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TREATMENT OF HYPERTENSION IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

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Hypertension and COPD

Hypertension is one of the most prevalent non-communicable diseases in the world, affecting 30–40% of the adult population. It is frequently associated with other diseases (e.g. diabetes mellitus, chronic kidney diseases, bronchial asthma, and chronic obstructive pulmonary disease – COPD) which may influence the selection of proper anti-hypertensive drugs. According to WHO data, 250 million people suffer from COPD worldwide, accounting for 5% of total mortality [1, 2]. COPD is a slowly progressing disease characterised by airflow obstruction within the airways and/or pulmonary parenchyma. Symptoms and complications may include shortness of breath, poor exercise tolerance, chronic productive or non-productive cough, wheezing, respiratory failure, and cor pulmonale. Most patients suffering from these symptoms are not aware of their disease or their treatment is insufficient. The most common co-morbid diseases in COPD are hypertension (28%), diabetes mellitus (14%), and ischaemic heart disease (10%) [2, 3]. According to international data, it is estimated that the coincidence of the two diseases may affect 2.5% of the adult population. COPD is regarded as an independent risk for cardiovascular diseases. Among patients with COPD, the prevalence of heart failure is 4×, coronary heart disease is 2×, angina pectoris and myocardial infarction are 2.5×, peripheral artery disease and arrhythmias 2.4×, and stroke is 1.5× higher than in the general population [4]. Furthermore, there is a pathophysiological link between COPD and hypertension, as hypoxia may enhance the production of free radicals and endothelial dysfunction, leading to hypertension and its cardiovascular complications. Separate guidelines are available for the diagnosis and treatment of these diseases [5, 6]. However, these issues are not discussed jointly in these international guidelines. The treatment of COPD includes inhaled therapies (anticholinergic agents, long-acting β-2 adrenoceptor agonists, and corticosteroids), pulmonary rehabilitation programmes, and the use of supplemental oxygen [6]. These drugs may affect the cardiovascular system (heart rate, blood pressure) and may increase the incidence of cardiovascular events (angina pectoris, myocardial infarction) [6, 7, 8, 9]. The goals of antihypertensive therapy are to normalise blood pressure, blood pressure, prevent cardiovascular morbidity, decrease mortality, extend lifespan and improve the quality of life for patients [5]. Because some anti-hypertensive drugs can affect airway function, the treatment of hypertension in patients with airway dysfunction is complex [7].

Treatment of hypertension in patients with COPD

Non-pharmacological treatment must include smoking cessation to prevent further deterioration of airway function and to decrease cardiovascular morbidity and mortality. Moderate physical exercise in patients with hypertension and COPD with pulmonary rehabilitation programmes provides improvements in respiratory symptoms, quality of life, and exercise endurance (6-minute walk test) [6]. Pharmacological therapy of hypertension involves, in most patients, drug combinations. For the selection of antihypertensive drugs the effects of these drugs on pulmonary function and the possible interatcions with agents used for COPD should be considered. There is insufficient RCT evidence to determine which drug is most effective. It important to know that there have been meta-analyses showing that cardio-selective β-blockers reduce cardiovascular morbidity and mortality in these patients.

Diuretics (DIU). Results of randomised, controlled clinical trials for diuretics in COPD are not available, but there are some observational studies and case reports. In principle, diuretics may be beneficial for the elimination of fluid retention developing in heart failure that frequently complicates COPD and also hypertension. Diuretics may inhibit pulmonary vascular remodelling. Acetazolamide has been found to increase ventilation in COPD. However, DIU may decrease the plasma level of potassium, and this effect may be added to the hypokalaemic effects of steroids and β-2 adrenoceptor agonists, drugs that are frequently used in COPD. Thiazides may also worsen CO2 retention, metabolic alkalosis-related hypoxia in hypoventilation patients, increase haematocrit and deteriorate mucus secretion in bronchi. Therefore DIU, in general, are not recommended for universal use in hypertensive patients with COPD [10, 13, 14]. In a 28 week study of hypertensive patients with COPD, who have been on standardised bronchodilator therapy, indapamide decreased blood pressure by 48/30 mm Hg (mean value) and respiratory function improved [15]. An other study showed that the combination therapy containing a thiazide diuretic was associated with a significantly lower risk of hospitalization for congestive heart failure [16]. Furosemide may be used in hypervolemic patients, and also in those having Grade III or IV chronic kidney diseases (eGFR <30 mL/min/m2) [17]. No results of studies using potassium sparing diuretics (triamteren, amiloride) or mineralocorticoid receptor antagonists (spironolactone, eplerenone) are available, however, potential benefit can be presumed by using these drugs because of antagonizing the hypokalemia caused by thiazides.

