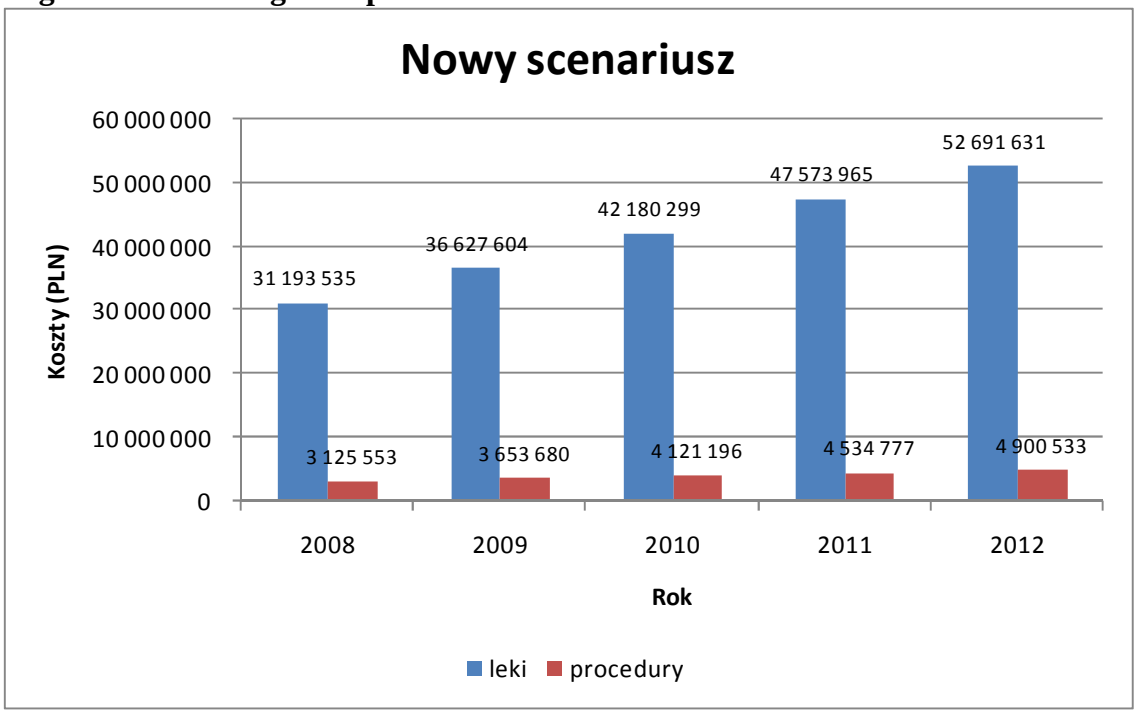


Figure 55.
Change of costs of the procedures used.

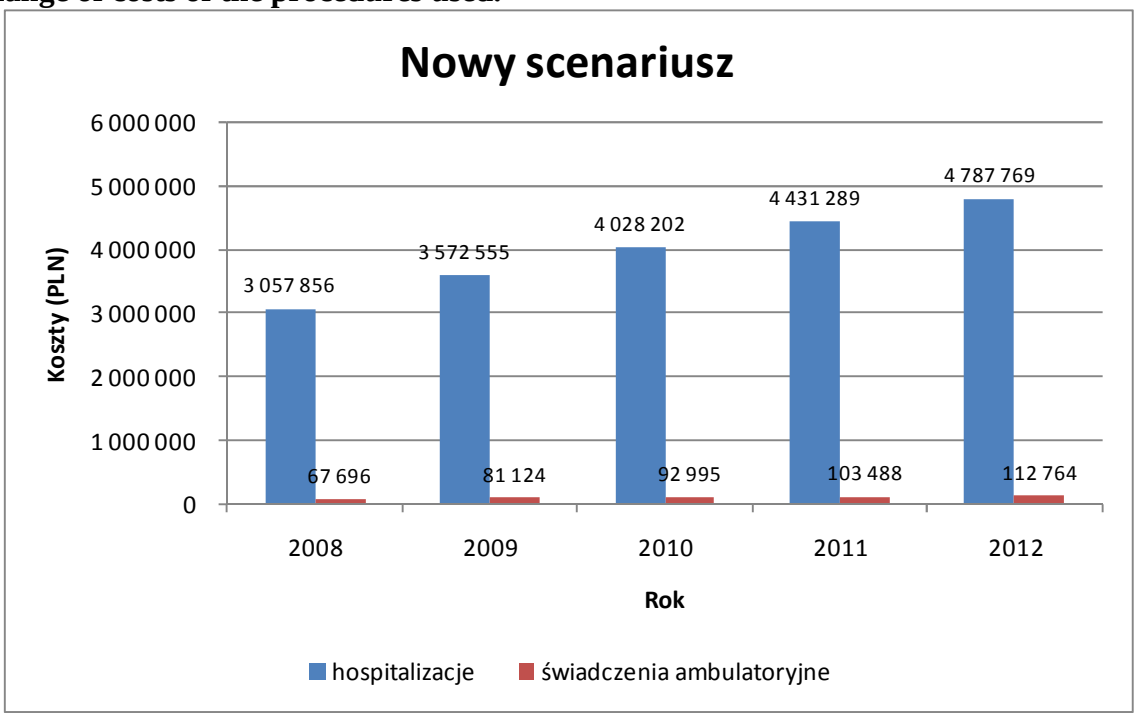


Table 25.
Costs in the new scenario.

	Year					Total
	2008	**2009**	**2010**	**2011**	**2012**	
Number of patients included	260	72	72	72	72	**546**
Patient-months of treatment in a specific year	2,581	3,093	3,546	3,946	4,300	**17,466**
Number of patients at the end of the year	236	276	311	343	371	**n.a.**
Drug costs (PLN):						
epoprostenol	5,745,247.36	4,944,907.01	4,685,951.48	4,629,045.68	4,642,845.14	**24,647,996.66**
treprostinil	9,291,980.85	11,449,447.80	13,581,068.06	15,686,374.16	17,744,526.82	**67,753,397.69**
iloprost	4,324,428.42	5,347,695.32	6,350,936.17	7,329,383.01	8,273,919.07	**31,626,361.99**
bosentan	6,996,597.22	8,722,982.84	10,203,700.02	11,491,282.26	12,620,080.55	**50,034,642.89**
sildenafil	4,538,219.18	5,806,552.43	6,950,505.13	7,983,664.51	8,915,309.04	**34,194,250.29**
Total costs of the analysed drugs	30,896,473.04	36,271,585.39	41,772,160.86	47,119,749.62	52,196,680.62	**208,256,649.52**
Costs of the remaining drugs	297,061.67	356,018.14	408,138.48	454,215.62	494,950.18	**2,010,384.10**
Total costs of pharmacotherapy	31,193,534.71	36,627,603.53	42,180,299.34	47,573,965.24	52,691,630.80	**210,267,033.62**
Procedure costs (PLN):						
hospitalisations	3,057,856.33	3,572,555.45	4,028,201.55	4,431,288.86	4,787,769.31	**19,877,671.50**
outpatient consultations	67,696.35	81,124.27	92,994.55	103,487.88	112,763.99	**458,067.05**
Total	3,125,552.68	3,653,679.72	4,121,196.11	4,534,776.75	4,900,533.30	**20,335,738.55**
Total costs (PLN):						
Total costs	**34,319,087.39**	**40,281,283.25**	**46,301,495.45**	**52,108,741.98**	**57,592,164.10**	**230,602,772.17**

4.3.3 Incremental analysis

Change from the "current practice" scenario to the new scenario would result in increase of mean monthly cost of treatment by 9,067.07 PLN. The target population would not change (neither with respect to incidence nor prevalence rates). Increase (in absolute numbers) of annual costs within the time horizon of five years would be (in subsequent years): 23.52, 27.44, 31.64, 35.85 and 39.91 million PLN.

Nearly all this increase would be the result of increased costs of the analysed drugs (99.94%). The percentages of cost increase related to specific drugs would be as follows: bosentan (31.41%), epoprostenol (15.57%), iloprost (12.08%), sildenafil (21.61%), treprostinil (19.33%).

Costs related to outpatient procedures do not change in the considered model.

Comparison of both scenarios with respect to specific cost categories is presented in the figures and the table below.

Figure 56.
Change of costs of the analysed drugs.

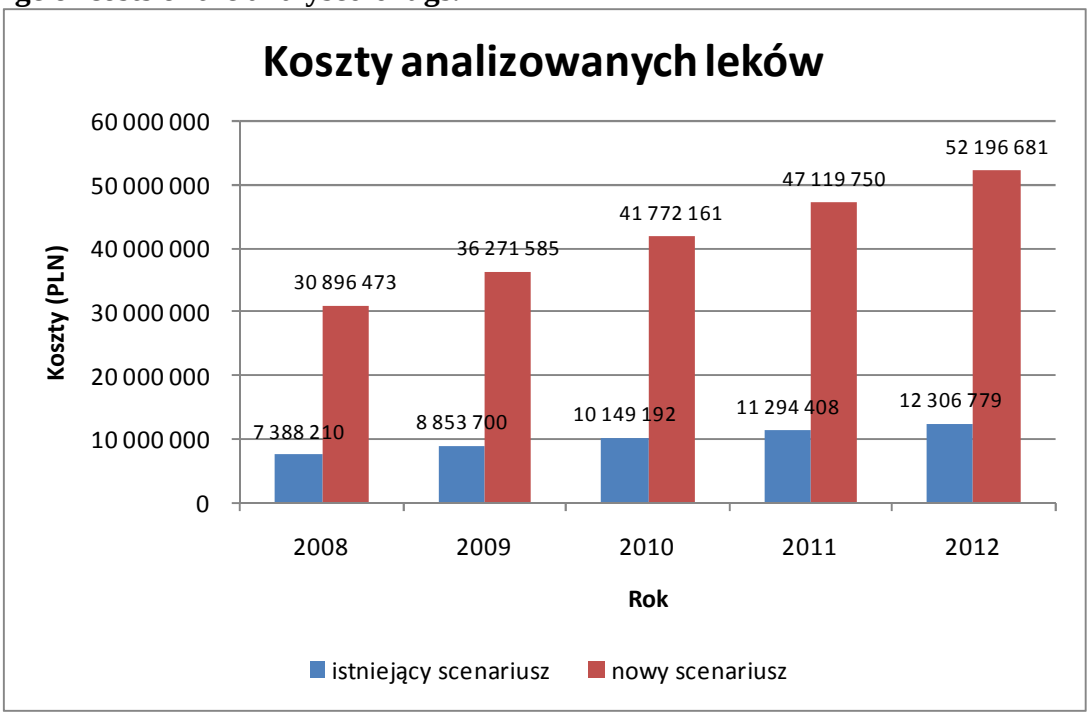


Figure 57.
Change of costs of the remaining drugs.

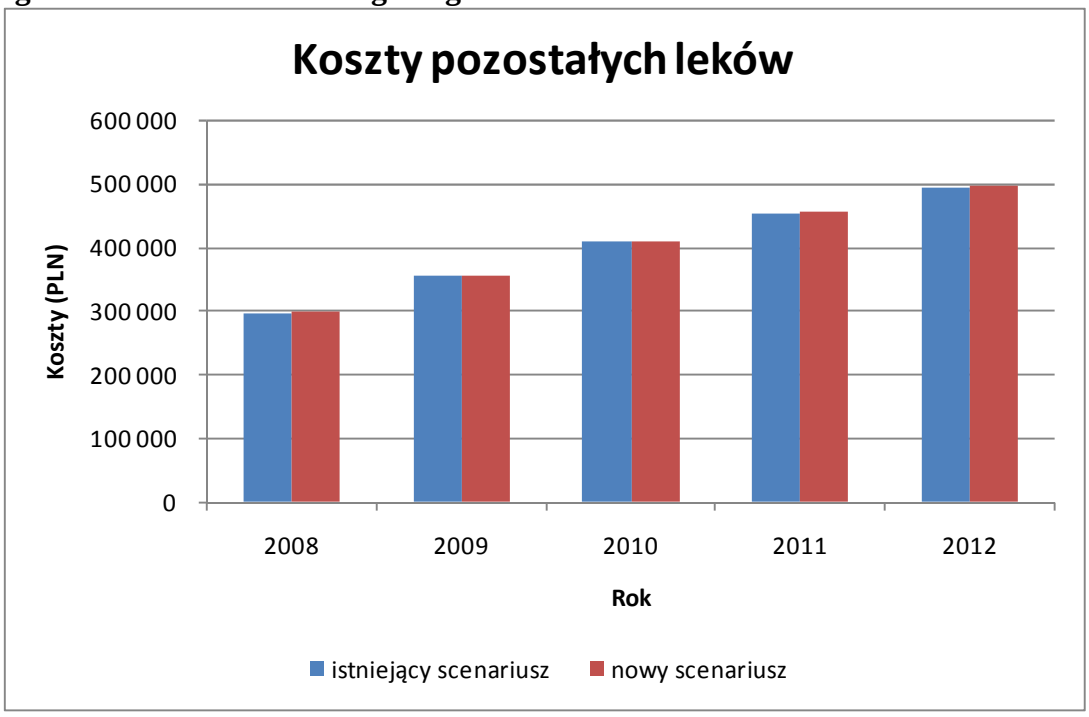


Figure 58.
Change of costs of all drugs.

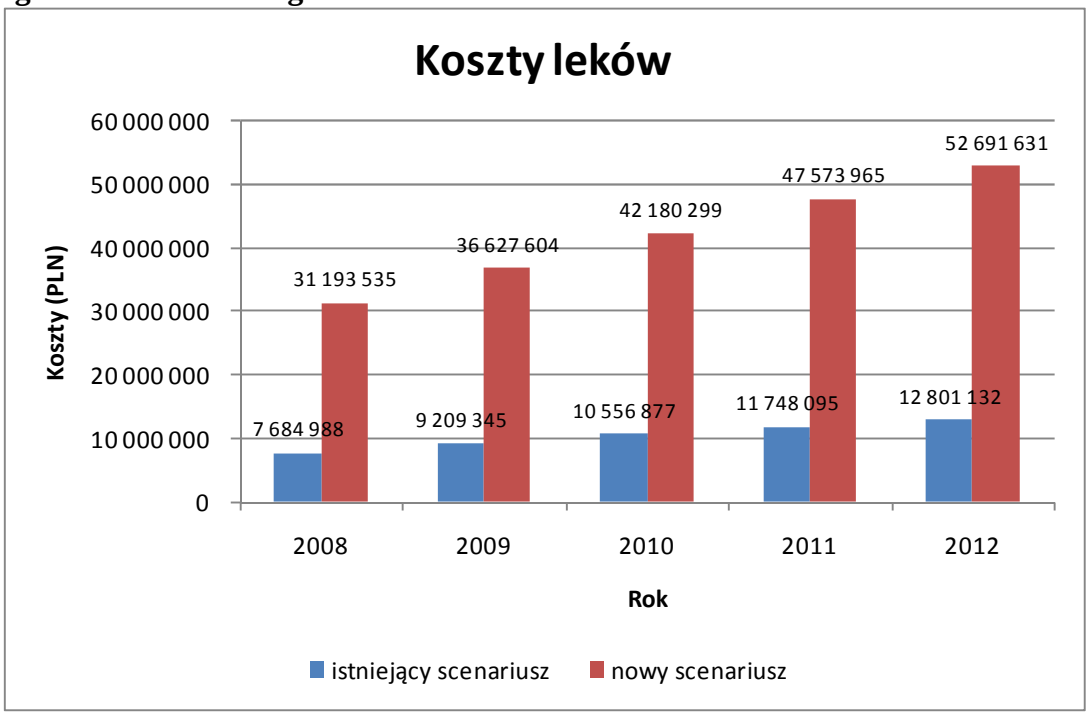


Figure 59.
Change of costs of medical procedures.

