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New opportunities to improve the treatment effectiveness of patients with stable angina

Aim	To study the antianginal and heart rate slowing effects in patients with stable angina (SA) who failed to achieve the heart rate (HR) goal and were switched from the beta-blocker (BB) metoprolol tartrate to a combination of metoprolol tartrate and ivabradine.
Material and methods	The study included 54 patients with SA not higher than functional class (FC) III (35 (64.8%) men and 19 (35.2%) women) aged 59 [48; 77] years. Prior to the study start and at 4 and 8 weeks of follow-up, electrocardiography (ECG) and 24-h ECG monitoring (24h-ECGM) were performed for all patients. The follow-up period duration was 8 weeks. The antianginal and heart rate slowing effects of therapy were clinically evaluated by a decrease in frequency of anginal attacks and patients' requirement for nitrates, a decrease in HR, and the effect on 24h-ECGM indexes characterizing myocardial ischemia. At the first stage, all patients were prescribed metoprolol tartrate (Egilok®, Egis, Hungary) 25 mg twice a day. Patients with resting HR still higher than 70 bpm after 4 weeks of treatment were switched from metoprolol tartrate to a fixed ivabradine/metoprolol combination (Implicor®, Servier, France) 5/25 mg twice a day. Thus, based on achieving/non-achieving the HR goal, two groups of patients were formed. Statistical analysis was performed with a STATISTICA 10,0 software package.
Results	After 4 weeks of therapy with metoprolol tartrate 25 mg twice a day, 18 (33.3%) patients of group 1 achieved the HR goal of 70 bpm, while 36 (66.7%) patients of group 2 did not achieve the goal. For further correction of HR, patients of group 2 were switched from metoprolol tartrate to ivabradine/metoprolol 5/25 mg twice a day. After 4 weeks of the ivabradine/metoprolol treatment, 31 (86.1%) patients achieved the HR goal with median resting HR of 62 [56; 70] bpm. The number of angina attacks decreased from 6 [3; 8] to 2 [1; 3] per week ($p<0.001$). 24hECGM showed that the mean diurnal HR decreased from 81 [76; 96] to 66 [56; 76] bpm ($p<0.001$); mean night HR decreased from 69 [73; 80] to 52 [43; 60] bpm ($p=0.012$); and the ischemic ST segment depression was absent.
Conclusion	Only 33.3% of patients with stable angina achieved the HR goal on metoprolol tartrate 25 mg twice a day. Supplementing the beta-blocker metoprolol tartrate at the same dose with ivabradine allowed 86.1% of patients to achieve the HR goal and exerted a pronounced anti-anginal effect.

Keywords	Stable angina; heart rate; myocardial ischemia; combination anti-anginal therapy
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Heart rate is considered to be an independent risk factor in overall and cardiovascular mortality [1, 2]. In this connection, the current Guidelines for the Management of Arterial Hypertension [3] and Guidelines on Chronic Coronary Syndromes [4] of the European Society of Cardiology focus special attention on heart rate and medicines having heart rate slowing properties, along with antihypertensive, antianginal, and anti-ischemic effects.

Highly selective beta-blockers perform a central role in the treatment of patients suffering from cardiovascular diseases [5, 6]. The use of beta-blockers in hypertension, coronary artery disease (CAD), chronic heart failure, and tachyarrhythmias was established to reduce the risk and rate of cardiovascular complications, as well as having a positive effect on clinical manifestations of the disease and improving the quality of life of patients (APSIS (Angina Prognosis Study in Stockholm) [7], TIBBS (Total Ischemic Burden Bisoprolol Study) [8], CIBIS-II (Cardiac Insufficiency Bisoprolol Survival Study) [9], MERIT-HF (Metoprolol CR/XL Randomized Intervention Trialin Chronic HF) [10], COPERNICUS (Carvedilol Prospective Randomized Cumulative Survival Study Group) [11], SENIORS

(Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors) [12], etc.).

