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The possibilities of using beta-blocker bisoprolol in patients with stable angina with concomitant bronchial asthma

Aim	To compare efficacy and safety of treatments with the calcium antagonist (CA) verapamil, the cardioselective β-blocker (BB) bisoprolol, and a combination therapy with bisoprolol and amlodipine in patients with stable angina (SA) with concurrent mild and moderate, persistent bronchial asthma (BA).
Material and methods	This open, prospective, randomized, comparative study included 120 patients with an IHD+BA comorbidity. Of these patients, 60 had mild persistent BA and 60 had moderate persistent BA. Each group was divided into 3 subgroup, each including 20 patients, based on the used regimen of antianginal therapy. Stepwise dose titration was performed every 2 weeks (subgroup 1 received the BB bisoprolol 2.5 mg – 5 mg – 10 mg; subgroup 2 received the CA verapamil 240 mg – 240 mg – 240 mg; subgroup 3 received bisoprolol 2.5 mg followed by the combination treatment with bisoprolol and amlodipine as a fixed combination 5+5 mg). All patients underwent a complete clinical and instrumental examination at baseline and at 2, 4, and 6 weeks of treatment. The antianginal effectivity and the effect on bronchial patency were evaluated.
Results	In patients with SA and mild persistent BA, the study of external respiration function (ERF) at 2, 4, and 6 weeks of treatment did not detect any significant difference in the forced expiratory volume in 1 second (FEV_1) between the treatment subgroups. In patients with SA and moderate persistent BA receiving the treatment, a significant decrease in FEV_1 ($p=0.022$) was observed in subgroup 1 receiving bisoprolol 10 mg at 6 weeks of treatment. In subgroups 2 and 3 during the treatment, significant differences were absent. In patients with SA and mild or moderate persistent BA, the heart rate was significantly decreased in all three subgroups; however, in subgroup 2 receiving verapamil, the changes were considerably smaller than in other subgroups.
Conclusion	The study results showed that the BB bisoprolol with dose titration every two weeks from 2.5 to 10 mg or the combination treatment with the BB bisoprolol and the CA amlodipine can be used as the antianginal therapy in patients with SA and mild persistent BA. The BB bisoprolol may be used in patients with SA and moderate persistent BA as the antianginal therapy, but only at doses not exceeding 5 mg to avoid the development of bronchial obstruction. The combination therapy with the BB bisoprolol 5 mg and the CA amlodipine 5 mg is indicated to enhance antianginal and vasoprotective effects.

Keywords	Ischemic heart disease; stable angina; bronchial asthma; antianginal therapy; beta-blockers; bisoprolol; amlodipine; verapamil
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The assumption that coronary artery disease (CAD) and bronchial asthma (BA) seldom occur together is being revised due to the combination being increasingly commonly encountered in clinical practice [1, 2]. According to the German Health Update (GEDA) register, arterial hypertension (AH) is the most common comorbidity in patients with BA (37.9%), while CAD is found in 16.7% of cases [2].

The treatment of CAD often presents difficulties in patients with BA, which are mainly associated with adverse bronchopulmonary side effects of some drugs [3, 4]. Due to evidence that non-selective beta-blockers administered for antianginal and antiarrhythmic purposes adversely affect bronchial patency in combination with BA in patients with CAD, they are often contraindicated or considered to be undesirable [4, 5]. However, highly selective beta-blockers are primarily used in patients with cardiovascular diseases (CVDs) [4, 9]. Due to their beta-blocker selectivity, they only antagonize beta1-adrenoceptors located in the myocardium, having almost no effect on beta2-adrenoceptors

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located in the bronchial wall [8]. Thus, the administration of highly selective beta-blockers to patients with CVDs, including those with concomitant BA, may be a promising approach [7, 8].

Objective

To compare the efficacy and safety of calcium channel blocker (CCB) verapamil, cardio-selective beta-blocker bisoprolol, and the combination of bisoprolol and amlodipine in patients who have stable angina (SA) along with concomitant mild to moderate persistent bronchial asthma (BA).