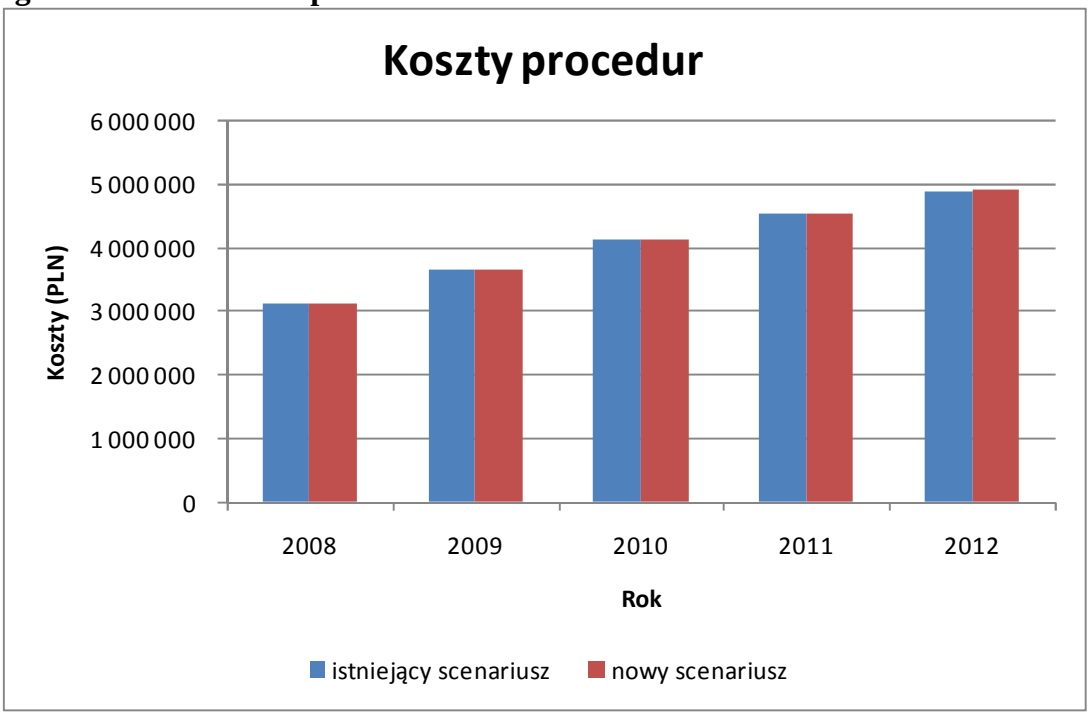


Figure 60.
Change of costs of hospitalisations.

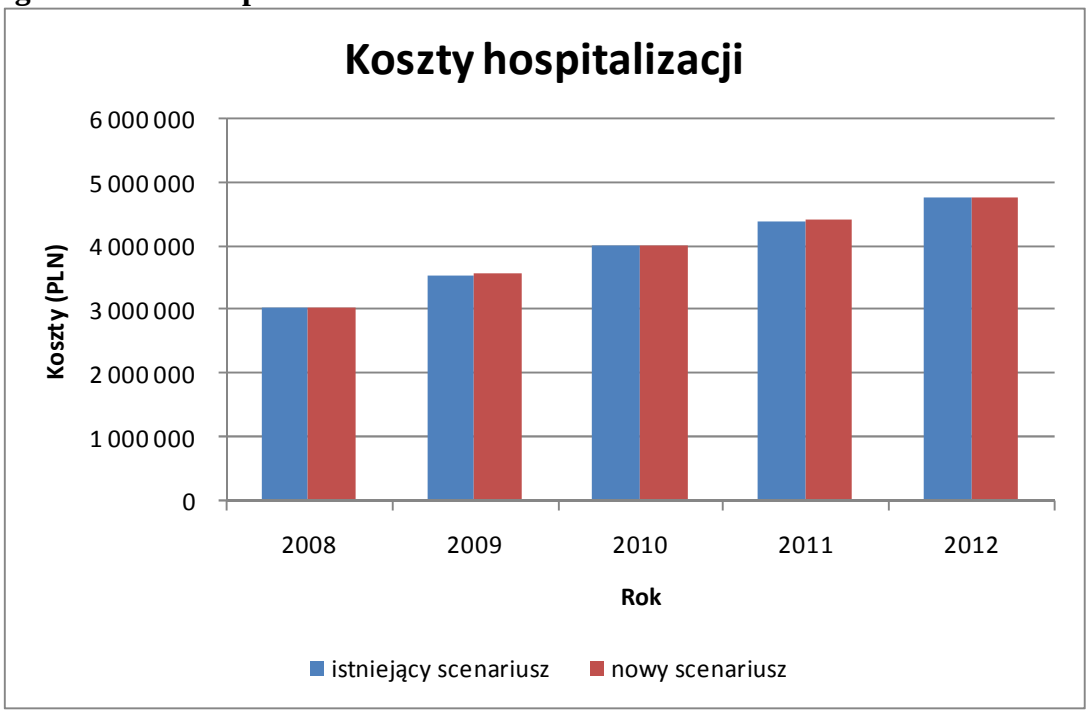


Figure 61.
Change of costs of outpatient services.

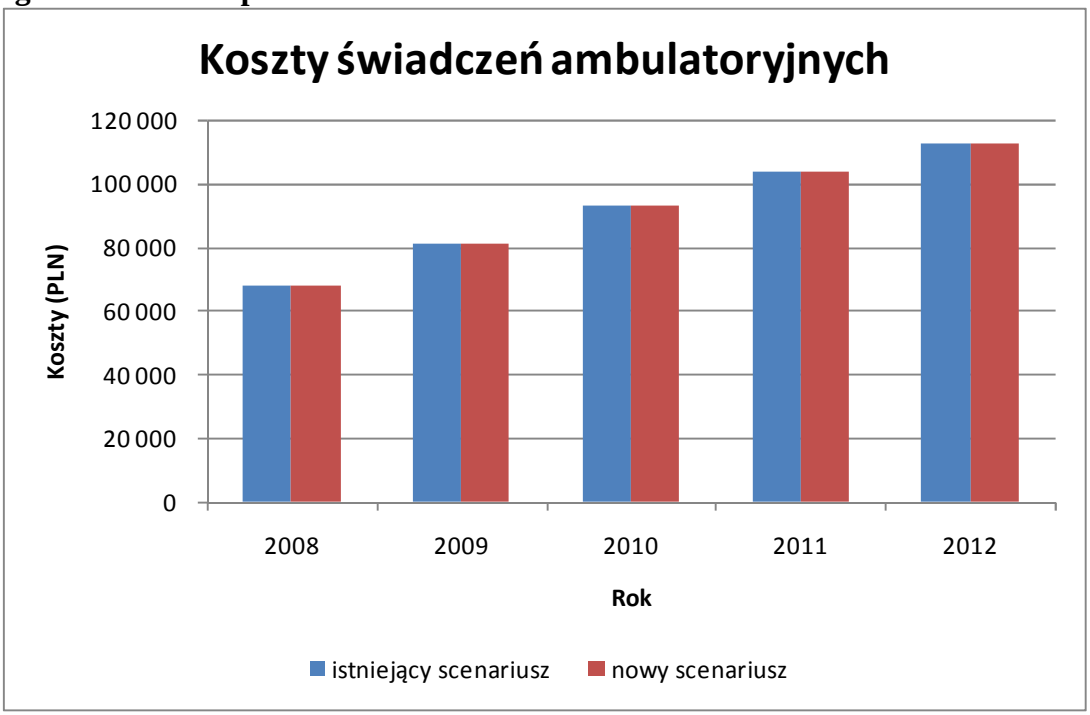


Figure 62.
Change of total costs.

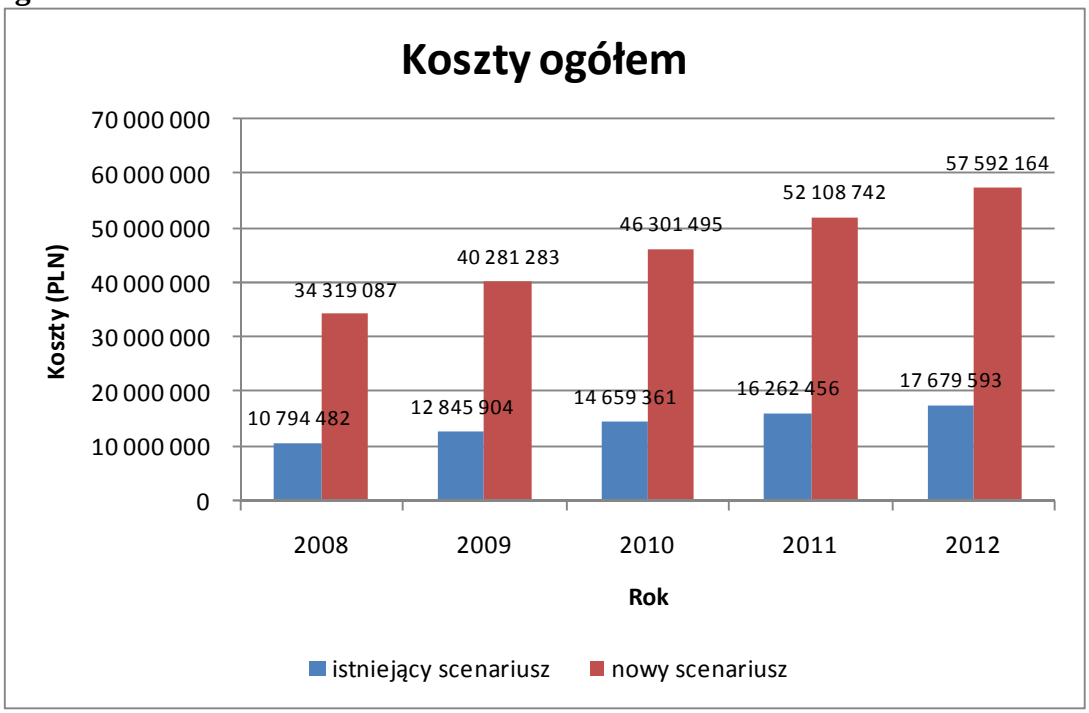


Table 26.
Results of incremental analysis.

	Year					Total
	2008	**2009**	**2010**	**2011**	**2012**	
Number of patients included						
Patient-months of treatment in a specific year	5,745,247.36	4,944,907.01	4,685,951.48	4,629,045.68	4,642,845.14	**24,647,996.66**
Number of patients at the end of the year	3,799,999.53	4,868,103.58	6,036,727.04	7,290,743.96	8,596,357.00	**30,591,931.11**
Drug costs (PLN):	2,477,002.15	3,133,822.49	3,813,124.59	4,505,209.57	5,196,601.74	**19,125,760.55**
epoprostenol	6,947,794.94	8,664,500.37	10,136,660.26	11,416,677.86	12,538,789.02	**49,704,422.46**
treprostinil	4,538,219.18	5,806,552.43	6,950,505.13	7,983,664.51	8,915,309.04	**34,194,250.29**
iloprost	23,508,263.16	27,417,885.88	31,622,968.50	35,825,341.59	39,889,901.94	**158,264,361.07**
bosentan	283.40	372.37	453.83	528.60	597.07	**2,235.28**
sildenafil	23,508,546.56	27,418,258.24	31,623,422.33	35,825,870.19	39,890,499.02	**158,266,596.35**
Total costs of the analysed drugs						
Costs of the remaining drugs	16,058.82	17,121.29	18,712.60	20,415.46	22,072.07	**94,380.24**
Total costs of pharmacotherapy	0.00	0.00	0.00	0.00	0.00	**0.00**
Procedure costs (PLN):	16,058.82	17,121.29	18,712.60	20,415.46	22,072.07	**94,380.24**
hospitalisations						
outpatient consultations	**23,524,605.38**	**27,435,379.53**	**31,642,134.93**	**35,846,285.66**	**39,912,571.08**	**158,360,976.59**

4.4 Analysis of the prevalence-based scenario

The prevalence-based scenario differs from the realistic one with respect to the method of the target population size estimation. Assumed incidence rate in the prevalence-based scenario was calculated in a way resulting in prevalence at the end of the analysed period being 570 patients, which reflects actual prevalence rate observed in France [4] and significantly exceeds the number of patients remaining under care of specialist centres in Poland.

The difference between the realistic and prevalence-based scenario lies therefore in proportional rescaling of the number of patients. This will not result in proportional rescaling of costs due to the fact that the model includes costs of initial diagnostics, which apply to the newly diagnosed patients only and not the patients previously diagnosed and treated at the beginning of the analysed period.

4.4.1 Current practice analysis

Mean cost of one patient-month of treatment in the "current practice" scenario is ca. 4,170.25 PLN and is equal to mean cost in the realistic scenario. Annual costs within the time horizon of five years would increase from 12.48 to 27.05 million PLN (the values in subsequent years would be: 12.48, 16.82, 20.66, 24.05 and 27.05 million PLN).

The cost structure is similar to that in the realistic scenario. Drug costs represent the dominant component (71.39% of total costs); among them, treprostinil and iloprost generate the highest costs (71.46% and 24.04% of total drug costs, respectively). Costs of medical procedures are mostly related to hospitalisations (97.8%).

Figure 63.
The number of patients newly diagnosed and treated in subsequent years.

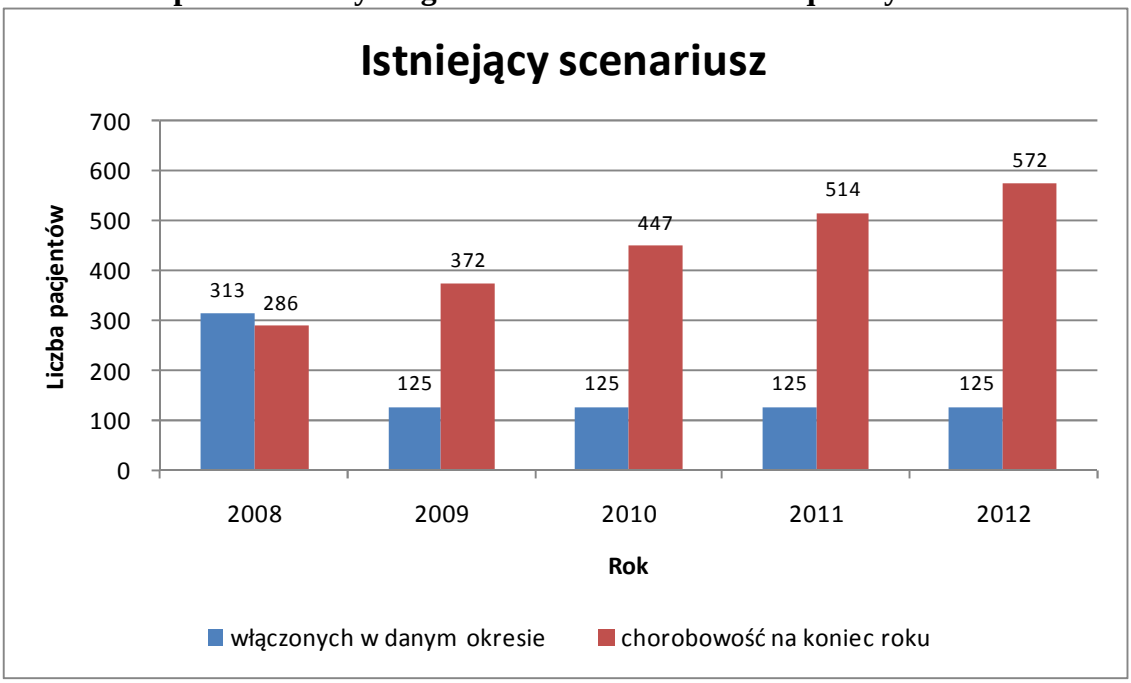


Figure 64.
Cost structure.