Beta-blockers are commonly used to achieve the target range of heart rate and restore the balance between demand and supply of oxygen to the myocardium in patients with CAD. The 2013 European Guidelines on Chronic Coronary Syndromes consider these antianginal drugs as the first line in the treatment of stable angina (SA). The 2019 European Guidelines on Chronic Coronary Syndromes also give priority to beta-blockers [4]. However, beta-blocker monotherapy does not achieve the full antianginal effect and target range of heart rate in all patients. Moreover, the administration of high-dose beta-blockers can be limited by concomitant pathology, particularly bronchopulmonary diseases [13]. As referred to in the clinical guidelines on chronic coronary syndromes and heart failure, agents such as ivabradine have also been used to selectively reduce sinus tachycardia rates in recent years, [4, 14, 15].

The antianginal and anti-ischemic efficacy of the selective If-channel inhibitor ivabradine was established in patients receiving monotherapy SA as well as in combination with other antianginal agents, including beta-blockers [16, 17]. The BEAUTIFUL study [2] showed that ivabradine administered supplementally to the standard therapy contributes to the reduction of cardiovascular risks in patients with stable CAD and heart failure along with reduced ejection fraction [2], particularly in patients with baseline heart rate >70 bpm and patients with stable angina [18].

Trials using fixed combinations have become particularly valuable in recent years. A prospective, multicenter, observational cohort study of the efficacy of the fixed combination of ivabradine and metoprolol in patients with SA in routine clinical practice showed statistically significant reductions in heart rate and functional class (FC) of angina following four months of treatment [19]. The addition of ivabradine to an optimal individual dose of beta-blockers is associated with a decreased rate of anginal events and improved quality of life of patients with SA and a history of coronary revascularization [19, 20].

The relevance of the present study is therefore assured by the common need arising in clinical practice to enhance the antianginal effect of beta-blockers when prescribed to decrease heart rate. The objective of this work was to study the antianginal and heart rate slowing effects of such treatments in patients with SA who did not achieve the target heart rate range and were transferred from beta-blocker metoprolol tartrate to a combination of metoprolol tartrate and ivabradine. The design of this primary prospective study is based on «comparison of results in the same patient» and «comparison of results in parallel groups».

Material and methods

The study included 54 patients with FC III SA at most, of whom 35 (64.8%) were male, while 19 (35.2%) were female at the age of 59 [48; 77] years old. SA was diagnosed based on generally accepted criteria following the clinical guidelines [4, 21]. FC II stable angina was diagnosed in 14 patients, FC III in 40 patients. 19 (35.2%) patients had a history of myocardial infarction without ST-segment elevation 6 to 18 months before. The patients underwent emergency or early selective angiography and percutaneous coronary intervention with one stent implanted in one coronary artery in 46 (85.2%) patients and two stents in 8 (14.8%) patients. The outcome was complete revascularization of the coronary vessel. The control angiography showed that residual stenosis was less than 20%; no other hemodynamically significant constrictions of coronary arteries were detected. A decrease by 50% or more in the diameter of the main coronary arteries was considered hemodynamically significant (stenotic coronary atherosclerosis) [22]. 32 (59.2%) patients had concomitant hypertension, 16 (29.6%) patients had Gold grade 2 chronic obstructive pulmonary disease (COPD) [23] lasting for 5.0 [3,0; 7,3] years, and 6 (11.1%) patients had type 2 diabetes mellitus (DM). All patients received drug therapy under the 2019 European Guidelines on Chronic Coronary Syndromes [4], including antiplatelets, angiotensin-converting enzyme inhibitors, hypolipidemias, various beta-blockers (bisoprolol 2.5 mg/day or nebivolol 2.5 mg/day). Patients with COPD received combination therapy to include inhaled bronchodilators, beta-blocker bisoprolol 2.5 mg/day, or calcium antagonist verapamil 80 mg/day as antianginal treatment. Patients with DM received adequate doses of glucose-lowering agents.

