Babushkina G. V.[1], Shaikhlislamova G. I.[2]

[1] «Bashkir State Medical University» Ufa, Russia

[2] City clinical hospital №13. Ufa, Russia

Ivabradine for treatment of heart failure with preserved ejection fraction

Aim	To evaluate the effect of combination ivabradine-containing therapy for chronic heart failure (CHF) with preserved ejection fraction on quality of life (QoL) and the primary composite endpoint during a one-year follow-up.
Material and methods	This study included 160 patients aged 45 to 65 years with NYHA functional class (FC) II–III CHF with preserved left ventricular ejection fraction (CHF-PEF) and grade I and II diastolic dysfunction associated with FC III stable angina with sinus rhythm and a heart rate (HR) higher than 70 bpm. Presence of CHF-PEF was confirmed by results of echocardiography and myocardial tissue Doppler imaging. During one year of prospective observation, effects of bisoprolol and ivabradine as a part of the combination therapy on the primary composite endpoint, including death from cardiovascular complications (CVC) and hospitalizations for myocardial infarction (MI) or CHF, were evaluated in patients with CHF-PEF. Patients were randomized to three groups: A, bisoprolol with dose titration from 2.5 to 10 mg; B, combination of bisoprolol 2.5–10 mg and ivabradine 10–15 mg/day; and C, ivabradine 10–15 mg/day. All patients were on a chronic background therapy, including angiotensin-converting enzyme inhibitors (lisinopril) or, if not tolerated, angiotensin II receptor blockers (valsartan), antiaggregants, statins (atorvastatin, rosuvastatin), and short-acting nitrates as required. If edema developed diuretics were added. The follow-up duration was one year.
Results	After 12 weeks of follow-up, the achievement of goal HR in group A was associated with a tendency to increased distance in the 6-min walk test from 279±19 to 341±21 m (p>0,05); in group B the distance increased from 243±25 to 319±29 m (p<0.05); and in group C the distance increased from 268±21 to 323±22 m (p<0.05). In the combination ivabradine and bisoprolol treatment group, results of the 24-h electrocardiogram monitoring showed a more pronounced anti-ischemic effect associated with a decrease in the number of myocardial ischemic episodes (p<0.05). QoL was evaluated with the Minnesota questionnaire against the background of treatment. At 12 weeks of observation, the total score decreased from 44.5±2.6 to 38.4±2.1 in group A; from 45±2.9 to 38±2.2 in group B; and from 50.9±3.2 to 42.7±2.8 in group C (p<0.05). The risk of acute MI and repeated hospitalization for CHF during the year of observation, as evaluated according to the Kaplan-Meier method, decreased in both bisoprolol and ivabradine combination treatment groups.
Conclusion	The inclusion of bisoprolol and ivabradine into the background therapy of CHF-PEF patients with stable IHD provided an improvement of QoL and a decrease in the risk of hospitalization for acute MI and CHF during the year of observation.

Keywords	Ivabradine; bisoprolol; chronic heart failure; preserved ejection fraction
For citation	Babushkina G. V., Shaikhlislamova G. I. Ivabradine for treatment of heart failure with preserved ejection fraction. Kardiologiia. 2020;60(10):33–37. [Russian: Бабушкина Г. В., Шайхлисламова Г. И. Включение ивабрадина в комплексное лечение пациентов с хронической сердечной недостаточностью и сохраненной фракцией выброса. Кардиология. 2020;60(10):33–37]

Corresponding author	Babushkina G. V. E-mail: kapora85@rambler.ru

Approximately 1–2% of the adult population of developed economy countries have heart failure (HF), with a prevalence of >10% risk of chronic HF (CHF) in patients over 70 years old [1, 2]. Among people aged over 65 with newly detected exertional dyspnea, every sixth patient will have unrecognized CHF, mostly with preserved left ventricular ejection fraction (LVEF) [3–5]. At the age of 55, the risk of developing CHF for the remainder of their life is 33% in males and 28% in females. Annual all-cause mortality in hospitalized and ambulatory patients with CHF is 17% and 7%, respectively, while the rate of hospital admissions is 44% and 32%, respectively [6]. While in 2015, the mean prevalence of chronic HF with preserved ejection fraction (HFpEF) was 50% in all patients with CHF, it has been predicted this number will increase to 80% or more by 2020 [5, 7–10].