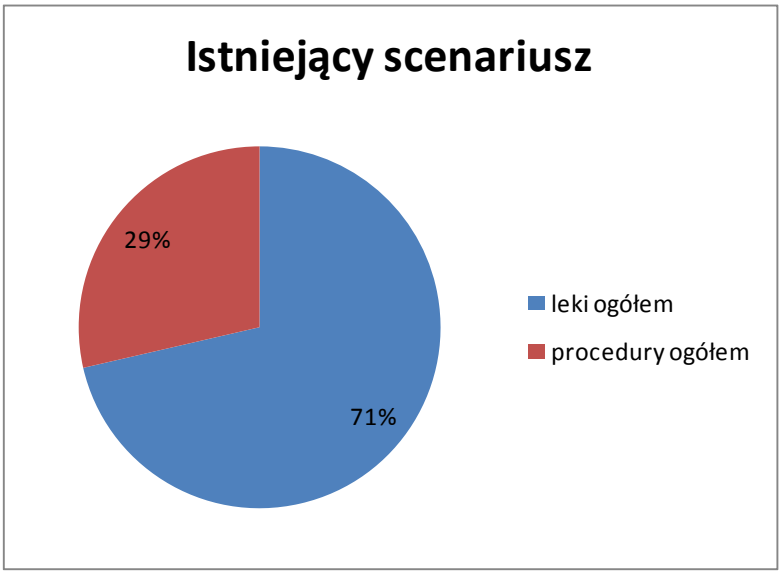


Figure 65.
Cost structure of the analysed drugs.

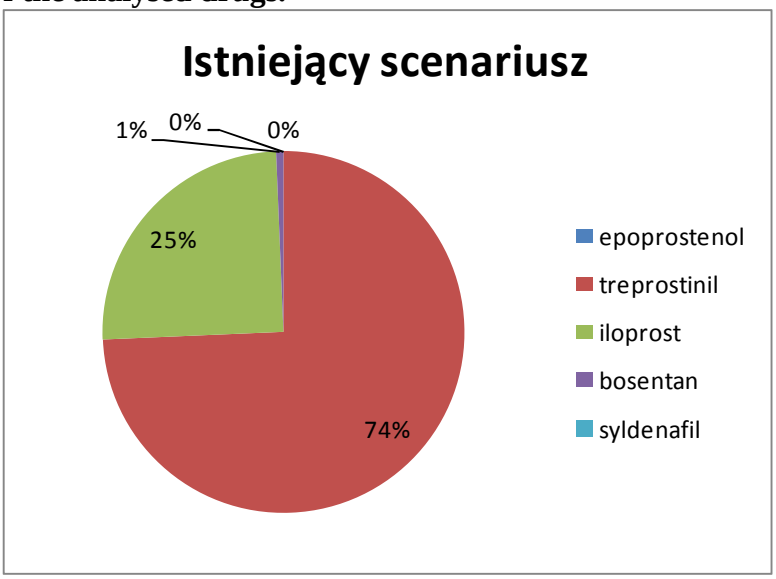


Figure 66.
Change of costs of the analysed drugs.

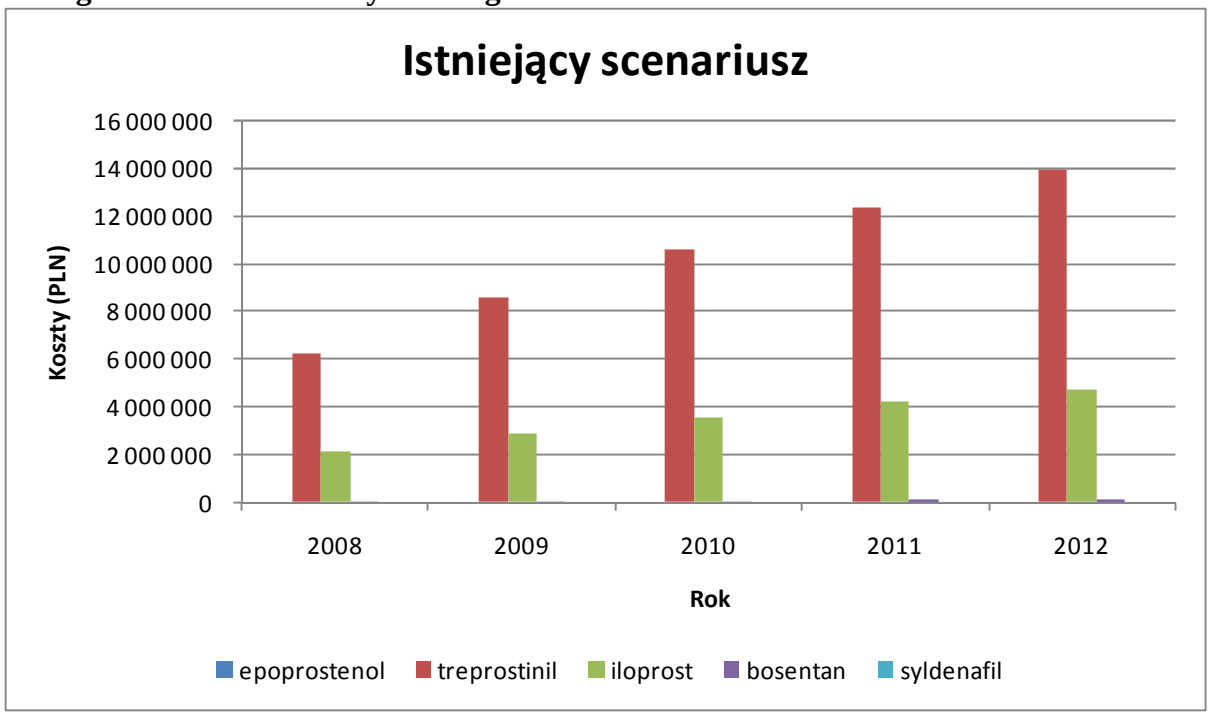


Figure 67.
Change of costs of all drugs.

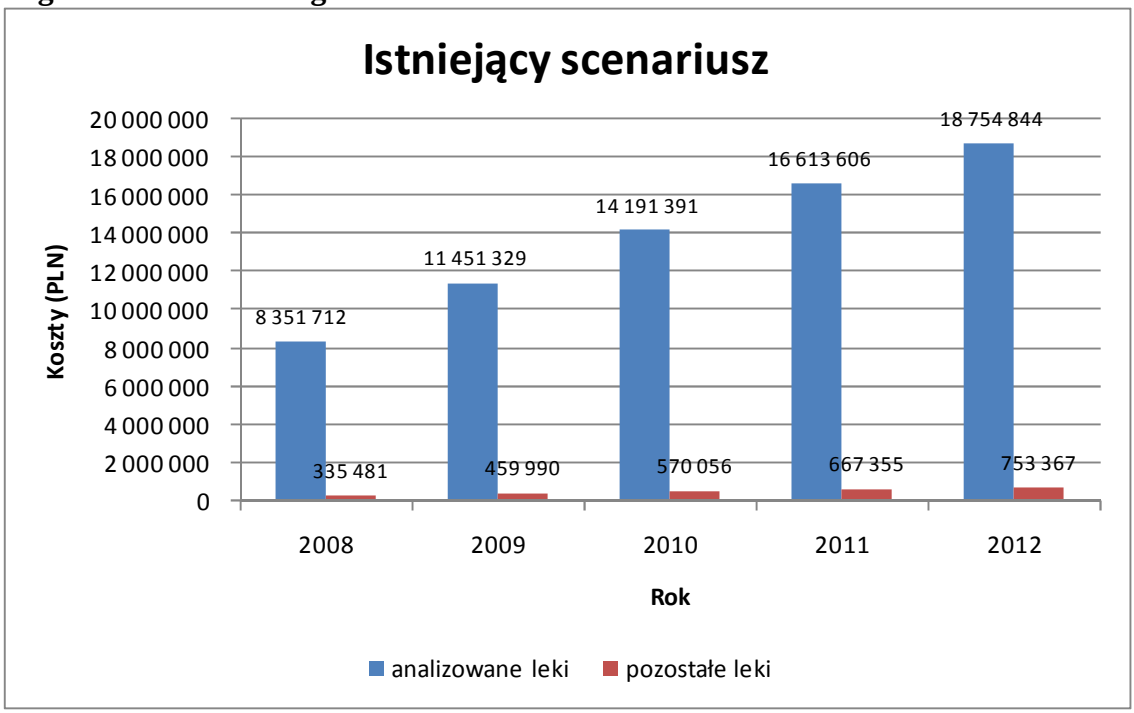


Figure 68.
Change of costs of drugs and procedures.

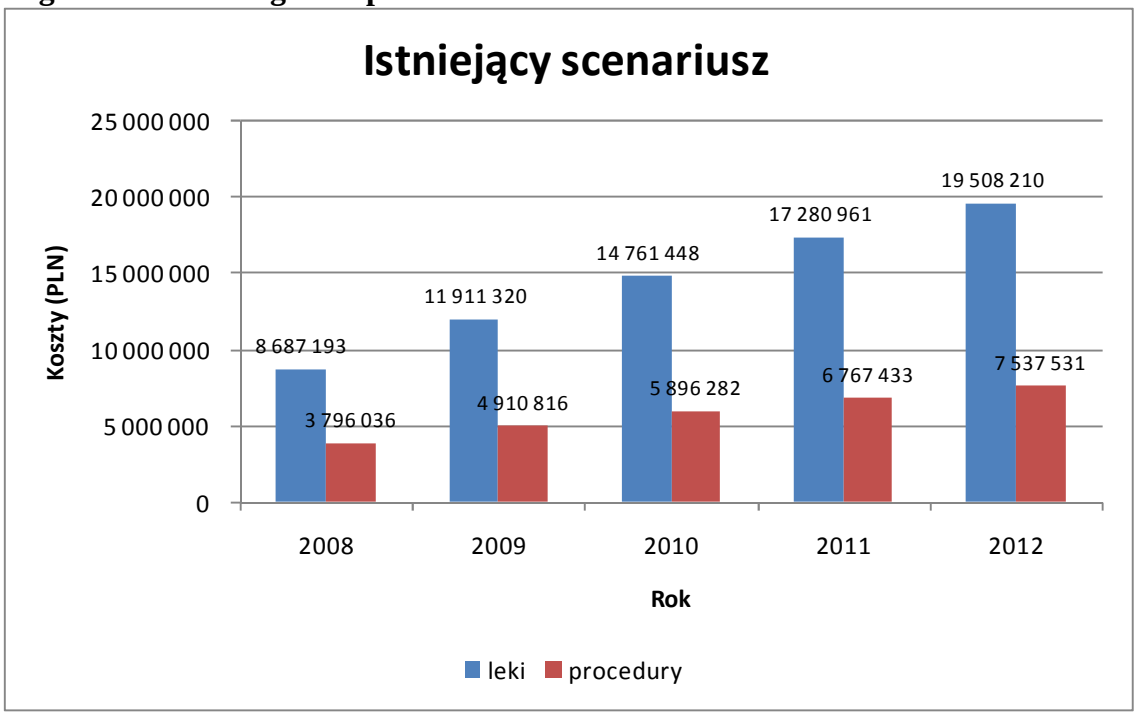


Figure 69.
Change of costs of the procedures used.

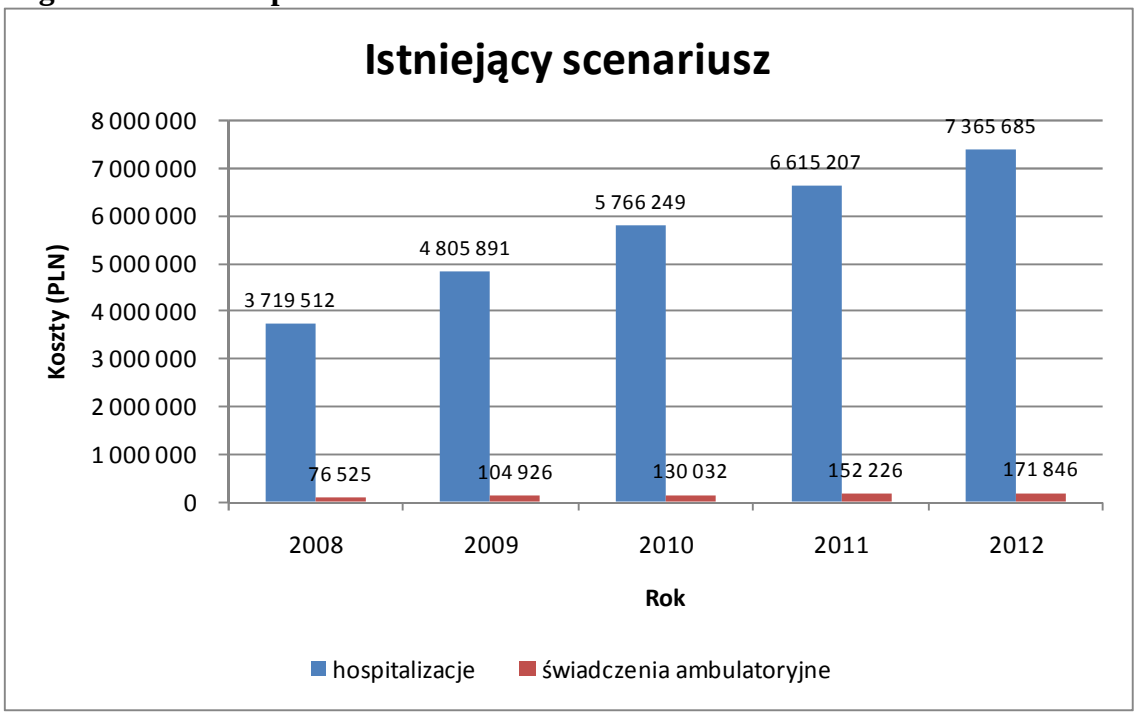


Table 27.
Costs in the "current practice" scenario.