The study included patients who had not achieved the target heart rate of 70 bpm prior to the commencement of the study [4]. The follow-up period lasted for eight weeks. The antianginal and heart rate lowering effects of the administered therapy were clinically estimated by rarer angina events and patients' needs in terms of nitrates, lower heart rate, and changes in the 24-hour ECG monitoring measurements of myocardial ischemia.

The following patients were excluded: patients with unstable angina, myocardial infarction within six months prior to the study; patients with Gold criteria 3–4 COPD, exacerbation of COPD, bronchial asthma due to the risk of broncho-obstructive syndrome in the case of beta-blocker use. Patients with the following

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abnormalities in resting electrocardiogram (ECG) or 24-hour ECG monitoring were also excluded from the study: atrioventricular and sinoatrial conduction disorders; paroxysmal, persistent supraventricular and ventricular arrhythmias; abnormalities preventing the interpretation of myocardial ischemia, such as baseline ST-segment depression ≥1 mm, signs of left ventricular hypertrophy with baseline ST-segment depression <1 mm, complete left bunch branch block.

The local ethics committee of the Nizhny Novgorod Medical Association approved the study (Report No. 7822020 dated 01/20/2020). All patients signed informed consent to participate in the study.

Patients underwent standard 12-lead ECG examination, estimation of the rate of angina attacks, and the use of short-acting nitrates both prior to commencing the study and following 4 and 8 weeks of treatment, respectively. All patients were subjected to 24-hour ECG monitoring using a 12-channel Holter cardiomonitor system Myokard-Holter 2 (NIMP ESN LLC, Russia). The findings were interpreted using the appropriate software. The following 24-hour ECG monitoring measurements were carried out: mean daytime and night-time-time heart rate; episodes of bradycardia and tachycardia; number and morphology of supraventricular and ventricular extrasystoles; the presence of paroxysmal supraventricular and ventricular rhythm disorders; atrioventricular and sinoatrial conduction disorders; bundle branch block; ST-segment changes (number and duration of episodes and maximum level of ST-segment depression). During the interpretation of ST-segment changes, transient depression of the horizontal or downsloping ST-segment by 1 mm or more, lasting for 0.08 seconds from the J point and totaling at least 1 minute during physical activity, as well as accompanied by clinical events of the anginal syndrome (based on the patient's diary), were considered as painful myocardial ischemia. Non-symptomatic ST-segment depression more than 2 mm was considered as painless myocardial ischemia.

At the first stage, all subjects received beta-blocker metoprolol tartrate (Egilok®, Egis Pharmaceuticals, Hungary) at a dose of 25 mg two times a day. Patients with heart rate >70 bpm following four weeks of treatment were transferred from metoprolol tartrate to a fixed combination of ivabradine/metoprolol (Implicor®, Les Laboratoires Servier Industrie, France) at a dose of 5/25 mg two times a day. The attending physician assessed the quality of treatment as «very good», «good», «satisfactory», «bad». Thus, groups were formed based on the achievement/non-achievement of the target levels of heart rate. Other therapies, including treatment of comorbidities, remained unchanged throughout the study.

Statistical processing of data was carried out using the STATISTICA 10.0 software package. The nature of the distribution of the analyzed characteristics was assessed using the Shapiro-Wilk test. If the distribution was normal, the results were presented as M±SD, where M is the mean value and SD is the standard deviation. If the distribution was different from normal, the data were presented as the median and the 25th and 75th percentiles, respectively. Repeat intra-group measurements were compared using the paired Wilcoxon and Friedman tests.

Results

After four weeks of administration of metoprolol tartrate 25 mg two times a day, 18 (33.3%) patients who achieved a resting heart rate <70 bpm constituted Group 1. The weekly number of clinical events of angina in Group 1 decreased from 9 [2; 6] to 4 [1; 6] ($p = 0.003$); the need for nitroglycerin administration was reduced from 10 [12; 6] to 4 [2; 7] tablets per week ($p < 0.001$).