Material and Methods

All patients met the following inclusion criteria: male and female individuals aged 45 to 75 years; CAD; stable angina functional class (FC) II and III; mild to moderate BA, non-acute, controlled; patients with heart rate (HR) >70 beats per minute at baseline.

The following exclusion criteria were applied: chronic obstructive pulmonary disease and other chronic bronchopulmonary diseases other than BA; unstable angina; patients with a less than 5-month history of myocardial infarction; heart failure with reduced ejection fraction and FC >III; respiratory failure (RF) grade >2 (mMRC Dyspnea Scale); uncontrolled AH with baseline blood pressure >180/100 mm Hg; acute inflammation, cancer.

The prospective study included 120 patients with CAD and BA, of which half (60) had mild persistent BA, while the other 60 patients had moderate persistent BA. Each group was divided into 3 subgroups of 20 people using the closed-envelope method depending on the administered antianginal therapy: Subgroup 1 – beta-blocker bisoprolol, Subgroup 2 – CCB verapamil, and Subgroup 3 – bisoprolol/amlodipine fixed combination (Figure 1).

Drug doses were titrated every 2 weeks (Subgroup 1 received bisoprolol 2.5 mg – 5 mg – 10 mg; Subgroup 2 received verapamil 240 mg – 240 mg – 240 mg; Subgroup 3 received bisoprolol 2.5 mg followed by bisoprolol/amlodipine fixed combination 5 mg/5 mg). Patients continued to receive the previous therapy: nitrates on demand during attacks of angina; angiotensin II receptor blockers; angiotensin-converting enzyme (ACE) inhibitors; disaggregants; statins; long-acting beta2 – agonists; inhaled glucocorticosteroids. Doses of bronchodilators did not change during the follow-up period. Some patients required dose reduction of an ACE inhibitor or an angiotensin II receptor blocker due to extremely low blood pressure (BP) caused by antianginal therapy.

In the group of patients with CAD and mild persistent BA (n=60), 29 patients were male (48.3%), while 31 were female (51.7%). Median age was 54.5 [48; 57] years; the duration of CAD and BA was 14.2 [13.9; 16.1] years and 19.7 [17.1; 22.2] years, respectively. Comorbidities such as AH and diabetes mellitus (DM) type 2 were found in 60 (100%) and 8 (13.3%) patients, respectively. A history of myocardial infarction (MI) was reported in 15 (25%) patients.

In the group of patients with CAD and moderate persistent BA (n=60), 27 patients were male (45%), while 33 were female (55%). The median age was 62.9 [58; 64] years. Patients had the following comorbidities: AH in 60 (100%) patients; DM type 2 in 9 (15%) patients; history of MI in 16 (26.6%) patients.

All patients underwent comprehensive clinical examination at baseline and after 2, 4, and 6 weeks of treatment: measurement of office BP and HR, 24-hour electrocardiogram (ECG) monitoring; echocardiography with measurement of mean pulmonary artery pressure (mPAP); pulmonary function tests (PFTs); endothelium-dependent vasodilation (EDV). Peak expiratory flow was measured twice a day during the first 6 days of the therapy.