	Year					Total
	2008	**2009**	**2010**	**2011**	**2012**	
Number of patients included	313	125	125	125	125	**814**
Patient-months of treatment in a specific year	2,918	4,001	4,958	5,804	6,552	**24,233**
Number of patients at the end of the year	286	372	447	514	572	**n.a.**
Drug costs (PLN):						
epoprostenol	0.00	0.00	0.00	0.00	0.00	**0.00**
treprostinil	6,208,194.92	8,512,276.82	10,549,085.22	12,349,623.84	13,941,299.99	**51,560,480.78**
iloprost	2,088,350.58	2,863,411.75	3,548,565.81	4,154,242.01	4,689,659.77	**17,344,229.92**
bosentan	55,166.63	75,640.92	93,740.20	109,739.97	123,883.76	**458,171.48**
sildenafil	0.00	0.00	0.00	0.00	0.00	**0.00**
Total costs of the analysed drugs	8,351,712.13	11,451,329.49	14,191,391.23	16,613,605.82	18,754,843.51	**69,362,882.18**
Costs of the remaining drugs	335,481.36	459,990.42	570,056.43	667,354.78	753,366.53	**2,786,249.52**
Total costs of pharmacotherapy	8,687,193.49	11,911,319.91	14,761,447.67	17,280,960.60	19,508,210.04	**72,149,131.70**
Procedure costs (PLN):						
hospitalisations	3,719,511.57	4,805,890.51	5,766,249.49	6,615,206.83	7,365,685.12	**28,272,543.51**
outpatient consultations	76,524.69	104,925.72	130,032.23	152,226.39	171,846.02	**635,555.04**
Total	3,796,036.25	4,910,816.22	5,896,281.72	6,767,433.21	7,537,531.14	**28,908,098.55**
Total costs (PLN):						
Total costs	**12,483,229.74**	**16,822,136.13**	**20,657,729.38**	**24,048,393.82**	**27,045,741.17**	**101,057,230.25**

4.4.2 Costs in the new scenario.

Mean cost of one patient-month of treatment in the "current practice" scenario is ca. 13,157.82 PLN and is equal to mean cost in the realistic scenario. Annual costs within the time horizon of five years would increase from 38.98 to 87.08 million PLN (the values in subsequent years would be: 38.98, 52.1, 64.51, 76.17 and 87.08 million PLN).

Drug costs represent the dominant component (90.89% of total costs); the percentages of costs related to specific drugs are as follows: bosentan (25.12%), epoprostenol (12.85%), iloprost (14.3%), sildenafil (16.38%), treprostinil (30.38%). Costs of medical procedures are mostly related to hospitalisations (97.81%).

Figure 70.
Cost structure.

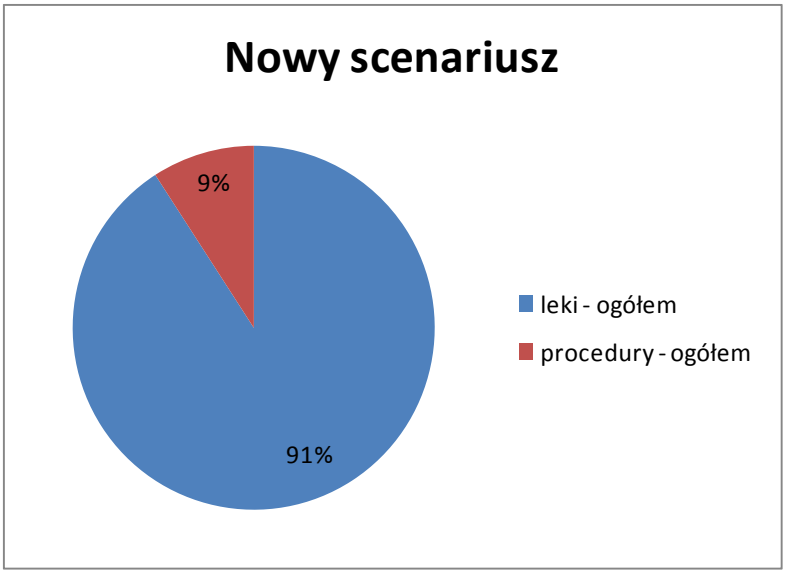


Figure 71.
Cost structure of the analysed drugs.

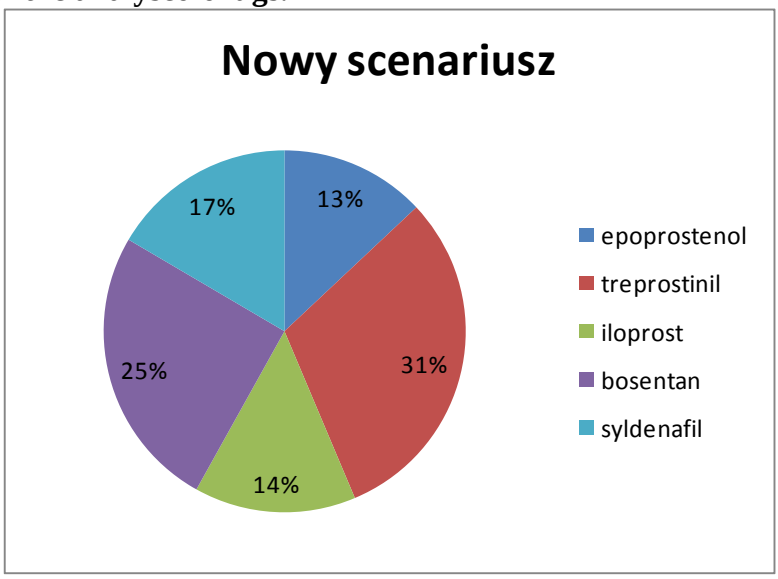


Figure 72.
Change of costs of the analysed drugs.

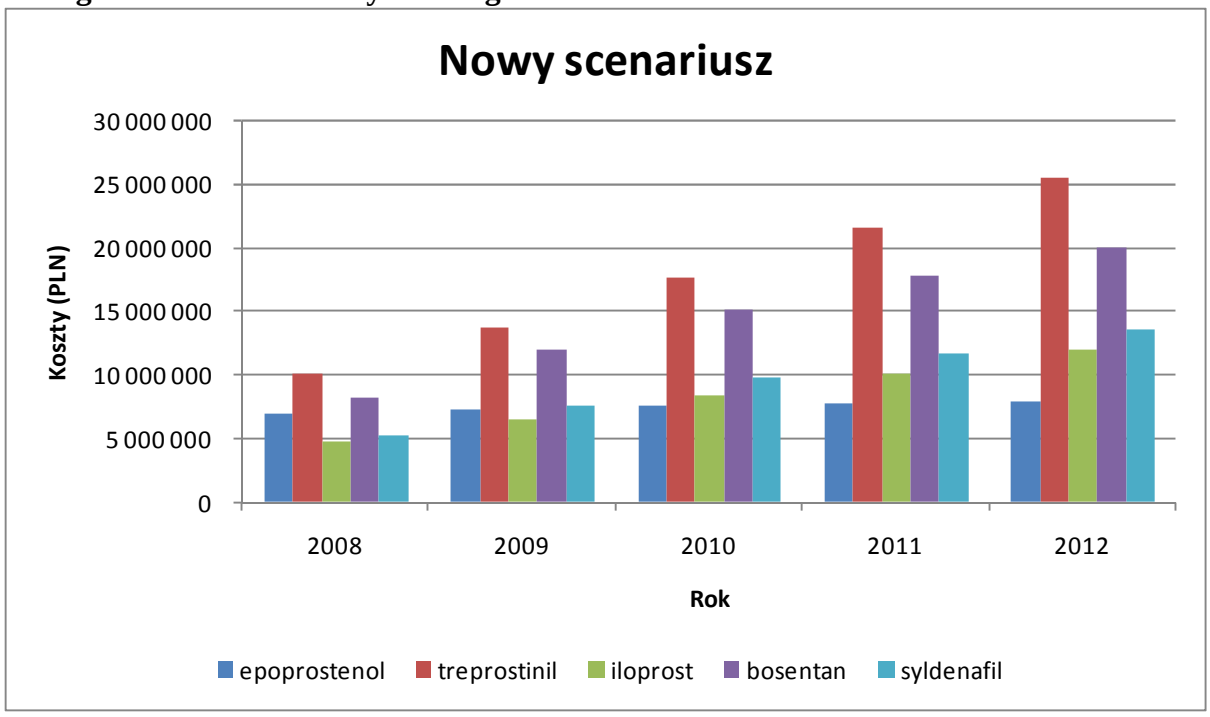


Figure 73.
Change of costs of all drugs.

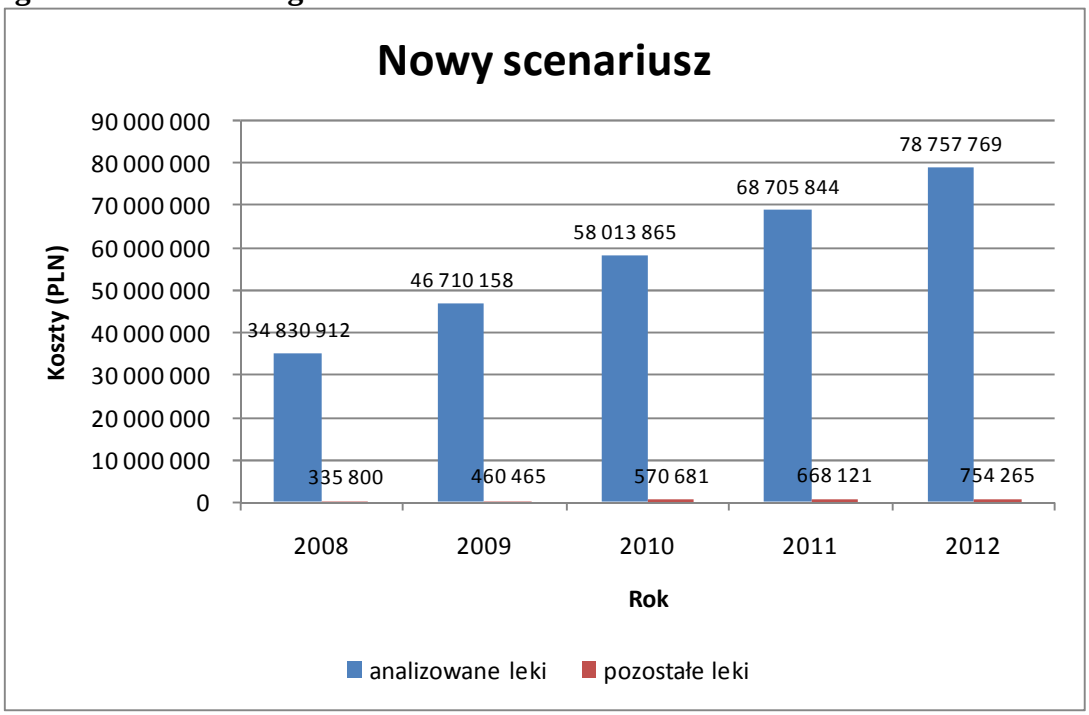


Figure 74.
Change of costs of drugs and procedures.

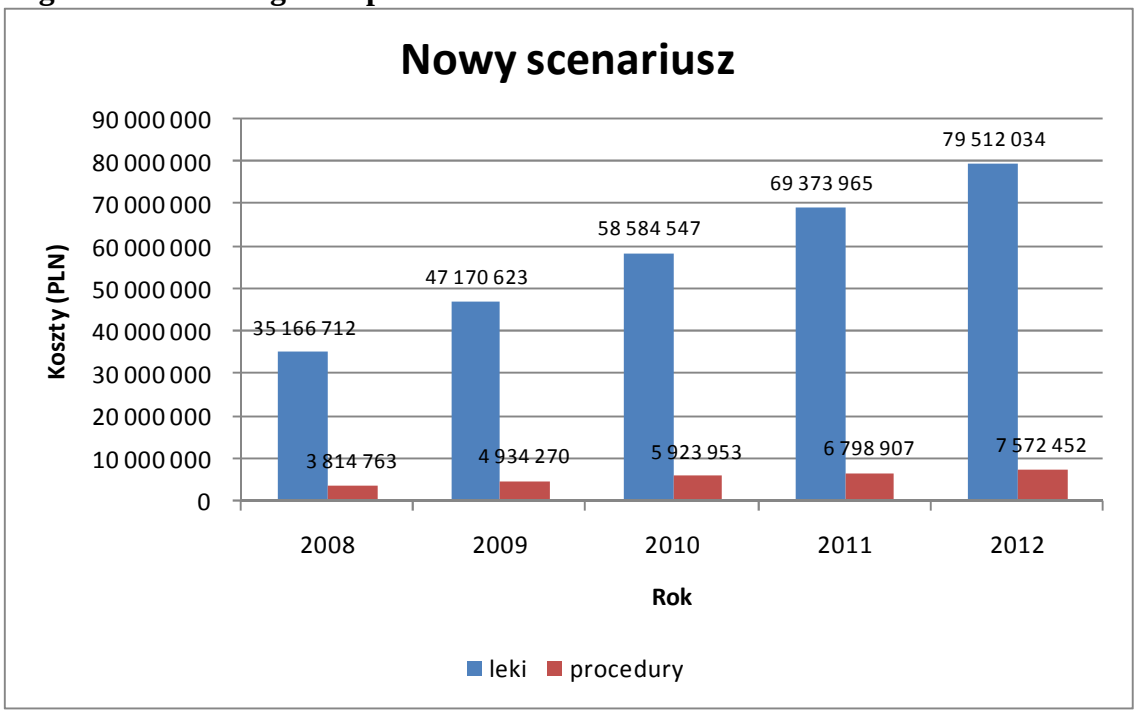


Figure 75.
Change of costs of the procedures used.

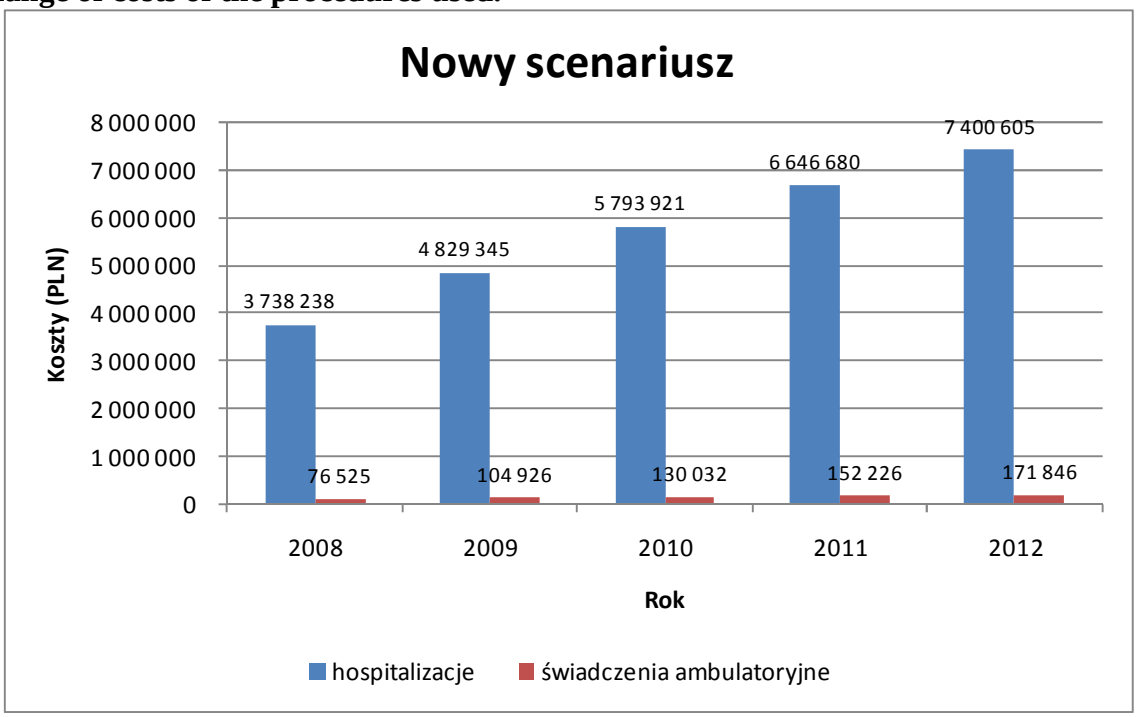


Table 28.
Costs in the new scenario.