According to 24-hour ECG monitoring, the mean daytime heart rate decreased by 12%, while the mean night-time heart rate decreased by 25% in Group 1 (p=0/018) (Table 1). There was a 66% decrease in the total number of ST-segment depression episodes and a 50% decrease in the duration of ST-segment depression. The number of supraventricular extrasystoles (SVES) decreased by 66%, while the number of ventricular extrasystoles (VES) decreased by 79% (Table 1).

36 (66.7%) subjects, who did not achieve the target heart rate range, constituted Group 2. In this group, the number of angina attacks reduced from 10 [2; 6] to 4 [4; 6] per week ($p < 0.005$), while the need for administered nitroglycerin fell from 11 [6; 6] to 4 [2; 8] tablets per week ($p = 0.04$). The mean daytime heart rate decreased by 21%, while the mean night-time heart rate decreased by 14% (Table 1). The number of ST-segment depression episodes decreased by 75%, the duration of ST-segment depression – by 60%. The number of SVES and VES decreased by 69 and 81%, respectively.

Interestingly, Group 2 patients had a higher heart rate before the start of treatment than Group 1 patients ($p < 0.05$); these patients were more likely to have concomitant COPD and type 2 DM, which can also cause sinus tachycardia.

In order to more effectively correct the heart rate and enhance the antianginal effect in Group 2 patients, metoprolol tartrate was replaced with the fixed combination of ivabradine/metoprolol 5/25 mg two times a day. After four weeks of the administration of

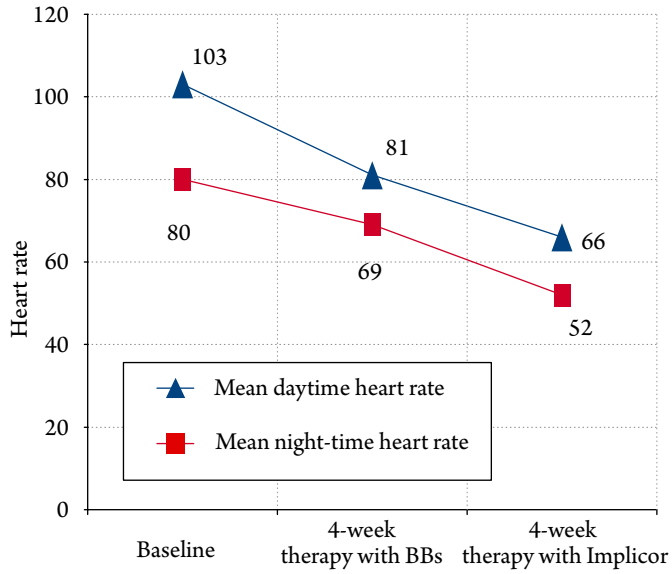
ivabradine/metoprolol, 31 (86.1%) patients achieved the resting target heart rate of 62 [56; 70] bpm. Through discontinuation of stress, the number of angina attacks decreased by 66%, from 6 [3; 8] to 2 [1;3] per week (p<0.001). Nitroglycerin was not used.

During 24-hour ECG monitoring, the mean daytime heart rate decreased from 81 [76; 96] to 66 [56; 76] bpm (p=0.012) (Figure 1). Ischemic ST-segment depression was not registered. The numbers of SVES and VES did not vary to a statistically significantly extent.

Most patients had lower angina FC by the end of the study: 12 (22.2%) patients had FC I; 36 (66.7%) – FC II; 6 (11.1%) – FC III.

All patients exhibited a good tolerance of the fixed antianginal combination of beta-blocker metoprolol tartrate and If-channel inhibitor ivabradine Implicor®. Adverse drug reactions, including visual symptoms caused by the ivabradine effect on the F-channel-related H-channels of the retina, were not reported in the subjects. The quality of treatment was assessed as «very good» and «good» in 34 (94.4%) patients.