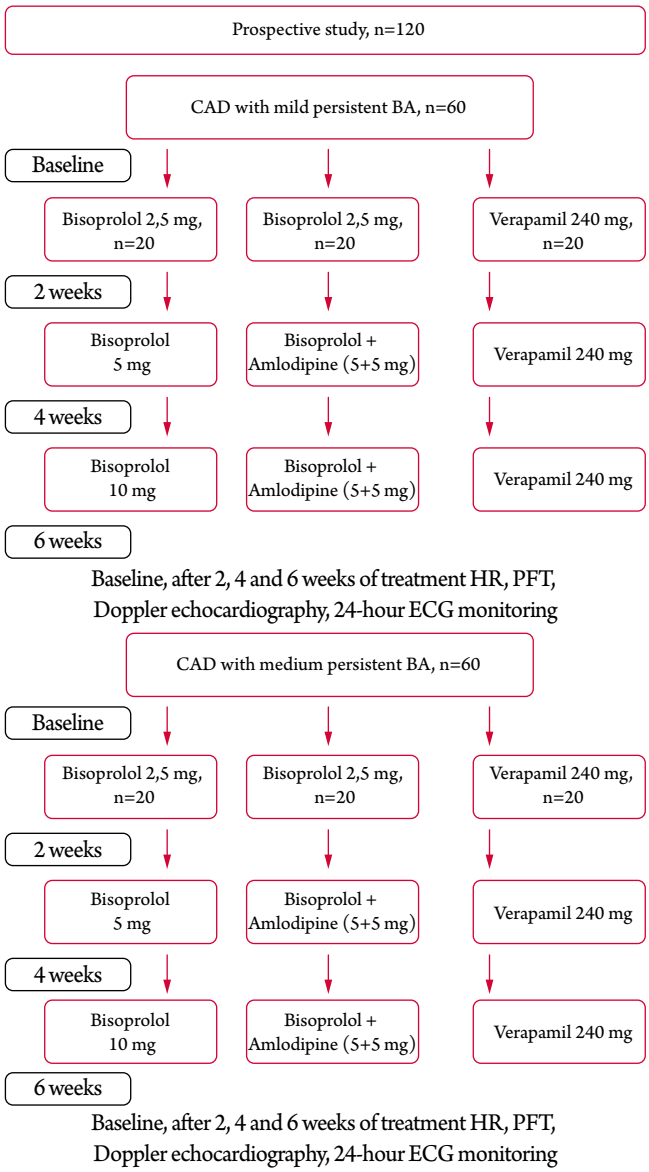
CAD was diagnosed following the 2020 Federal Clinical Guideline for Stable Coronary Artery Disease [10]. The diagnosis of BA was determined following the 2019 Global Initiative for Asthma (GINA) guidelines [11]. The presence or absence of BA control was estimated using the Asthma Control Questionnaire 5 (ASQ-5<0.75) (GINA; 2019).

All patients completed the self-control diary (BP, HR, peak expiratory flow (PEF), and adverse events) every day.

The antianginal effect of the therapy was estimated based on changes in the number of nitroglycerin tablets taken, the number of angina attacks per week, trends in angina attacks, as well as the depth and duration of myocardial ischemia according to the 24-hour ECG monitoring. In order to identify the pleiotropic effects of the treatment, endothelial function was examined by EDV and changes in mPAP were estimated by Doppler echocardiography. The effect on bronchial patency was evaluated by PFTs (FEV_1 above all).

The study was approved by the ethics committee of the Privolzhsky Research Medical University (Nizhny Novgorod, Russia) (Minutes No.15 dated

Figure 1. Study design



CAD – coronary artery disease; BA – bronchial asthma; HR – PFT – pulmonary function test; ECG – electrocardiogram.

26.10.2020). Patients signed informed consent to participate in the study.

The data were processed using the parametric and non-parametric statistical methods in Statistica 10.0 (StatSoft) and SPSS Statistics 25 (IBM). The distribution of the indicators of interest was determined by the Shapiro-Wilk test. The mean values close to the normal distribution were expressed using standard deviations (M±SD, where M is the mean and SD is the standard deviation). Univariate analysis of variance was used to compare more than two samples for the analysis of quantitative variables. If differences were found, pairwise comparisons were conducted using the post-hoc Scheffe test.

Results

Changes of indicators in patients with CAD and mild persistent BA

The analysis of data from patients with SA and mild persistent BA revealed the following. In Subgroup 1 (bisoprolol), PEF was 340.4±33.25 L/min at baseline and 347.12±8.6 L/min on Day 6 of treatment (p=0.064). In Subgroup 2 (verapamil), PEF was 333.6±42.4 L/min at baseline and 348.6±12.2 L/min on Day 6 of treatment (p=0.652). In Subgroup 3 (bisoprolol/amlodipine after the second titration step), PEF was 335.6±21.46 L/min at baseline and 348.4±2.8 L/min after 6 days of treatment (p=0.218).

PFTs conducted in 2, 4, and 6 weeks of treatment showed no statistical difference in FEV_1 between the subgroups (Figure 2).