	Year					Total
	2008	**2009**	**2010**	**2011**	**2012**	
Number of patients included	313	125	125	125	125	**814**
Patient-months of treatment in a specific year	2,918	4,001	4,958	5,804	6,552	**24,233**
Number of patients at the end of the year	286	372	447	514	572	**n.a.**
Drug costs (PLN):						
epoprostenol	6,845,753.06	7,232,488.67	7,520,181.83	7,740,020.82	7,910,942.86	**37,249,387.24**
treprostinil	9,983,286.85	13,666,088.42	17,535,940.00	21,474,661.09	25,391,055.89	**88,051,032.27**
iloprost	4,674,209.09	6,443,704.25	8,276,589.85	10,116,933.07	11,924,542.85	**41,435,979.11**
bosentan	8,201,458.46	11,889,777.17	15,013,825.32	17,691,982.64	20,009,767.00	**72,806,810.58**
sildenafil	5,126,204.80	7,478,099.64	9,667,328.30	11,682,246.46	13,521,460.20	**47,475,339.40**
Total costs of the analysed drugs	34,830,912.26	46,710,158.15	58,013,865.31	68,705,844.07	78,757,768.81	**287,018,548.60**
Costs of the remaining drugs	335,799.53	460,465.20	570,681.38	668,121.30	754,264.86	**2,789,332.28**
Total costs of pharmacotherapy	35,166,711.79	47,170,623.35	58,584,546.69	69,373,965.38	79,512,033.67	**289,807,880.88**
Procedure costs (PLN):						
hospitalisations	3,738,237.88	4,829,344.54	5,793,921.05	6,646,680.19	7,400,605.50	**28,408,789.16**
outpatient consultations	76,524.69	104,925.72	130,032.23	152,226.39	171,846.02	**635,555.04**
Total	3,814,762.57	4,934,270.26	5,923,953.28	6,798,906.57	7,572,451.52	**29,044,344.19**
Total costs (PLN):						
Total costs	**38,981,474.35**	**52,104,893.61**	**64,508,499.97**	**76,172,871.95**	**87,084,485.19**	**318,852,225.07**

4.4.3 Incremental analysis

Change from the "current practice" scenario to the new scenario would result in increase of mean monthly cost of treatment by 8,987.58 PLN. The target population would not change (neither with respect to incidence nor prevalence rates). Increase (in absolute numbers) of annual costs within the time horizon of five years would be (in subsequent years): 26.5, 35.28, 43.85, 52.12 and 60.04 million PLN.

Nearly all this increase would be the result of increased costs of the analysed drugs (99.94%). The percentages of cost increase related to specific drugs would be as follows: bosentan (33.24%), epoprostenol (17.11%), iloprost (11.07%), sildenafil (21.81%), treprostinil (16.77%).

Costs related to outpatient procedures do not change in the considered model.

Comparison of both scenarios with respect to specific cost categories is presented in the figures and the table below.

Figure 76.
Change of costs of the analysed drugs.

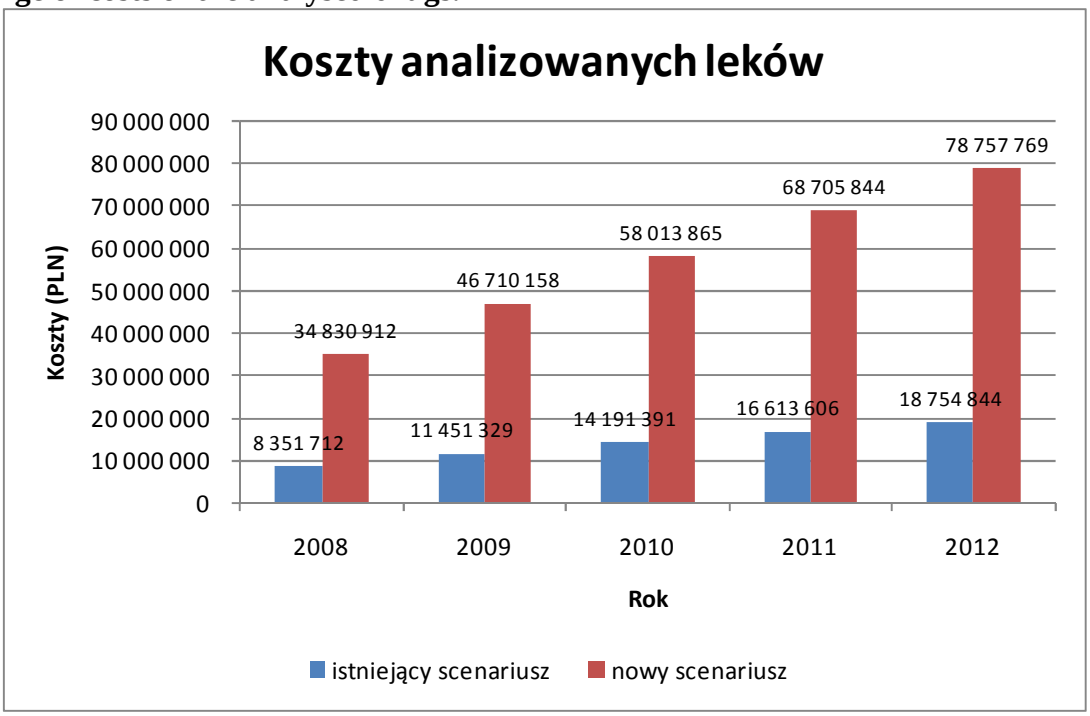


Figure 77.
Change of costs of the remaining drugs.

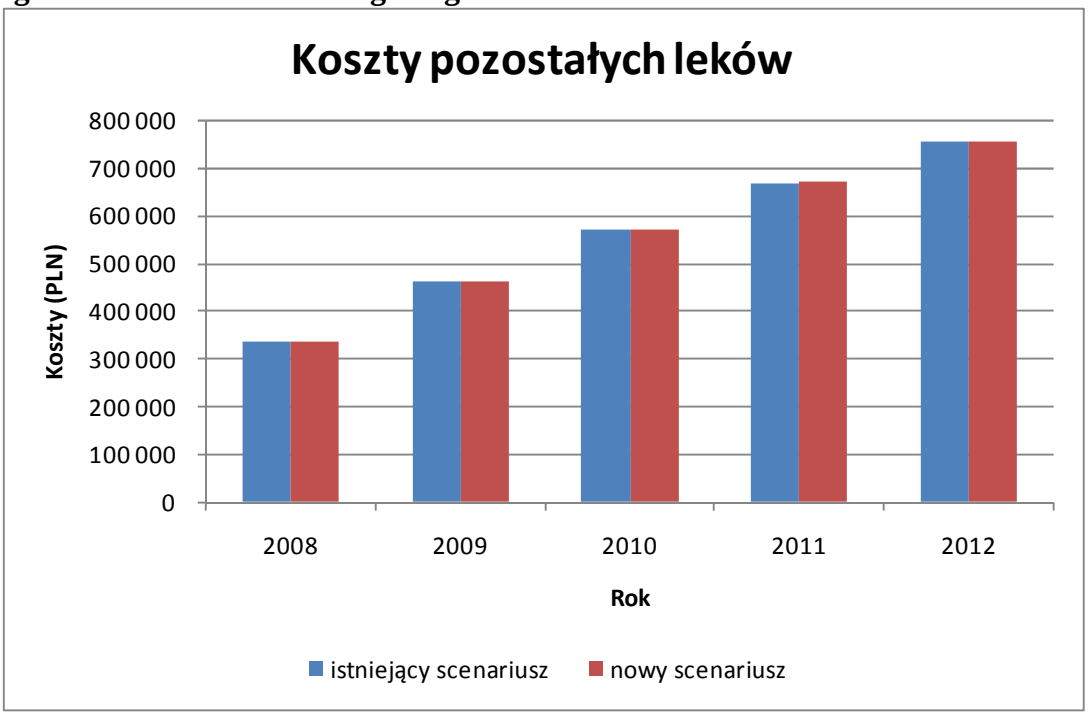


Figure 78.
Change of costs of all drugs.

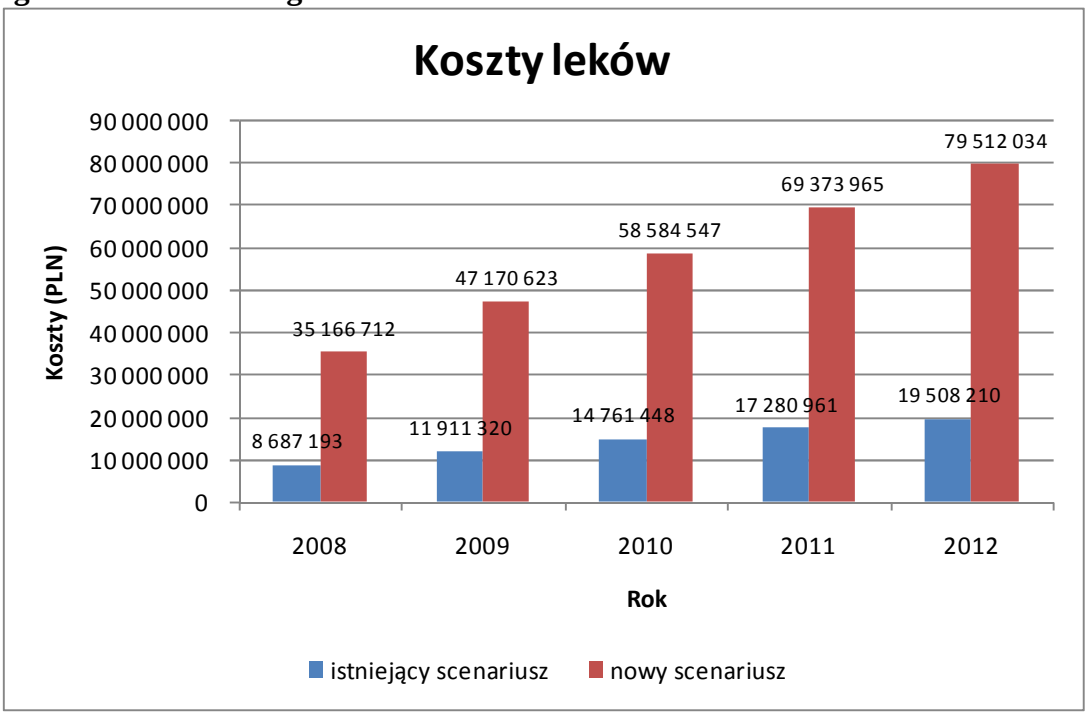


Figure 79.
Change of costs of medical procedures.

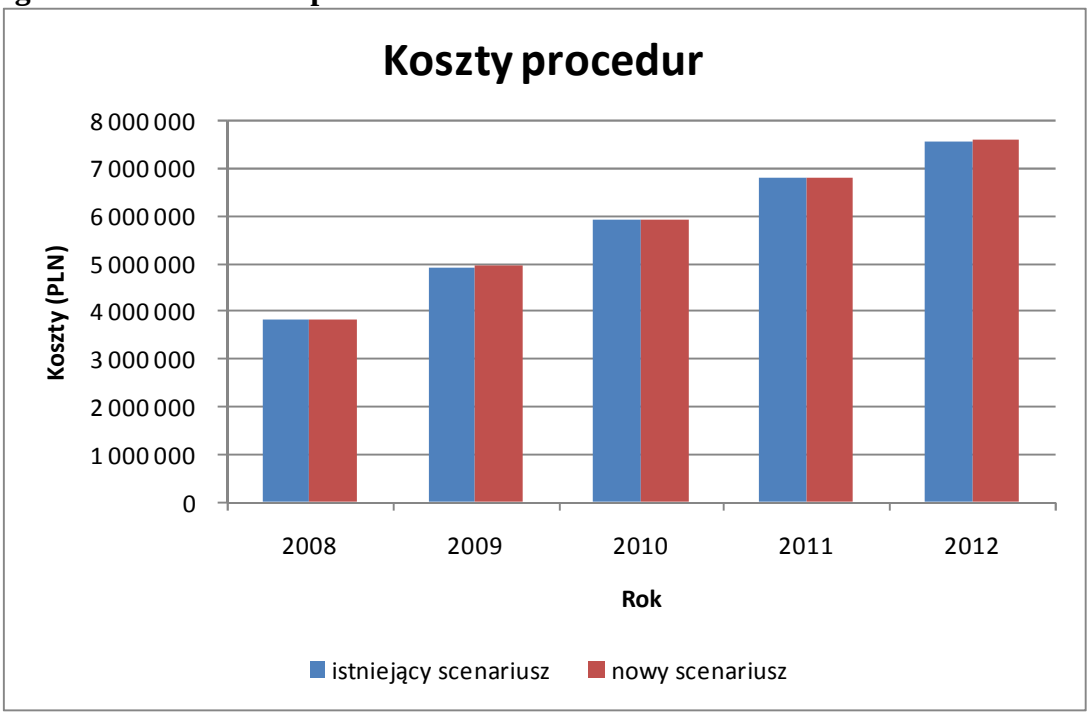


Figure 80.
Change of costs of hospitalisations.

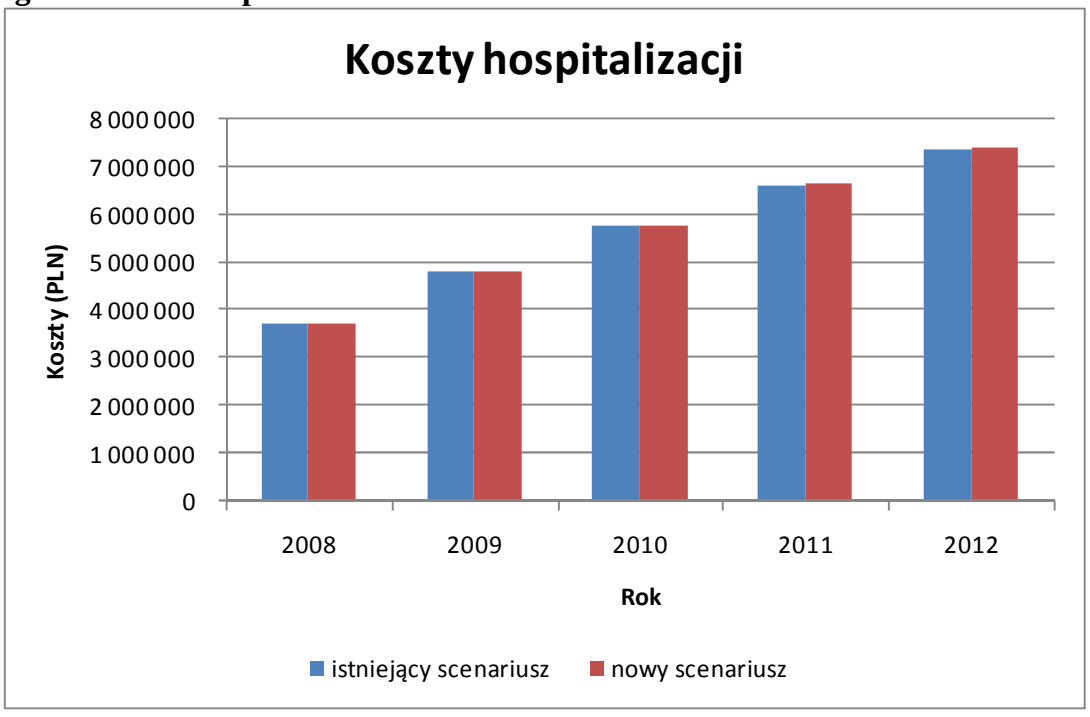


Figure 81.
Change of costs of outpatient services.

