Pulmonary hypertension (PH) is a rare multi-factorial disorder with a severe course. Despite significant progress in diagnosis and therapy, PH remains a disease with a high mortality rate. Current pharmacotherapy improves quality of life and prolongs longevity, but does not completely reverse pathological and haemodynamic changes. Preclinical trials are needed, including those on animal models; however, no ideal animal model fully reflects the human form of PH. However, the choice of animal model can influence the findings, and hence the drugs used as candidates for further evaluation in later clinical studies.

The aim of the study was to evaluate several variables which can determine the development and severity of PH in animal models, such as method of PH induction (type, dosage, route of administration of inductor), induction time and animal species. The most popular animal models of PH were included: chronic hypoxia (CH), monocrotaline (MCT) and their modifications: the Sugen 5416 model, combined monocrotaline and chronic hypoxia (MCT+CH), left pneumonectomy with monocrotaline (LP+MCT), and chronic hypoxia with hypercapnia (CH+HC). The most commonly-examined parameters in preclinical trials were studied: mean/systolic pressure in right ventricle (RVP/RVSP), mean pulmonary arterial pressure (mPAP), right ventricle hypertrophy (RVH) and wall thickness of pulmonary arteries (WT). It also compares the efficacy of potential agents tested in animal PH models classified for publication. Three hypotheses were formulated with regard to PH model: the classification of the animal models, the degree of development and severity of induced hemodynamic and hypertrophic changes, and the effectiveness of potential drugs.

A systemic review was performed of a number of experimental studies of PH. The search corpus comprised selected articles from Medline and ISI Web of Science, from 1 January 1991 to 31 December 2015. In total, 290 articles were included. In order to estimate the overall effect size, single-factor and multifactorial analyses were performed, such as meta-analysis with evaluation of heterogeneity, sensitivity, cumulative analysis, subgroup analysis, meta-regression and publication bias. Animal models of PH vary with regard to PH development and severity. The type of induction method and time to develop PH appear to most significantly determine the worsening of disease. The effect size was expressed as difference in means (D) between vehicle and treated animal groups. Most preclinical experiments were based on classic models, i.e. chronic hypoxia and monocrotaline, which provoke a poorer response than newer modifications. Longer PH induction periods significantly worsen the studied parameters; however, monocrotaline dose and inter-species differences appear to have a less significant impact on elevation in hemodynamic and pathological parameters. Regarding inter-species differences, less pronounced right ventricle systolic pressure, right ventricle hypertrophy and

pulmonary artery wall thickness were observed in mice than rats in a chronic hypoxia model. Regarding the association between choice of anaesthetic agent and haemodynamic parameters, the most commonly-used agents were pentobarbital sodium, isoflurane, urethane, chloral hydrate and combined xylazine with ketamine. Further analysis found isoflurane to induce the greatest worsening in right ventricle systolic pressure and mean pulmonary arterial pressure.

A total number of 206 substances, classified into 26 groups, were analysed [168]. The efficacy of particular agents was evaluated and expressed as difference in means (D) and response ratio (R). An R-value of 1.0 indicates that one agent was able to completely reverse the altered PH parameters. The results were dependent on the effect size of D or R. The response ratio decreased publication bias and study heterogeneity. The results also demonstrated smaller scatter for the effect measure (R) than the difference of mean values (D). Therefore, the response ratio (R) was used for further detailed calculations.

The agents were assessed as potentially effective drugs according to preventive or therapeutic efficacy. The substances used in preventive models were found to improve PH parameters more significantly than those in therapeutic regimens. The obtained results can demonstrate a greater potential of the tested substances used in preventive models to improve both hemodynamic and hypertrophic parameters. The following 10 most frequently examined groups were chosen for more detailed analysis: anti-inflammatories, anti-remodelling agents, ATP-sensitive potassium channel openers, estrogen derivatives/receptor agonists, HMG-CoA reductase inhibitors (statins), plant-derived compounds, RAAS regulators, Rho/ROCK inhibitors, Ser-Thr protein/tyrosine kinase inhibitors and serotonin pathway agents. The agents that demonstrated the greatest improvements on haemodynamic and pathologic parameters were iptakalim (an ATP-sensitive potassium channel opener), fasudil (a Rho/ROCK inhibitor), XNT and NSC-354317 (novel ACE2 activators, anti-inflammatories), n-3 polyunsaturated fatty acids and NF-κB inhibitors. These may be considered as potential candidates for further clinical trials.

Animal models of PH differ greatly, and these differences can result in a weaker or stronger response, manifested as poorer haemodynamic or pathological parameters. The selection of an appropriate test model can determine the success of a preclinical experiment, and the proper evaluation of a new agent. It can also increase the chances that the obtained results will be repeated in clinical trials. Stricter guidelines are needed to define the rules and conditions for experimental trials of PH based on animal models.