Thus, the prescribed drugs did not produce a negative effect on PEF in the first days of treatment and pulmonary function indicators (especially FEV_1) in any subgroup of patients with CAD and mild persistent BA; no adverse effect on bronchial patency was demonstrated; consequently, they can be considered to be safe.

Clinical condition and hemodynamics were assessed in all three subgroups. By Week 6 of the treatment, the number of administered nitroglycerin tablets decreased from 5.1±1.2 to 0.09±0.06 tablets per week (p=0.001), while the mean number of angina attacks decreased from 5.7±1.08 to 0.9±0.7 per week (p=0.001) in Subgroup 1. The need for nitroglycerin decreased from 5.8±1.4 to 2.02±0.07 tablets per week (p=0.001); in Subgroup 2, the mean number of angina attacks decreased from 5.2±1.1 to 2.09±0.23 per week (p=0.001). In Subgroup 3, the administration of nitroglycerin was decreased from 4.2±1.3 to 0.07±0.03 tablets per week (p=0.001), while the mean number of angina attacks decreased from 6.21±1.06 to 0.7±0.47 per week (p=0.001).

According to the office HR measurement and 24-hour ECG monitoring, decreased HR was statistically significant in all three subgroups; however, the trend was significantly lower in Subgroup 2 (verapamil) than in other subgroups. It should be noted that HR was 65.4±4.8 bpm (p=0.001 vs. baseline) and 68.6±4.2 bpm (p=0.002 vs. baseline), respectively, following 6 weeks of treatment, which is statistically lower than in subgroup 2. It is noteworthy that increasing bisoprolol to 10 mg resulted in a statistically significantly lower HR in Subgroup 1 than in Subgroup 3 (bisoprolol/amlodipine; Figure 3).

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Figure 2. Trends in FEV1 in the study groups of patients with CAD and mild persistent BA during the treatment with various antianginal drugs

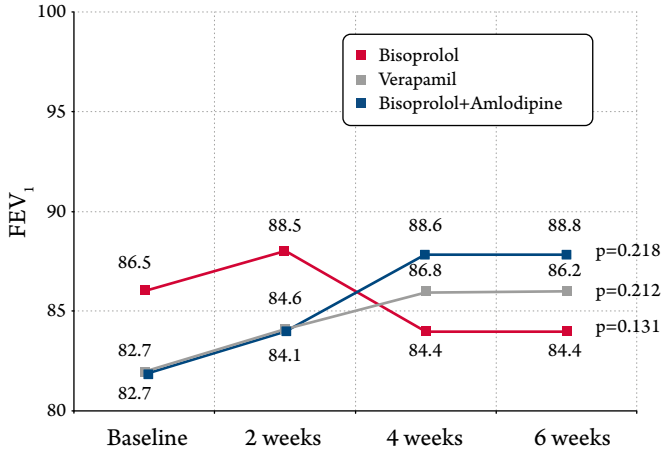
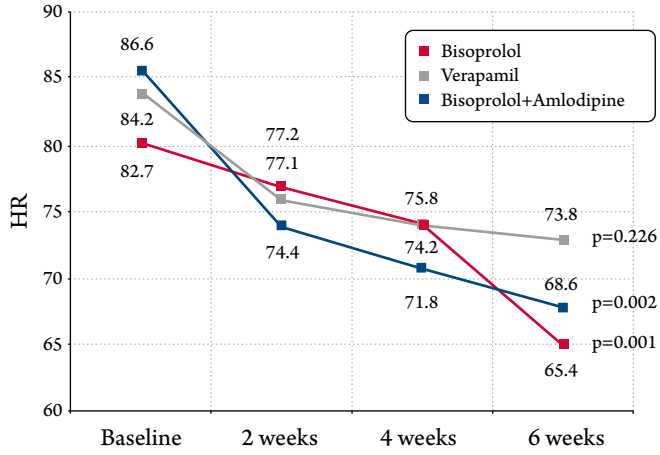


Figure 3. Trends in HR in the study groups of patients with CAD and mild persistent BA during the treatment with various antianginal drugs



According to the 24-hour ECG monitoring, a statistically significant decrease in the number of myocardial ischemia episodes, depth, and duration of ischemia, as well as in the number of supraventricular premature beats (SVPBs) and ventricular premature beats (VPBs), was observed in all three subgroups.