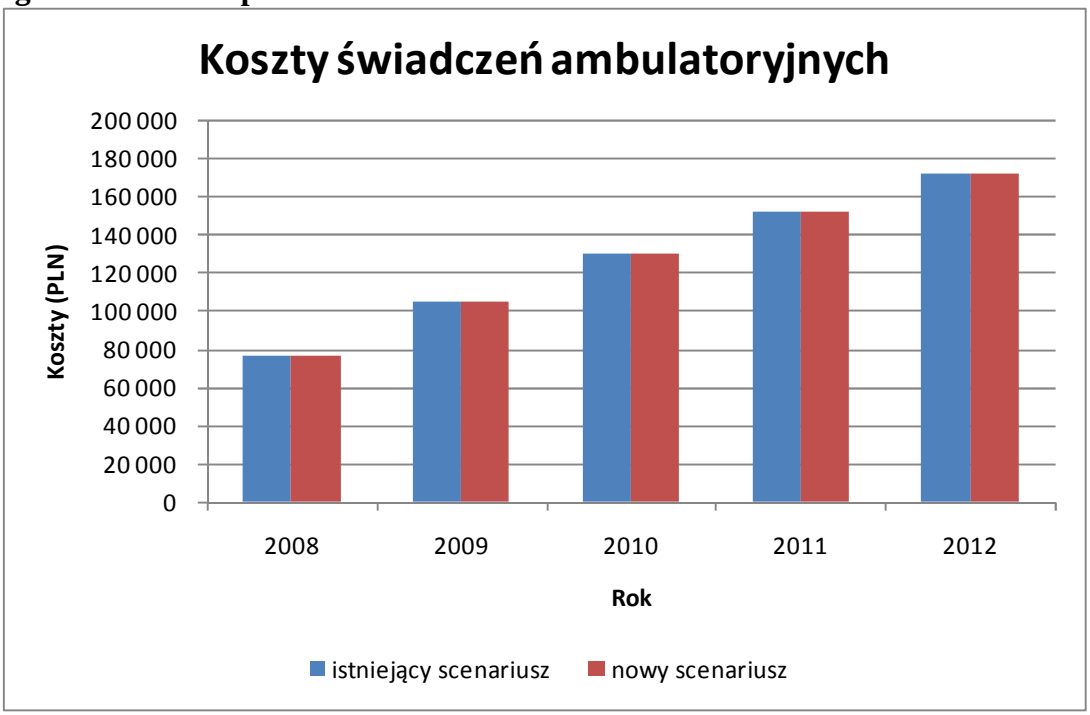


Figure 82.
Change of total costs.

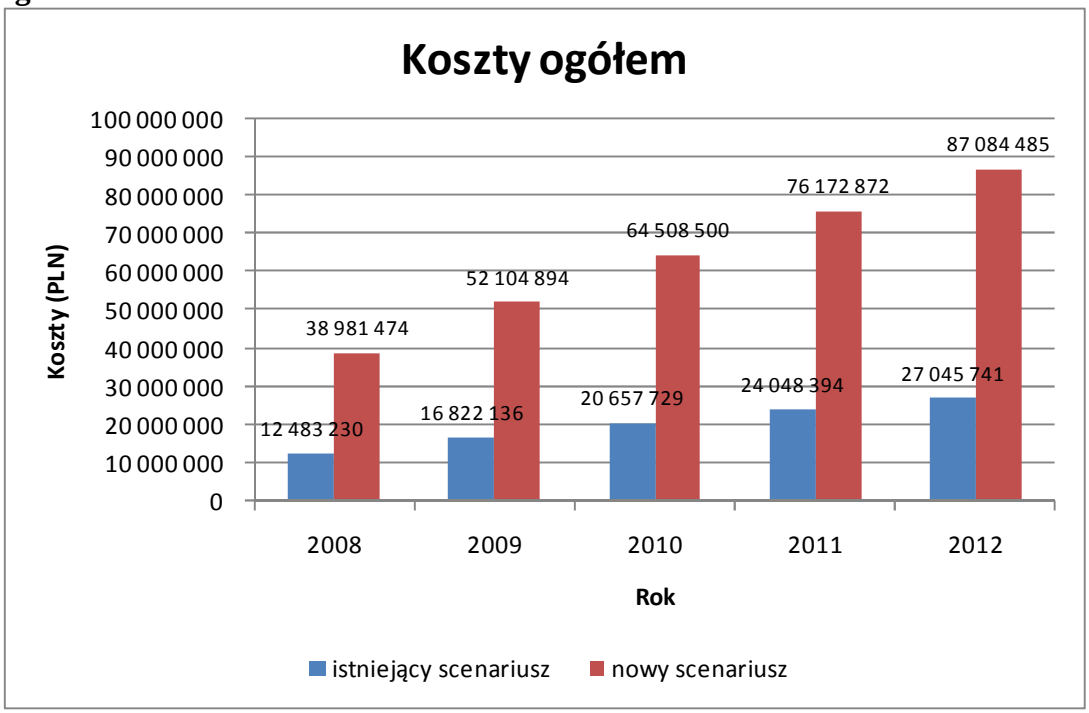


Table 29.
Results of incremental analysis.

	Year					Total
	2008	**2009**	**2010**	**2011**	**2012**	
Drug costs (PLN):						
epoprostenol	6,845,753.06	7,232,488.67	7,520,181.83	7,740,020.82	7,910,942.86	**37,249,387.24**
treprostinil	3,775,091.93	5,153,811.60	6,986,854.79	9,125,037.25	11,449,755.91	**36,490,551.48**
iloprost	2,585,858.51	3,580,292.51	4,728,024.03	5,962,691.06	7,234,883.08	**24,091,749.19**
bosentan	8,146,291.83	11,814,136.24	14,920,085.12	17,582,242.67	19,885,883.24	**72,348,639.11**
sildenafil	5,126,204.80	7,478,099.64	9,667,328.30	11,682,246.46	13,521,460.20	**47,475,339.40**
Total costs of the analysed drugs	26,479,200.13	35,258,828.67	43,822,474.07	52,092,238.26	60,002,925.30	**217,655,666.43**
Costs of the remaining drugs	318.17	474.78	624.95	766.52	898.34	**3,082.75**
Total costs of pharmacotherapy	26,479,518.30	35,259,303.44	43,823,099.03	52,093,004.77	60,003,823.63	**217,658,749.18**
Procedure costs (PLN):						
hospitalisations	18,726.31	23,454.03	27,671.56	31,473.36	34,920.38	**136,245.65**
outpatient consultations	0.00	0.00	0.00	0.00	0.00	**0.00**
Total	18,726.31	23,454.03	27,671.56	31,473.36	34,920.38	**136,245.65**
Total costs (PLN):						
Total costs	**26,498,244.61**	**35,282,757.48**	**43,850,770.59**	**52,124,478.13**	**60,038,744.02**	**217,794,994.82**

4.5 Sensitivity analysis in the realistic scenario

4.5.1 Analysis of key parameters

The tables below present the results of calculations with selected model input parameters changed by +/- 10%. The results presented include also relative change of the results, defined as mean absolute change of the result calculated after increase/decrease of an input parameter divided by the result obtained for the base value of this parameter.[††††]

The greatest effect on costs in the new scenario was observed for the following parameters: incidence rate (4.37%), body weight (3.53%), price of bosentan (3.06%), price of sildenafil (2.15%), price of treprostinil (2.05%). Non-ideal confectioning will change total costs by 2.67% when taken into account.

[††††] I.e. relative change = ((VALUE OF THE INPUT PARAMETER + 10%) – (VALUE OF THE INPUT PARAMETER - 10%))/(2 * BASE VALUE).

Table 30.
Effect of body weight (adults and children pooled) on the results aggregated for the whole time horizon of the analysis.

Parameter (outcome)	Value of the input parameter -10%	Base value of the input parameter	Value of the input parameter +10%	Relative change
In the "current practice" scenario				
Costs of the analysed drugs (PLN), including:	40,993,793.27	44,285,747.66	47,577,702.04	7.43%
bosentan	292,526.29	292,526.29	292,526.29	0.00%
epoprostenol	0.00	0.00	0.00	n.a.
iloprost	11,073,677.53	11,073,677.53	11,073,677.53	0.00%
sildenafil	0.00	0.00	0.00	n.a.
treprostinil	29,627,589.46	32,919,543.85	36,211,498.23	10.00%
Total costs (PLN)	60,448,746.60	63,752,822.27	67,056,897.94	5.18%
In the new scenario				
Costs of the analysed drugs (PLN), including:	176,782,600.64	185,053,540.93	193,324,481.22	4.47%
bosentan	43,326,004.75	43,326,004.75	43,326,004.75	0.00%
epoprostenol	18,842,085.45	20,935,650.50	23,029,215.55	10.00%
iloprost	28,736,467.08	28,736,467.08	28,736,467.08	0.00%
sildenafil	30,281,666.20	30,281,666.20	30,281,666.20	0.00%
treprostinil	55,596,377.16	61,773,752.40	67,951,127.64	10.00%
Total costs (PLN)	196,321,586.34	204,604,647.92	212,887,709.50	4.05%
Increase				
Costs of the analysed drugs (PLN), including:	135,788,807.37	140,767,793.27	145,746,779.18	3.54%
bosentan	43,033,478.46	43,033,478.46	43,033,478.46	0.00%
epoprostenol	18,842,085.45	20,935,650.50	23,029,215.55	10.00%
iloprost	17,662,789.55	17,662,789.55	17,662,789.55	0.00%
sildenafil	30,281,666.20	30,281,666.20	30,281,666.20	0.00%
treprostinil	25,968,787.70	28,854,208.55	31,739,629.41	10.00%
Total costs (PLN)	135,872,839.75	140,851,825.65	145,830,811.56	3.53%

Table 31.
Effect of incidence rate on the results aggregated for the whole time horizon of the analysis.

Parameter (outcome)	Value of the input parameter -10%	Base value of the input parameter	Value of the input parameter -10%	Relative change
In the "current practice" scenario				
Costs of the analysed drugs (PLN), including:	42,279,576.90	44,285,747.66	46,291,918.42	4.53%
bosentan	279,274.67	292,526.29	305,777.90	4.53%
epoprostenol	0.00	0.00	0.00	n.a.
iloprost	10,572,033.33	11,073,677.53	11,575,321.72	4.53%
sildenafil	0.00	0.00	0.00	n.a.
treprostinil	31,428,268.89	32,919,543.85	34,410,818.80	4.53%
Total costs (PLN)	60,768,469.63	63,752,822.27	66,737,174.91	4.68%
Number of patients with clinical improvement	308.77	326.36	343.95	5.39%
In the new scenario				
Costs of the analysed drugs (PLN), including:	176,896,340.32	185,053,540.93	193,210,741.55	4.41%
bosentan	40,967,540.28	43,326,004.75	45,684,469.22	5.44%
epoprostenol	19,630,551.56	20,935,650.50	22,240,749.44	6.23%
iloprost	27,720,506.12	28,736,467.08	29,752,428.04	3.54%
sildenafil	28,906,172.35	30,281,666.20	31,657,160.06	4.54%
treprostinil	59,671,570.01	61,773,752.40	63,875,934.79	3.40%
Total costs (PLN)	195,464,841.75	204,604,647.92	213,744,454.09	4.47%
Number of patients with clinical improvement	481.84	510.47	539.09	5.61%
Increase				
Costs of the analysed drugs (PLN), including:	134,616,763.42	140,767,793.27	146,918,823.13	4.37%
bosentan	40,688,265.61	43,033,478.46	45,378,691.32	5.45%
epoprostenol	19,630,551.56	20,935,650.50	22,240,749.44	6.23%
iloprost	17,148,472.78	17,662,789.55	18,177,106.33	2.91%
sildenafil	28,906,172.35	30,281,666.20	31,657,160.06	4.54%
treprostinil	28,243,301.12	28,854,208.55	29,465,115.99	2.12%
Total costs (PLN)	134,696,372.12	140,851,825.65	147,007,279.19	4.37%
Number of patients with clinical improvement	173.08	184.11	195.15	5.99%

Table 32.
Effect of frequency of use of medical procedures on the results aggregated for the whole time horizon of the analysis.

Parameter (outcome)	Value of the input parameter -10%	Base value of the input parameter	Value of the input parameter -10%	Relative change
In the "current practice" scenario				
Total costs (PLN)	61,984,006.99	63,752,822.27	65,521,637.55	2.77%
In the new scenario				
Total costs (PLN)	202,827,627.96	204,604,647.92	206,381,667.88	0.87%
Increase				
Total costs (PLN)	140,843,620.98	140,851,825.65	140,860,030.33	0.01%

Table 33.
Effect of price of bosentan on the results aggregated for the whole time horizon of the analysis.

Parameter (outcome)	Value of the input parameter -10%	Base value of the input parameter	Value of the input parameter -10%	Relative change
In the "current practice" scenario				
Costs of the analysed drugs (PLN), including:	44,256,495.03	44,285,747.66	44,315,000.29	0.07%
bosentan	263,273.66	292,526.29	321,778.92	10.00%
Total costs (PLN)	63,723,569.64	63,752,822.27	63,782,074.90	0.05%
In the new scenario				
Costs of the analysed drugs (PLN), including:	180,720,940.46	185,053,540.93	189,386,141.41	2.34%
bosentan	38,993,404.28	43,326,004.75	47,658,605.23	10.00%
Total costs (PLN)	200,272,047.44	204,604,647.92	208,937,248.39	2.12%
Increase				
Costs of the analysed drugs (PLN), including:	136,464,445.43	140,767,793.27	145,071,141.12	3.06%
bosentan	38,730,130.62	43,033,478.46	47,336,826.31	10.00%
Total costs (PLN)	136,548,477.81	140,851,825.65	145,155,173.50	3.06%

Table 34.
Effect of price of epoprostenol on the results aggregated for the whole time horizon of the analysis.

Parameter (outcome)	Value of the input parameter -10%	Base value of the input parameter	Value of the input parameter -10%	Relative change
In the "current practice" scenario				
Costs of the analysed drugs (PLN), including:	44,285,747.66	44,285,747.66	44,285,747.66	0.00%
epoprostenol	0.00	0.00	0.00	n.a.
Total costs (PLN)	63,752,822.27	63,752,822.27	63,752,822.27	0.00%
In the new scenario				
Costs of the analysed drugs (PLN), including:	182,959,975.88	185,053,540.93	187,147,105.98	1.13%
epoprostenol	18,842,085.45	20,935,650.50	23,029,215.55	10.00%
Total costs (PLN)	202,511,082.87	204,604,647.92	206,698,212.97	1.02%
Increase				
Costs of the analysed drugs (PLN), including:	138,674,228.22	140,767,793.27	142,861,358.32	1.49%
epoprostenol	18,842,085.45	20,935,650.50	23,029,215.55	10.00%
Total costs (PLN)	138,758,260.60	140,851,825.65	142,945,390.70	1.49%

Table 35.
Effect of price of iloprost on the results aggregated for the whole time horizon of the analysis.

Parameter (outcome)	Value of the input parameter -10%	Base value of the input parameter	Value of the input parameter -10%	Relative change
In the "current practice" scenario				
Costs of the analysed drugs (PLN), including:	43,178,379.91	44,285,747.66	45,393,115.41	2.50%
iloprost	9,966,309.77	11,073,677.53	12,181,045.28	10.00%
Total costs (PLN)	62,645,454.52	63,752,822.27	64,860,190.02	1.74%
In the new scenario				
Costs of the analysed drugs (PLN), including:	182,179,894.22	185,053,540.93	187,927,187.64	1.55%
iloprost	25,862,820.37	28,736,467.08	31,610,113.79	10.00%
Total costs (PLN)	201,731,001.21	204,604,647.92	207,478,294.63	1.40%
Increase				
Costs of the analysed drugs (PLN), including:	139,001,514.32	140,767,793.27	142,534,072.23	1.25%
iloprost	15,896,510.60	17,662,789.55	19,429,068.51	10.00%
Total costs (PLN)	139,085,546.70	140,851,825.65	142,618,104.61	1.25%

Table 36.
Effect of price of sildenafil on the results aggregated for the whole time horizon of the analysis.