Figure 1. Changes in heart rate based on 24-hour ECG monitoring in Group 2 (n=36)



Discussion

Beta-blocker metoprolol tartrate has an evident and pronounced antianginal, anti-ischemic, and antiarrhythmic effect. In the case of stable angina and high heart rate, patients receiving metoprolol tartrate 50 mg/day could be transferred to higher doses. However, concomitant pathologies, such as bronchial asthma, severe COPD, and peripheral atherosclerosis of the lower extremities typical can prevent the use of higher doses of beta-blockers or even result in their abandonment altogether. Moreover, it has been recently shown that the inclusion of ivabradine in the treatment of patients with chronic CAD can have a more pronounced anti-ischemic effect than that of increased doses of beta-blockers [24]. This can be explained in terms of ivabradine not only having beta-blocker-like properties, such as reduction of myocardial contractility and prolongation of diastole, but also additional properties, e.g., improved collateral blood flow, which can have a positive effect on the clinical course of CAD. Our study demonstrated that using ivabradine with beta-blockers not only allows the target heart rate to be achieved but also significantly reduces the number of angina attacks and increases exercise tolerance, which undoubtedly improves the quality of life of patients.

Study limitations

The main limitation of our study consists in its non-comparative, non-randomized, non-controlled design. Groups were formed based on the achievement/non-achievement of target heart rates. A control group in which patients continued to use higher doses of beta-blockers dose instead of adding ivabradine would have allowed us to conclude with more confidence that the antianginal combination treatment is superior to a full-

Table 1. Measures of 24-hour ECG monitoring at baseline and after four weeks of treatment with metoprolol tartrate in patients of Groups 1 and 2

Parameter	Group 1 (n = 18)		Group 2 (n = 36)	
	Baseline	After 4 weeks of treatment	Baseline	After 4 weeks of treatment
Mean daytime heart rate, bpm	82 [72; 91]	72 [67; 76]*	103 [90; 123]#	81 [76; 96]*
Mean night-time heart rate, bpm	70 [67; 72]	56 [47; 66]*	80 [76; 85]#	69 [73; 80]*
Total number of SVES	328 [120; 420]	111 [85; 202]*	407 [345; 456]	123 [101; 163]*
Total number of VES	104 [32; 125]	21 [12; 35]*	158 [120; 178]	30 [20; 45]*
Number of ST-segment depression episodes	6 [2; 8]	2 [1; 4]*	8 [3; 10]	2 [1; 5]*
Duration of ST-segment depression, min.	24 [16; 30]	12 [4; 14]*	35 [12; 40]#	14 [8; 20]

** p < 0.05 – significance of differences in Groups 1 and 2 at baseline and post-treatment;
# p < 0.05 – significance of differences between Groups 1 and 2 at baseline;
SVES – supraventricular extrasystoles; VES – ventricular extrasystoles.

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dose monotherapy. However, according to the 2019 Guidelines on Chronic Coronary Syndromes [4], in real-world clinical practice, a physician has the right to determine the appropriate patient management strategy and stages of the administration of antianginal agents.

We conclude that a combination therapy consisting of a beta-blocker and If-channel inhibitor ivabradine is appropriate for use in the treatments of FC II–III angina. The use of this combination reduces the number of angina attacks, resting and stress-induced ischemic changes, as well as helping to achieve a target heart rate <70 bpm, which is the priority strategic objective of the treatment of patients with SA.

Conclusions

Only in 33.3% of patients with SA using metoprolol tartrate 25 mg two times a day achieve the target heart rate range; moreover, these patients still have angina attacks and need nitroglycerin, which, of course, implies additional correction of the treatment. Our study showed that additional ivabradine used with beta-blocker metoprolol tartrate – i.e., a transfer to the fixed combination drug Implicor® while keeping the same dose of beta-blocker – solves several problems simultaneously: helping to achieve the target heart rate in 86.1% of patients, reducing the number anginal events, decreasing angina FC, and improving the clinical course of CAD without causing any side effects.

Thus, the combined antianginal therapy with beta-blocker and If-channel inhibitor ivabradine in patients with SA is shown to have a pronounced anti-ischemic effect, allowing the achievement of optimal heart rate and avoiding typical side effects that may occur when higher doses of beta-blockers are used.

No conflict of interest is reported.

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