The comparative analysis of mPAP in patients with CAD and mild persistent BA demonstrated the following. By Week 6 of treatment, mPAP decreased from 21.77±2.31 to 19.60±6.62 mm Hg in Subgroup 1 (bisoprolol); from 22.20±2.29 to 21.03±3.5 mm Hg in Subgroup 2 (verapamil); from 22.53±2.08 to 18.5±7.87 mm Hg in Subgroup 3 (bisoprolol/amlodipine; p=0.016). Analysis showed that mPAP decreased in all subgroups during the treatment. However, the positive trend was more pronounced in Subgroup 3; this was most likely due to the additional pleiotropic effects of amlodipine, such as a positive effect on the pulmonary circulation hemodynamics and thus an indirect effect on the course of BA.

Endothelial function was examined by EDV to identify the pleiotropic effects produced during the treatment. Baseline EDV was 7.24±1.6% in Subgroup 1 (bisoprolol), 7.12±1.06% in Subgroup 2 (verapamil), and 7.42±1.21% in Subgroup 3 (bisoprolol/amlodipine; p=0.112). The assessment of EDV showed that the brachial artery diameter increased following decompression to 8.42±1.22% in Subgroup 1 (p=0.001); 7.78+2.28% in Subgroup 2 (p=0.07); and 8.88+2.31% in Subgroup 3 (p=0.001). Delta EDV versus baseline was 1.2±1.1% in Subgroup 1, 0.6±0.3% in Subgroup 2, and 1.5±1.4% in Subgroup 3 (p=0.02). Thus, the largest positive changes of EDV were detected in Subgroup 3 the same way as for mPAP, which suggests once again that amlodipine has an additional vasoprotective effect (Table 1).

Changes of indicators in patients with CAD and moderate persistent BA

A similar analysis was conducted in patients with SA and moderate persistent BA. In Subgroup 1 (bisoprolol), PEF was 338.6±42.4 L/min at baseline and 337.4±12.6 L/min on Day 6 of treatment (p=0.002). In Subgroup 2 (verapamil), PEF was 342.6±28.6 L/min at baseline and 345.12±34.6 L/min on Day 6 of treatment (p=0.072). In Subgroup 3 (bisoprolol/amlodipine), PEF was 333.4±25.6 L/min at baseline and 336.81±16.6 L/min after 6 days of treatment (p=0.061). Thus, there were no significant changes in PEF in the patient subgroups within 6 days of treatment.

FEV_1 decreased statistically significantly (p=0.022) in Subgroup 1 by Week 6 of treatment with bisoprolol 10 mg. No statistically significant differences were found in Subgroup 2 and Subgroup 3 during the treatment (Figure 4).

Thus, according to our data, despite the high degree of cardioselectivity, bisoprolol 10 mg can have an adverse effect on bronchial patency in patients with SA and moderate persistent BA, which means that this drug should only be used in such patients at a dose of not more than 5 mg/day.

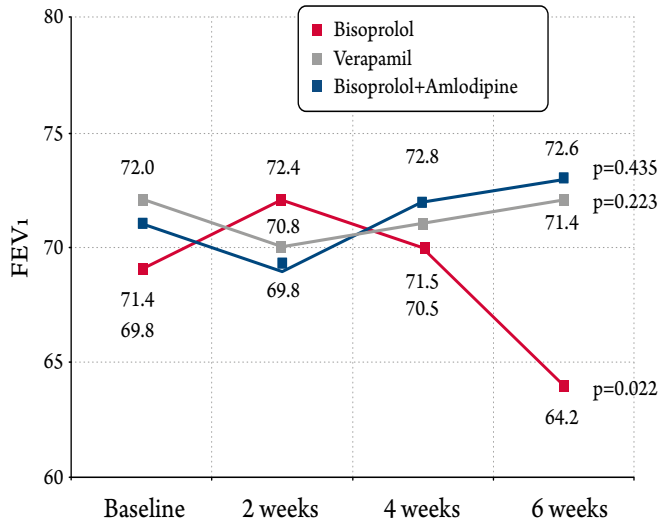
In Subgroup 1, the mean number of angina attacks decreased from 5.6±1.6 to 0.08±0.06 per week (p=0.001) during the treatment, while the administration of nitroglycerin decreased from 7.5±1.2 to 0.9±0.7 tablets per week (p=0.001). Since the mean number of angina attacks decreased from 8.1±1.1 to 3.8±0.6 per week (p=0.001), the