Parameter (outcome)	Value of the input parameter -10%	Base value of the input parameter	Value of the input parameter -10%	Relative change
In the "current practice" scenario				
Costs of the analysed drugs (PLN), including:	44,285,747.66	44,285,747.66	44,285,747.66	0.00%
sildenafil	0.00	0.00	0.00	n.a.
Total costs (PLN)	63,752,822.27	63,752,822.27	63,752,822.27	0.00%
In the new scenario				
Costs of the analysed drugs (PLN), including:	182,025,374.31	185,053,540.93	188,081,707.55	1.64%
sildenafil	27,253,499.58	30,281,666.20	33,309,832.82	10.00%
Total costs (PLN)	201,576,481.30	204,604,647.92	207,632,814.54	1.48%
Increase				
Costs of the analysed drugs (PLN), including:	137,739,626.65	140,767,793.27	143,795,959.89	2.15%
sildenafil	27,253,499.58	30,281,666.20	33,309,832.82	10.00%
Total costs (PLN)	137,823,659.03	140,851,825.65	143,879,992.27	2.15%

Table 37.
Effect of price of treprostinil on the results aggregated for the whole time horizon of the analysis.

Parameter (outcome)	Value of the input parameter -10%	Base value of the input parameter	Value of the input parameter -10%	Relative change
In the "current practice" scenario				
Costs of the analysed drugs (PLN), including:	40,993,793.27	44,285,747.66	47,577,702.04	7.43%
treprostinil	29,627,589.46	32,919,543.85	36,211,498.23	10.00%
Total costs (PLN)	60,460,867.88	63,752,822.27	67,044,776.65	5.16%
In the new scenario				
Costs of the analysed drugs (PLN), including:	178,876,165.69	185,053,540.93	191,230,916.17	3.34%
treprostinil	55,596,377.16	61,773,752.40	67,951,127.64	10.00%
Total costs (PLN)	198,427,272.68	204,604,647.92	210,782,023.16	3.02%
Increase				
Costs of the analysed drugs (PLN), including:	137,882,372.42	140,767,793.27	143,653,214.13	2.05%
treprostinil	25,968,787.70	28,854,208.55	31,739,629.41	10.00%
Total costs (PLN)	137,966,404.80	140,851,825.65	143,737,246.51	2.05%

Table 38.
Effect of frequency of oxygen therapy in patients treated with the new drugs on the results aggregated for the whole time horizon of the analysis.

Parameter (outcome)	Value of the input parameter -10%	Base value of the input parameter	Value of the input parameter -10%	Relative change
In the "current practice" scenario				
Total costs (PLN)	63,701,470.90	63,752,822.27	63,804,173.64	0.08%
In the new scenario				
Total costs (PLN)	204,444,552.48	204,604,647.92	204,764,743.36	0.08%
Increase				
Total costs (PLN)	140,743,081.57	140,851,825.65	140,960,569.72	0.08%

4.5.2 Analysis for full doses

Calculations were repeated assuming full available doses, i.e. the assumed daily dose was 250 mg for bosentan, 60 mg for sildenafil and 7 vials for iloprost. The results indicated that confectioning has a relatively significant effect on the results – both in the "current practice" scenario and in the new scenario total costs increased by ca. 2.5%.

Table 39.
Effect of non-ideal confectioning on the results aggregated for the whole time horizon of the analysis.

Parameter (outcome)	Value in basic analysis	Value for non-ideal confectioning	Relative change
In the "current practice" scenario			
Costs of the analysed drugs (PLN), including:	44,285,747.66	45,815,441.05	3.45%
bosentan	292,526.29	298,622.97	2.08%
epoprostenol	0.00	0.00	n.a.
iloprost	11,073,677.53	12,597,274.23	13.76%
sildenafil	0.00	0.00	n.a.
treprostinil	32,919,543.85	32,919,543.85	0.00%
Total costs (PLN)	63,752,822.27	65,282,515.66	2.40%
In the new scenario			
Costs of the analysed drugs (PLN), including:	185,053,540.93	190,350,015.69	2.86%
bosentan	43,326,004.75	44,228,983.68	2.08%
epoprostenol	20,935,650.50	20,935,650.50	0.00%
iloprost	28,736,467.08	32,690,238.22	13.76%
sildenafil	30,281,666.20	30,721,390.89	1.45%
treprostinil	61,773,752.40	61,773,752.40	0.00%
Total costs (PLN)	204,604,647.92	209,901,122.68	2.59%
Increase			
Costs of the analysed drugs (PLN), including:	140,767,793.27	144,534,574.64	2.68%
bosentan	43,033,478.46	43,930,360.71	2.08%
epoprostenol	20,935,650.50	20,935,650.50	0.00%
iloprost	17,662,789.55	20,092,963.99	13.76%
sildenafil	30,281,666.20	30,721,390.89	1.45%
treprostinil	28,854,208.55	28,854,208.55	0.00%
Total costs (PLN)	140,851,825.65	144,618,607.01	2.67%

5 ANALYSIS OF HEALTH-RELATED EFFECTS

Health-related effects were estimated for the population in the realistic scenario depending on treatment methods applied, i.e. for the "current practice" scenario and the new scenario. The outcome measure was the number of patients reclassified into a lower NYHA class; see section 3.6.

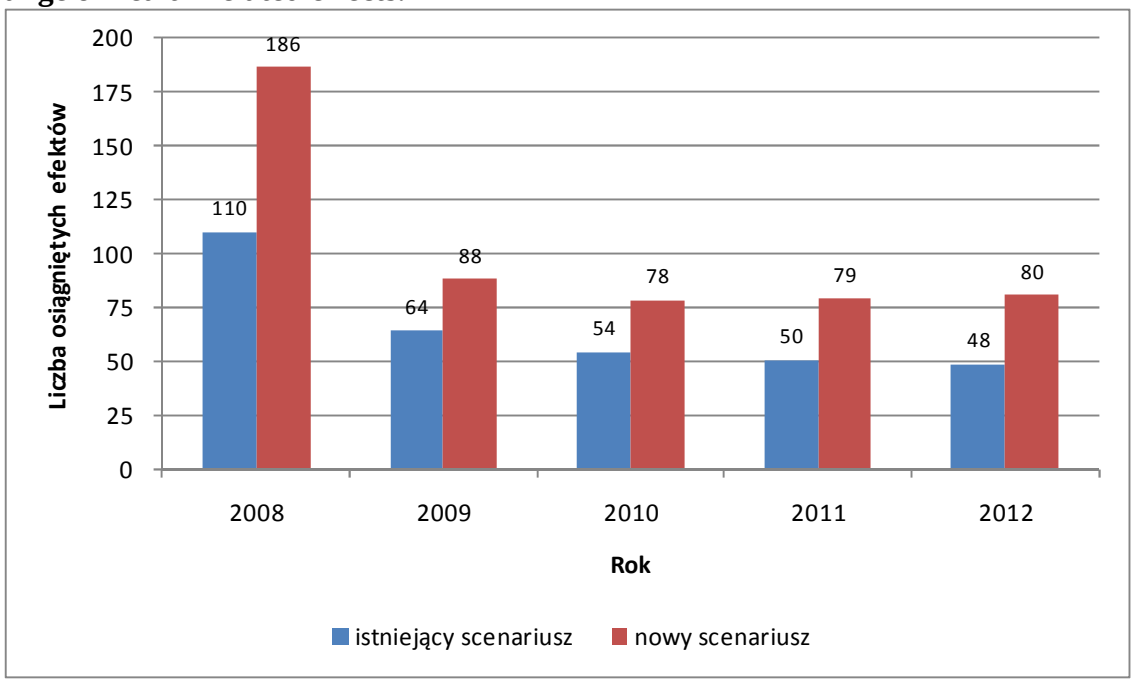
Total number of patients with clinical improvement was 326.36 for the "current practice" scenario and 510.47 for the new scenario, i.e. the number of cases of improvement in the NYHA scale increased by 184.11 (56%).

Detailed data are summarised in the table and the figure below.

Table 40.
Clinical improvement achieved in the "current practice" scenario and the new scenario.

Scenario	Year					Total
	2008	2009	2010	2011	2012	
Patient-months of treatment in both scenarios	2,482	2,826	3,130	3,398	3,636	**15,472**
Number of patients with clinical improvement in the "current practice" scenario	110	64	54	50	48	**326**
Number of patients with clinical improvement in the new scenario	186	88	78	79	80	**510**

Figure 83.
Change of health-related effects.



6 ANALYSIS OF USED RESOURCES

Results of the analysis of resources used for treatment of the population estimated in the realistic scenario are presented below. Basic resource categories were analysed.

In some cases change from the "current practice" scenario to the new scenario had no effect on the results – in these cases only one value of utilization (the same for both scenarios) is presented.

Table 41.
Used medical resources

Category	Year				
	2008	**2009**	**2010**	**2011**	**2012**
hospitalisations (number of cases):					
diagnostics	56	56	56	56	56
treatment of exacerbation	347.73	395.90	438.48	476.12	509.39
periodic control	304.79	347.01	384.33	417.32	446.49
oxygen therapy (patient-months)	868.21	988.47	1,094.78	1,188.76	1,271.84
atrial septostomy	9.93	11.30	12.52	13.59	14.54
type I pulmonary outpatient consultation	8.69	9.89	10.95	11.89	12.73
type II pulmonary outpatient consultation	17.62	20.06	22.22	24.13	25.81
type III pulmonary outpatient consultation	225.61	256.87	284.49	308.91	330.50
type I cardiology outpatient consultation	55.10	62.73	69.48	75.44	80.72
type II cardiology outpatient consultation	514.77	586.07	649.11	704.83	754.09
type III cardiology outpatient consultation	388.43	442.24	489.80	531.85	569.02
sepsis (new scenario only)	1.03	0.80	0.70	0.67	0.65
pneumothorax (new scenario only)	1.03	0.80	0.70	0.67	0.65
uncomplicated pneumonia:					
current practice	1.55	1.76	1.95	2.12	2.27
new scenario	5.99	7.07	8.03	8.91	9.72
change	4.45	5.31	6.08	6.8	7.45
drugs:					
bosentan (125 mg tablets):					
current practice	192.80	219.51	243.12	263.99	282.44
new scenario	27,287.77	32,006.08	36,100.67	39,707.69	42,906.32
change	27,094.96	31,786.57	35,857.55	39,443.70	42,623.88
epoprostenol (mg):					
current practice	0.00	0.00	0.00	0.00	0.00
new scenario	6,720.85	5,295.05	4,774.35	4,602.73	4,562.45
change	6,720.85	5,295.05	4,774.35	4,602.73	4,562.45
iloprost (vials):					
current practice	24,175.97	27,524.77	30,485.10	33,102.04	35,415.41

new scenario	57,449.42	68,383.41	78,710.43	88,570.71	97,964.78
change	33,273.45	40,858.65	48,225.33	55,468.68	62,549.37
sildenafil (20 mg tablets):					
current practice	0.00	0.00	0.00	0.00	0.00
new scenario	135,497.28	164,959.58	190,911.00	214,004.05	234,624.36
change	135,497.28	164,959.58	190,911.00	214,004.05	234,624.36
treprostinil (mg):					
current practice	11,581.11	13,185.30	14,603.40	15,857.00	16,965.18
new scenario	19,930.53	23,676.38	27,228.00	30,660.43	33,973.41
change	8,349.42	10,491.08	12,624.61	14,803.43	17,008.23

7 DISCUSSION

In this report results of the analysis concerning the effect of reimbursement of bosentan, epoprostenol, iloprost, sildenafil and treprostinil on the payer's budget in different scenarios (realistic, pessimistic, optimistic and prevalence-based) are presented. These scenarios differ with respect to one input parameter: incidence rate of PAH. This results in nearly proportional change of absolute outcome values (i.e. costs, total number of patients, the number of patients with clinical improvement) – the change is not truly proportional due to the fact that the analysis includes costs of initial diagnostics (incurred only for the newly diagnosed patients).

Below the most important conclusions are presented; these are true for all scenarios described above.

Undoubtedly the largest cost category are costs of the analysed drugs – these generate nearly 100% of all drug costs, ca. 72% of costs in the "current practice" scenario and as much as ca. 91% of costs in the new scenario. Introduction of the new scenario will result in more equal distribution of costs between the five analysed drugs. In the "current practice" scenario two drugs generate more than 95% of costs of the analysed drugs: treprostinil (ca. 71%) and iloprost (ca. 24%); in the new scenario these drugs will generate 33.06% and 15.38%, respectively, while bosentan, epoprostenol and sildenafil will generate 23.19%, 11.21% and 16.21%, respectively.

The change from current practice to the new scenario of treatment will result in increase of mean monthly cost from ca. 4,100 PLN to ca. 13,200 PLN.

At the same time, the number of patients, whose condition improves (according to the NYHA scale), will increase. For current practice this number is 326 (in case of the population size estimated according to the realistic scenario), while for the new scenario – 510, which means increase by ca. 56%.

Incidence rate has the greatest effect on accuracy of estimation of costs and savings. Other elements of significant effect on total costs are: confectioning of the drugs and costs of the analysed drugs, in particular bosentan, sildenafil and treprostinil. The effect of these prices on results of the analysis is similar to that of mean patient's body weight.

8 LIMITATIONS OF THE ANALYSIS

The most important limitation of this analysis is unavailability of epidemiological data concerning prevalence and incidence rate of pulmonary arterial hypertension in Poland. A survey

among the clinicians dealing with this disease filled up this gap to a certain degree, but did not make it possible to obtain precise data concerning effectiveness of specific methods of treatment used in Poland, in particular with respect to probability of death and necessity of change to a different treatment method or combination therapy. On the other hand, data obtained from the systematic review indicate lack of statistically significant differences between the analysed drugs with respect to mortality; however, these data do not concern combination therapies. For this reason assumptions described in section 3 were made.

Specificity of present Polish market is another aspect of the problem. Since some of the analysed drugs (Revatio®) are not registered in Poland, other preparations containing the same active agent (Viagra®, Maxigra®) are used. Some patients receive treatment during and after completion of clinical trials. Costs are thus incurred by pharmaceutical companies with no effect on the payer's budget. It is difficult to predict the progress of events (continuation, popularity and structure of clinical trials) if novel drugs are not introduced; it is therefore also difficult to assess credibly future costs in the "current practice" scenario, i.e. the reference scenario for any budget impact analysis.

At present estimation of frequency of use of specific drugs after introduction of their reimbursement is not possible; thus, it is not possible to assess incurred costs and their structure. Extrapolation of present structure does not seem justified as this structure results from clinical trials being conducted and availability of drugs containing the same active agent. For this reason it was decided to base this analysis on the clinicians' opinion. It can be argued that at least in the initial years after the drugs reimbursement the survey results based on experts' opinion should well approximate the real drug use pattern. In the subsequent years the more experience the clinicians will collect the more likely the drug usage pattern will change. There is no reliable way to estimate this changes.