β-adrenoceptor antagonists (BBL). The worsening or precipitation of asthma by non-selective β-blockers is well recognised, but the "cardio-selective" β-1-adrenoceptor blockers and those exerting mild β-2-agonist activity (e.g. celiprolol), or those which increase the production of nitric oxide (NO) (nebivolol), affect airway function to either a much lesser extent, or not at all. Therapy with selective β-1 blockers decreased total as well as cardiovascular mortality. They may also decrease the incidence of acute exacerbations of airways obstruction [18 19, 20, 21]. In a recent trial acute decompensated HF patients with COPD the mortality rate was higher in patients without β-blockers compared with those taking β-blockers. The use of β-blockers was the only factor significantly correlated with the mortality rate. These findings support the recommendations to use β-1 selective blockers in HF patients with COPD [22]. Other studies showed that carvedilol a nonselective β and α adrenoceptor blocker was well tolerated in patients with COPD with no reversible airway obstruction [23]. Therefore, if needed in hypertensive patients with COPD, with coronary

heart disease, or with congestive heart failure, the highly selective β-1 blockers can be recommended for hypertension. β-blockers are also associated with a significant reduction in COPD exacerbations regardless of severity of airflow obstruction [24]. Patients with COPD discharged with β-blockers after an MI had a lower all-cause mortality as compared to patients not prescribed β-blockers [25]. Non-selective BBL decreases while cardio-selective BBL improves the bronchodilatory effects of β-2 mimetics due to the β-2 receptor up-regulation [26].

Calcium channel blockers (CCB). CCBs induce smooth muscle relaxation in bronchi and inhibit the decrease in forced expiratory volume (FEV1). They may potentiate the β-2 receptor mediated bronchodilation and decrease non-specific bronchial reactivity; therefore, use of CCBs may be beneficial in hypertensive patients with COPD. These drugs usually do not exert severe side effects on the airways. However, it is important to note that CCBs may worsen the normal ratio of perfusion/ventilation, and consequently increase hypoxia; therefore, oxygen saturation monitoring is recommended [10, 11, 14].

Angiotensin-converting enzyme inhibitors (ACEI). It has been known that ACEIs may cause coughs and exacerbate, or even induce, asthma. However, ACEIs have been proven to decrease cardiovascular morbidity and mortality of hypertensive patients as well as those with coronary heart disease and heart failure. They also decrease COPD-induced hospitalisation of patients. ACEIs may reduce the hypokalaemic effects of β-2 receptor agonists [27, 28], agents that are frequently used in COPD. The incidence of ACEI-related cough was not more frequent in patients with chronic bronchitis than in other populations [28]. However, ACEIs may worsen the clinical stage in some patients with asthma. The increased availability of bradykinin (which increases cough) and substance P (which causes bronchoconstriction) probably contribute to this unwanted effect [13]. In trials, ACEI-related side effects were rare, and the tolerability of drugs was good.

Angiotensin receptor blockers (ARB). An important advantage of ARBs against ACEIs is that they practically do not cause cough, and ARB-related angioneurotic oedema is very rare. Patients with a history of ACEI-induced cough tolerate ARB as well as they do a placebo [29]. However, in one study, losartan increased cough probably because of the inhibition of the endogenous release of nitric oxide [8]. However, in another study, losartan inhibited the metacholine-induced bronchospasm, and consequently decreased the reduction of FEV1 [30]. Use of ARBs is useful because the hypoxia increases the activity of the RAAS [10, 14, 27].

α-1 Adrenoceptor antagonists. These drugs do not affect airway resistance. Airway function in COPD was not changed by these drugs; therefore they may be used in hypertensive patients with COPD [10]. Prazosin was found to partially inhibit cold air-induced broncho-constriction. Terazosin was well tolerated in patients with hypertension and COPD [11]. Doxazosin was also well tolerated and did not exacerbate preexisting airflow limitation [12].

α- + β-adrenoceptor antagonists. Labetalol does not change airway resistance, but carvedilol may increase bronchial spasm. However, in patients with heart failure and COPD, carvedilol did not worsen airway function and was well tolerated [23].

5-Hydroxytryptamine modifiers. Urapidil, in saddition to 5-HT1A receptor stimulation, is an α-adrenoceptor blocker. Both effects cause broncho-dilation; therefore, urapidil may also be for hypertensive patients with COPD [10].

α-2 Adrenoceptor amd imidazoline I-1 receptor agonists. The α-2 adrenoceptor agonists may potentiate the histamine-induced bronchial spasm; therefore, they cannot be suggested for use on hypertensive patients with COPD [10]. There are no data for the use of the imidazoline I-1-receptor agonists (rilmenidine, moxonidine). Hoewer, by the decrease in central sympathetic tone and reduction of the activity of RAAS, these drugs might be beneficial.

Conclusions. In patients with hypertension and COPD, it is essential to include non-pharmacological measures and it is absolutely crucial to stop smoking. Individual patients may not respond in the same way to pharmacological treatment. CCBs, ARBs or ACEIs, or CCB/RAS blocker combinations, as the initial drugs of choice, are recommended. If the response is poor, thiazides or thiazide-like diuretics, highly β-1 selective adrenoceptor blocking agents, especially those with ancillary properties (e.g. nebivolol, celiprolol as well as carvedilol), or α-1 adrenoceptor antagonists can be considered. Consequently, it is important to adopt a flexible approach.

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