Table 1. Key hemodynamic indicators and FEV_1 in patients with CAD with mild persistent BA after 6 weeks of treatment with several types of antianginal drugs

Indicator	Subgroup 1, bisoprolol 10 mg	Subgroup 2, verapamil 240 mg	Subgroup 3, bisoprolol 5 mg + amlodipine 5 mg	p-value
PEF, L/min	347.12±8.6	348.6±12.2	348.4±2.8	p_{mg}=0.218
FEV_1, %	84.4±4.8	86.2±4.2	88.83±2.6	p_{mg}=0.261
HR, bpm	65.4±4.8	73.8±2.6	68.6±4.2	p_{mg}<0.001; p_{1-3}=0.001; p_{1-2}=0.001; p_{2-3}=0.001
SVPBs	182.6±24.4	194.4±16.6	178.6±18.6	p_{mg} =0.004; p_{1-3}=0.003; p_{1-2}= 0.001; p_{2-3} =0.001
VPBs	64.3±4.4	68.8±6.2	55.8±6.2	p_{mg} =0.003; p_{1-3}= 0.001; p_{1-2}= 0.001; p_{2-3} =0.002
mPAP, mm Hg	19.60±6.62	21.03±3.5	18.15±7.87	p_{mg}=0.03; p_{1-3}= 0.008; p_{1-2}= 0.011; p_{2-3} =0.004
EDV, %	8.42±1.22	7.78±2.28	8.88±+2.31	p_{mg}=0.002; p_{1-3}=0.001; p_{1-2}=0.001; p_{2-3}=0.001

PEF – peak expiratory flow; FEV_1 – forced expiratory volume exhaled in 1 second; HR – heart rate; SVPBs – supraventricular premature beats; VPBs – ventricular premature beats; mPAP – mean pulmonary artery pressure; EDV – endothelium-dependent vasodilation.

Figure 4. Trends in FEV1 in the study groups of patients with CAD and moderate persistent BA during the treatment with various antianginal drugs



need for nitroglycerin decreased from 6.4±1.2 to 5.04±0.04 tablets per week (p=0.001) in Subgroup 2. In Subgroup 3, the mean number of angina attacks decreased from 8.01±1.2 to 0.8±0.12 per week (p=0.001) and the administration of nitroglycerin decreased from 6.6±1.4 to 0.06±0.02 tablets per week (p=0.001).

Although decreased HR was statistically significant in all three subgroups according to office HR measurement and 24-hour ECG monitoring, the trend was significantly lower in Subgroup 2 (verapamil) than in other subgroups (Figure 5).

According to the 24-hour ECG monitoring, the number of various arrhythmia cases decreased in all three subgroups. The analysis of trends in SVPBs and VPBs after 6 weeks of treatment showed a significant decrease in premature beats in all three subgroups. It should be noted that there was a statistically significant difference between patients of Subgroup 3 (bisoprolol/amlodipine) and patients of Subgroup 1 and Subgroup 2 in favor of a significant reduction in both SVPBs and VPBs after 6 weeks of treatment (p=0.001).

In the subgroup of patients receiving bisoprolol, mPAP decreased from 22.27±1.76 to 20.4±4.2 mm Hg by Week 6 of treatment. In the verapamil subgroup, the trend was weak and mPAP decreased from 23.20±2.17 to 21.6±4.6 mm Hg by Week 6 of treatment. The most significant changes were observed in the bisoprolol/amlodipine subgroup by week 6: mPAP was 21.38±4.96 mm Hg and 19.4±2.2 mm Hg at baseline and at Week 6, respectively (p=0.01). Thus, decreased mPAP was statistically significant in the subgroups of patients with CAD and moderate BA taking bisoprolol and bisoprolol/amlodipine combination; in the latter case, it was statistically more significant, which may be due to additional vasoprotective effects of amlodipine.