This analysis is also limited by lack of credible clinical evidence concerning effect of the analysed drugs on reduction of use of other procedures; calculation of potential savings is therefore not possible. Another limitation is the potential off-label usage of analysed drugs (NYHA class misclassification) and dose escalation. However these impact would be difficult to quantify and should be of minor importance assuming appropriate drug use monitoring.

Most of the problems listed above may be solved by the registry of pulmonary arterial hypertension which will be kept in years 2007-2008 within the POLKARD program. Therefore it seems justified to recommend repetition of this analysis after sufficient information has been accumulated, e.g. in the second half of 2009.

9 SUMMARY

This report presents results of budget impact analysis concerning reimbursement of the following drugs: bosentan (Tracleer), epoprostenol (Flolan), iloprost (Ventavis), sildenafil (Revatio) and treprostinil (Remodulin), used in treatment of NYHA III/IV pulmonary arterial hypertension in Poland.

For current practice, expected annual cost in a time horizon of five years (in subsequent years) may be estimated at: 10.3, 11.67, 12.89, 13.97 and 14.92 million PLN; registration and reimbursement of the above drugs would result in increase of these costs to: 32.95, 36.8, 40.94, 45.02 and 48.9 million PLN, i.e. by 22.65, 25.12, 28.05, 31.05 and 33.98 million PLN, respectively.

Main cost category in treatment of PAH in the "current practice" scenario are costs of used drugs, comprising 72.26% of total costs in a time horizon of five years. In current practice nearly all these costs are generated by direct import of two drugs: treprostinil (71.46% of drug

costs) and iloprost (24.04% of drug costs). Registration and reimbursement of the analysed drugs would still increase drug costs to 91.31% of total costs. However, distribution of costs associated with use of specific drugs would be more equal: bosentan (23.19%), epoprostenol (11.21%), iloprost (15.38%), sildenafil (16.21%), treprostinil (33.06%).

Registration of the analysed drugs will practically have no effect on hospitalisation (the change will be due to changed frequency of adverse events) or outpatient service costs.

Alternative scenarios, differing with respect to the target population size, have been considered. Changes in population size result in nearly proportional changes in costs. In two scenarios – the pessimistic and the optimistic one – changes of costs due to reimbursement of the analysed drugs in a time horizon of 5 years range from 21.87 to 23.52 million PLN in the first year and from 28.72 to 39.91 million PLN in the last year, respectively. The analysis included also a prevalence-based scenario, in which the costs incurred by the payer increase by 26.5 million PLN in the first year and 60.04 million PLN in the fifth year. It should be stressed that the number of patients remaining at present under care of specialist centres is significantly lower than the number assumed in that scenario.

Sensitivity analysis demonstrated that the following input parameters have the most significant effect on total costs and their increase due to registration of the analysed drugs: assumed incidence rate (taken into account in different scenarios), confectioning of the drugs, costs of the analysed drugs, in particular bosentan, sildenafil and iloprost, and the patient's average body weight.

Use of non-drug medical procedures, including oxygen therapy (potentially less often used by patients treated with any of the analysed drugs), has an insignificant effect on results of the analysis.

On the other hand it should be noted that registration of the analysed drugs will result in increased number of patients with clinical improvement, i.e. reclassification into a lower NYHA class. Change from current practice to the new scenario will result in increase of this number by ca. 56% (from 326 to 510) within a time horizon of 5 years.

The most important limitations of this analysis are: lack of epidemiological data concerning prevalence and incidence rates for PAH in Poland, present specificity of the Polish market (i.e. use of generics instead of non-registered drugs, treatment provided within clinical trials) making it difficult to analyse costs of current practice and predict their evolution in the new scenario and lack of credible clinical evidence concerning effect of the analysed drugs on reduction of use of other procedures and therefore potential savings.

Many of these problems may be solved by the registry of pulmonary arterial hypertension which will be kept in years 2007-2008 within the POLKARD program. Therefore it seems justified to recommend repetition of this analysis after sufficient information has been accumulated.

APPENDIX – WORKBOOK DESCRIPTION

A part of this report is an MS Excel 2007 workbook (filename: TNP_BI.xlsm). This workbook contains worksheets available (containing modifiable input parameters and results) and unavailable (containing selected parameters that should not be modified) for the user as well as calculation sheets.

In general, cells that may be modified by the user are distinguished by blue background. The user may also modify the values of the "combi" cells. The remaining cells should not be modified by the user.

The following worksheets are available for the user:

- daneKliniczne (clinical data) – this worksheet contains epidemiological information: prevalence rate at the beginning of the analysed period, incidence rate during this period and other epidemiological issues related to change of current practice;
- cenyProcedur (procedure prices) – this worksheet contains information concerning medical procedures taken into account in the model and their prices;
- cenyLeków (drug prices) – this worksheet contains information concerning drugs taken into account in the model, their prices and dosage;
- metodaLeczenia… (treatment method …) – a range of worksheets defining treatment methods used in different regimens of management:
  - metodaLeczenia1 (treatment method 1) – defines current practice;
  - metodaLeczenia2 (treatment method 2) – defines the method of management in the new scenario for those patients, who were already treated with at least one of the analysed drugs at the beginning of the analysed period;
  - metodaLeczenia3-10 (treatment method 3-10) – define methods of treatment for different states in the new scenario;
  - metodaLeczenia11-12 (treatment method 11 and 12) – unused worksheets;
- schematLeczenia() (treatment protocol()) – defines probabilities of death for treatment methods not included in the Markov model (defined in "metodaLeczenia1" and "metodaLeczenia2");
- schematLeczenia1 (treatment protocol 1) – this worksheet defines parameters of management in treatment protocol based on the Markov model in the new scenario;
- wyniki (results) – this worksheet contains results;
- wykresy (figures) – this worksheet contains results presented in figures.

The following worksheets are hidden from the user:

- listyDanych (data lists) – a technical worksheet containing description of the "combi" cells
- efektyTerapeutycznePar – this worksheet is used for parametrisation of frequency of clinical improvement achieved with specific treatment methods;
- dzialNiepPar – an auxiliary worksheet for calculation of frequency of adverse events;
- daneZAnkiet (survey data) – this worksheet connects epidemiological data (body weight, percentage of adults) with survey data concerning calculation of drug doses;
- populacjaDynamika (population change) – this worksheet is used for calculation of the number of patients included in the treated group at subsequent stages, taking into account different subpopulations in considered scenarios;

- metodyLeczenia-kosztyProcedur and metodyLeczenia-kosztyLekow (treatment methods – procedure costs and drug costs) – these worksheets are used for calculation of costs of procedures and drugs, respectively, at subsequent stages for treatment methods defined in appropriate worksheets (metodaLeczenia…);
- dynamikaSchemat0 and dynamikaSchemat1 (change protocol 0 and 1) – these worksheets are used for calculation of frequency of events at subsequent stages, taking into account survival, treatment methods used and clinical improvement achieved.

APPENDIX – PEER REVIEW

Final review of the report (17.12.2008):

"Use of bosentan, epoprostenol, iloprost, sildenafil and treprostinil in treatment of pulmonary arterial hypertension in Poland. Budget impact analysis"

.Reviewers: Dr Yen-Fu Chen and Dr David Moore

This budget impact assessment is well undertaken. It has adopted methods in accordance with the recommendations specified in the Polish and international guidelines. Data used in the analysis were appropriately drawn from the accompanying systematic review of randomised controlled trials and survey of all Polish centres treating patients with pulmonary arterial hypertension. The response from authors to our comments is adequate and major caveats in model assumptions in relation to paucity of data have been highlighted.

The authors should be congratulated for the completeness of the report.

GLOSSARY

analysed drugs – bosentan (Tracleer), epoprostenol (Flolan), iloprost (Ventavis), sildenafil (Revatio), treprostinil (Remodulin)

"current practice" scenario – scenario reflecting current practice, including treatment methods used at present (according to the survey results – structure of drugs and procedures generating costs for the payer)

new scenario – expected situation after reimbursement of the analysed drugs has been introduced; its definition is complex as it assumes different treatment of two subpopulations changing with time: the patients already treated with the analysed drugs at the beginning of the analysed period (treatment is continued in this subpopulation) and those not treated previously with these drugs (included in the treated group).

remaining drugs – standard treatment of PAH, i.e. anticoagulants, calcium channel blockers, diuretics, and digitalis glycosides

price volume agreement – an agreement between the drug manufacturer and the payer limiting annual costs incurred by the payer for treatment of one patient to the sum agreed; costs exceeding this sum are covered by the manufacturer

optimistic scenario – sub-analysis, in which upper limit of estimation of the target population was assumed, i.e. upper limits of 95% confidence intervals for incidence rates and percentages of patients in NYHA class III/IV were taken into account

pessimistic scenario – sub-analysis, in which lower limit of estimation of the target population was assumed, i.e. lower limits of 95% confidence intervals for incidence rates and percentages of patients in NYHA class III/IV were taken into account

realistic scenario – sub-analysis, in which target population size was estimated in the most credible way, i.e. mean values for incidence rates and percentages of patients in NYHA class III/IV were taken into account

treatment regimen – a method of treatment within the new scenario using the analysed drugs, including structure of the first-line drugs as well as probabilities of transition between them and introduction of combination therapies

combination therapy – a therapy, in which at least two of the analysed drugs (from different therapeutic groups) are used at the same time

ABBREVIATIONS AND ACRONYMS

AHTAPol – Agency for Health Technology Assessment in Poland

n.a. – not applicable

n.d. – no data

PVA – price volume agreement

REFERENCES

1. Aldashev i wsp. Phosphodiesterase type 5 and high altitude pulmonary hypertension. Thorax. 2005; 60: 683-687
2. Appelbaum L.,Yigla M., Bendayan D. et al. Primary pulmonary hypertension in Israel: a national survey. Chest 2001; 119: 1801-1806
3. Badesch DB, Tapson VF, McGoon MD i wsp. Continuous intravenous epoprostenol for pulmonary hypertension due to the scleroderma spectrum of disease. A randomized, controlled trial; Ann Intern Med 2000; 132: 425-434
4. Barst RJ, Langleben D, Badesch D i wsp. Treatment of pulmonary arterial hypertension with the selective endothelin-a receptor antagonist sitaxsentan; J Am Coll Cardiol 2006; 47: 2049-2056
5. Barst RJ, Rubin LJ, Long WA i wsp. 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: 296-302
6. Becla L, Osińska B, Malottki K. Bosentan, epoprostenol, iloprost, sildenafil i treprostinil w leczeniu tętniczego nadciśnienia płucnego. Analiza efektywności klinicznej., Agencja Oceny Technologii Medycznych, Warszawa 2007.
7. Channick RN, Simonneau G, Sitbon O i wsp. Effects of the dual endothelin receptor antagonist bosentan in patients with pulmonary hypertension: a randomised placebo-controlled study; Lancet 2001; 358: 1119-1123
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. Galie N, Beghetti M, Gatzoulis MA i wsp. Bosentan therapy in patients with Eisenmenger syndrome: a multicenter, double-blind, randomized, placebo-controlled study; Circulation 2006; 114: 48-54
10. Galie N, Ghofrani HA, Torbicki A i wsp. Sildenafil use in pulmonary arterial hypertension (super) study group. Sildenafil citrate therapy for pulmonary arterial hypertension; N Engl J Med. 2005; 353: 2148-57
11. Galie N., Torbicki A., Barst R. i wsp. 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. Eur Heart J. 2004; 25: 2243-2278
12. Grünig E., Dehnert Ch., Mereles D. i wsp. Enhanced Hypoxic Pulmonary Vasoconstriction in Families of Adults or Children With Idiopathic Pulmonary Arterial Hypertension. Chest 2005; 128: 630S-633S
13. Grupa robocza ds. opracowania wytycznych przeprowadzania oceny technologii medycznych. Wytyczne przeprowadzania Oceny Technologii Medycznych (HTA), Kraków-Warszawa, 2007
14. Hermanowski T, Niewada M, Kowalik E, Jakubczyk M. Leczenie tętniczego nadciśnienia płucnego w Polsce. Wyniki badania ankietowego. 2007
15. Humbert M, Sitbon O, Chaouat A i wsp. Pulmonary Arterial Hypertension in France. Results from a National Registry, Am J Respir Crit. Care Med 2006; 173: 1023-1030
16. Hyduk A, Croft JB, Ayala C i wsp. Pulmonary hypertension surveillance--United States, 1980-2002. MMWR Surveill Summ. 2005; 54:1-28

17. Klepetko W, Mayer E, Sandoval J i wsp. Interventional and surgical modalities of treatment for pulmonary arterial hypertension. J Am Coll Cardiol 2004; 43: 73S-80S
18. Kuriyama T. Epidemiology of primary pulmonary hypertension in Japan. Nippon Rinsho 2001; 59: 1047-52
19. Leki po Dyplomie 1/2007, Warszawa, Medical Tribune Polska sp. z o.o.
20. Mandecki T. Kardiologia. PZWL, Warszawa, 2000
21. Meyer i wsp. Peripheral airway obstruction in primary pulmonary hypertension. Thorax. 2002; 57: 473-476
22. Ministerstwo Zdrowia, Rozstrzygnięcie konkursu na wybór realizatora programu pn. „Narodowego programu profilaktyki i leczenia chorób układu sercowo-naczyniowego na lata 2006-2008, http://www.mz.gov.pl/wwwmz/index?mr=m241614181&ms=416&ml=pl&mi=418&mx=0&mt=&my=153&ma=08649, na dzień 2007.08.25;
23. Narodowy Fundusz Zdrowia, http://www.nfz.gov.pl/new/art/2834/SZP_projekt.zip, na dzień 2007.09.29;
24. Olschewski H, Simonneau G, Galie N i wsp. Inhaled iloprost for severe pulmonary hypertension. N Engl J Med 2002; 347: 322-329
25. Podolec P., Gackowski A., Kaźnica-Wiatr M., Żmudka K. „Nadciśnienie płucne" W: W. Tracz, P. Podolec, P. Hoffman (red.) „Echokardiografia praktyczna" Tom II, Medycyna Praktyczna, Kraków, 2005, 357-376
26. Rubin LJ, Badesch DB, Barst RJ i wsp. Bosentan therapy for pulmonary arterial hypertension. N Engl J Med 2002; 346: 896-903
27. Rubin LJ, Mendoza J, Hood M i wsp. Treatment of primary pulmonary hypertension with continuous intravenous prostacyclin (epoprostenol) results of a randomized trial; Ann Intern Med 1990; 112: 485-491
28. Sastry BKS, Narasimhan C, Reddy K, Raju S. Clinical efficacy of sildenafil in primary pulmonary hypertension; JACC 2004; 43: 1149–1153
29. Simonneau G, Barst R, Galie N i wsp. Continuous subcutaneous infusion of treprostinil, a prostacyclin analogue, in patients with pulmonary arterial hypertension; Am J Respir Crit. Care Med 2002; 165: 800–804
30. Simonneau G., Galie N., Rubin L.J. et al. Clinical clasification of pulmonary hypertension. J Am Col Cardiol 2004; 43: 55-125.
31. Torbicki A., Kurzyna M. "Nadciśnienie płucne" W: A. Szczeklik (red.) "Choroby wewnętrzne" tom I, Medycyna Praktyczna, Kraków, 2005, 351-360
32. Wang S. Heart-lung transplantation for severe pulmonary hypertension with severe heart failure: presentation of four cases. Transplantation Proceedings 1003; 35: 450-452
33. Wykaz Leków Refundowanych numer I/2007, Piotrków Trybunalski, JWC, 2007;

INDEX OF TABLES

INDEX OF FIGURES