In patients with CAD and moderate persistent BA, baseline EDV was 6.12±1.8%, 7.02±1.4%, and 6.13±1.2% in Subgroups 1, 2, and 3, respectively. The analysis of EDV showed that mean brachial artery diameter following decompression was 7.32±2.18% (p=0.001) in Subgroup 1 (bisoprolol) following 6 weeks of treatment. In Subgroup 2 (verapamil), the corresponding figure was 7.18±1.16% (p=0.06). In Subgroup 3 (bisoprolol/amlodipine), the mean increase in the brachial artery diameter was 7.68±2.22% (p=0.001). Delta EDV versus baseline was 1.1±1.0% in Subgroup 1, 0.4±0.2% in Subgroup 2, and 1.6±1.2% in Subgroup 3 (p=0.04).

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Thus, the most beneficial effect on the vascular wall as shown by EDV was observed in Subgroup 3 (bisoprolol/amlodipine) as compared with patients taking bisoprolol and verapamil (Table 2).

Discussion

According to several recent studies, CAD is one of the most common comorbidities in patients with BA [2]. A meta-analysis of eleven studies (n=666, 355) suggests that patients with BA are at 32% higher risk of developing CAD; this is especially female patients [12]. The relation between CAD and a phenotype of BA, such as late-onset asthma was also proven [12]. It was also shown that 3.8% of patients with uncontrolled or poorly controlled BA develop atrial fibrillation [13], along with increased risk of hospitalizations, cardiovascular events, and cardiovascular death [13–15]. Thus, it is necessary to carefully select effective antianginal and antiarrhythmic therapy for patients with CAD and concomitant BA. In stable forms of CAD, beta-blockers, along with CCBs, remain the first line of therapy. However, their administration requires that the bronchopulmonary system be monitored to avoid adverse effects on pulmonary function.

The present study provided evidence of the possibility for using bisoprolol in patients with CAD and concomitant BA, as well as determining the conditions for this use. Beta-blockers can be used in patients with BA if at least two conditions are met: high selectivity of A drug; stable course of BA and full control over the symptoms. It should be kept in mind that bronchodilation is less likely to develop the higher the selectivity of the beta-blockers and the lower the dose used in patients with BA. Therefore, the treatment of such patients should be initiated with lower doses of beta-blockers and subsequent titration.

The study was limited to assessing the efficacy and safety of a specific highly selective beta-blocker bisoprolol in patients with SA and concomitant BA with a limited follow-up period of 6 weeks. However, the possibility of using other highly selective beta-blockers such as metoprolol succinate and nebivolol without adverse bronchopulmonary effects can be assumed in this category of patients.

Along with the combination of bisoprolol 5 mg and CCB amlodipine 5 mg, antianginal therapy of patients with SA and non-acute mild persistent BA with beta-blocker bisoprolol titrated 2.5 mg to 10 mg does not reduce bronchial patency and has more pronounced antianginal, heart rate lowering, and

Figure 5. Trends in HR in the study groups of patients with CAD and moderate persistent BA during the treatment with various antianginal drugs

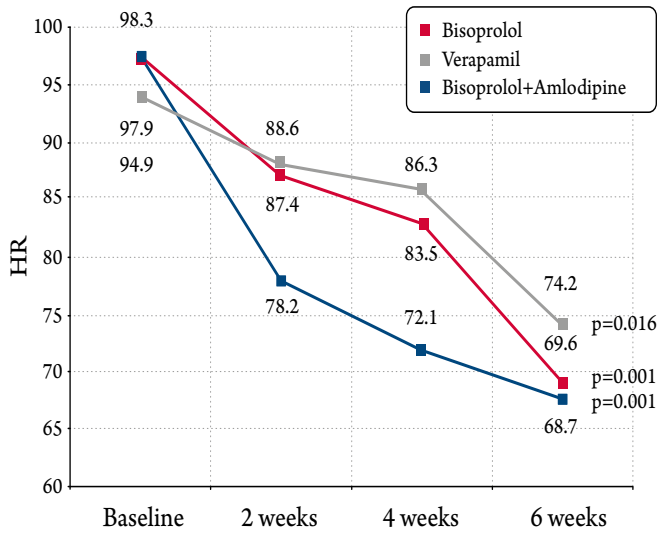

Table 2. Key hemodynamic indicators and FEV_1 in patients with CAD with moderate persistent BA after 6 weeks of treatment with several types of antianginal drugs

Indicator	Sub-group 1, bisoprolol 10 mg	Sub-group 2, verapamil 240 mg	Sub-group 3, bisoprolol 5 mg+ amlo-dipine 5 mg	p-value
PEF, L/min	337.4±12.6	345.12±34.6	336.81±16.6	p_{mg}=0.872
FEV_1, %	64.2±2.4	72.6±6.2	72.4±4.2	p_{mg}=0.143
HR, bpm	69.6±6.1	74.2±8.4	68.7±4.2	p_{mg}=0.112
SVPBs	196.23±11.4	242.14±13.6	214.6±16.6	p_{mg}=0.002; p_{1-3}= 0.001; p_{1-2}= 0.001; p_{2-3} =0.001
VPBs	96.6±6.1	124.4±1.2	88.16±2.3	p_{mg}=0.002; p_{1-3}= 0.001; p_{1-2}= 0.001; p_{2-3} =0.001
mPAP, mm Hg	20.4±4.2	21.6±4.6	19.4±2.2	p_{mg}=0.03; p_{1-3}= 0.001; p_{1-2}= 0.001; p_{2-3} =0.001
EDV, %	7.32±2.18	7.18+1.16	7.68±2.22	p_{mg}=0.01; p_{1-3}=0.001; p_{1-2}=0.001; p_{2-3} =0.001

PEF – peak expiratory flow; FEV_1 – forced expiratory volume exhaled in 1 second; HR – heart rate; SVPBs – supraventricular premature beats; VPBs – ventricular premature beats; mPAP – mean pulmonary artery pressure; EDV – endothelium-dependent vasodilation.

antiarrhythmic effects than conventional therapy with CCB verapamil 240 mg / day.

Antianginal therapy with beta-blocker bisoprolol titrated from 2.5 mg to 5 mg does not reduce bronchial patency in patients with SA and non-acute moderate persistent BA; however, when the dose is increased to 10 mg, bronchial obstruction tends to develop.

Combined antianginal therapy with beta-blocker bisoprolol 5 mg and CCB amlodipine 5 mg is safe and has more pronounced antianginal, heart rate lowering, and antiarrhythmic effects than conventional therapy with CCB verapamil 240 mg / day. The combination of beta-blocker bisoprolol and CCB amlodipine produces additional beneficial effects on the cardiovascular system and the course of BA, such as decreasing pulmonary artery pressure and improving endothelial function.

Thus, combining beta-blocker bisoprolol with CCB amlodipine AK in the treatment of patients with SA and non-acute mild to moderate persistent BA not only contributes to the antianginal effect, but also improves endothelial function and further reduces pulmonary artery pressure compared to monotherapy with beta-blocker bisoprolol or CCB verapamil.

Conclusion

Our study demonstrated the possibility of using highly selective beta-blocker bisoprolol in patients with stable angina and concomitant mild to moderate bronchial asthma and presented the regimen of sequential administration of antianginal drugs with dose titration in this category of patients. According to our findings, beta-blocker bisoprolol with dose titration every two weeks from 2.5 mg to 10 mg or the combination of beta-blocker bisoprolol and calcium channel blocker amlodipine can be used in patients with stable angina and mild persistent bronchial asthma as antianginal therapy.

Beta-blocker bisoprolol can be administered as antianginal treatment in patients with moderate persistent bronchial asthma at a dose of not more than 5 mg to prevent the development of bronchial obstruction. Antianginal and vasoprotective effects of beta-blocker bisoprolol 5 mg is enhanced by using calcium channel blocker amlodipine 5 mg.

No conflict of interest is reported.

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