The SHIFT trial findings showed that the concept of the neurohormonal blockade in CHF can be supplemented by the effective reduction of heart rate (HR) [11]. In patients with CHF, HR and risk of all-cause death, cardiovascular death, and hospitalization rates are directly correlated. A decrease in HR in such patients, especially with beta-

blockers, is accompanied by an improved prognosis [12, 13]. However, beta-blockers cannot be administered in all patients with CHF, and reliable control of HR is not always attainable. Ivabradine can be prescribed for this purpose. It does not affect the inotropic function of the heart and decrease HR by inhibiting ion current in sinoatrial f-channels. The efficacy of including ivabradine in the complex treatment of patients with CHF, LV systolic dysfunction, and EF ≤35% has been demonstrated [14, 15]. However, there are no recommendations for its use in CHF with LV diastolic dysfunction and preserved EF. Few studies have addressed this problem [16].

Material and methods

We conducted a study of 160 patients (63% male and 37% female) with HFpEF (EF ≥50%) FC II–III (NYHA) and diastolic dysfunction type I and type II with stable angina FC III, sinus rhythm, and HR >70 bpm. Of them, 134 (84%) patients also had arterial hypertension (AH) (grade I in 59 patients, grade 2 in 44 patients, and grade 3 in 31 patients). The mean age was 57.7 years (45–65 years).

Among patients included in the study, 59 (37%) patients were active smokers. Dyslipidemia was found in 83 (52%) patients, and 134 (84%) patients with hypertension had increased LV mass index. Abdominal obesity was present in 57 (36%) patients.

CAD and AG were diagnosed in hospital using the standard criteria provided in the relevant diagnosis and treatment guidelines (ESC 2013). The presence of HFpEF (≥50% EF) was confirmed by the results of patient examination following the National Guidelines for Diagnosis and Treatment of CHF (2013), and structural change indicators: left atrial volume index, LV mass index, and functional changes.

LV diastolic function (DF) was evaluated by a pulsed Doppler transmitral flow study. The type of LV diastolic filling was determined for each specific case based on transmitral flow measurements: type I diastolic dysfunction (DD) corresponded to slow relaxation; and type II to pseudo-normalization. In order to analyze LVDF, the following indicators were determined: E – the peak rate of LV early diastolic filling; A – the peak rate of LV late diastolic filling; E/A ratios; and DT – deceleration time of LV early diastolic filling; IVRT – izolymic relaxation time of the LV. Normal transmitral blood flow was diagnosed with IVRT <100 ms, DT 150–250 ms, E/A 1–1.5; hypertrophic type (a type of impaired relaxation) with IVRT ≥100 ms, DT >200 ms, E/A <0.8; and pseudo-normal filling type with IVRT >100 ms, DT 160–200 ms, E/A 0.8–1.5 [17]. According to myocardial tissue Doppler, E/E' was 8.1±2.7 in type I and 15.3±2.1 in type II.

The exclusion criteria were: myocardial infarction (MI); atrial fibrillation; sinoatrial and atrioventricular blocks; cardiomyopathy; valvular heart disease; anemia; cancer; pericardial diseases; thyroid diseases; and diabetes mellitus.

All patients signed informed consent to be included in the study. Patients were informed of the possible side effects of the drugs administered. The ethics committee and the meeting of the academic council of the Bashkir State Medical University approved the study protocol.

Three representative groups of patients with HFpEF (A, B, and C) were compared. Patients were randomized by sex, age, and major clinical and functional indicators. The follow-up period was limited to 12 weeks. In Group A, bisoprolol in a dose titrated from 2.5 to 10 mg was used. In group B, a combination of bisoprolol titrated from 2.5 to 10 mg with ivabradine titrated from 10 to 15 mg/day, and in group C, ivabradine 10–15 mg/day was administered. Patients continuously received background drug therapy, including angiotensin-converting enzyme inhibitors (lisinopril), in the event of intolerance, angiotensin II receptor blockers (valsartan), antiagregants, statins (atorvastatin, rosuvastatin), short-acting nitrates, if required, as well as antiarrhythmic drugs. Diuretics were added in the event of swelling syndrome. Patients underwent the following examinations: physical examination; echocardiography and Doppler echocardiography; 24-hour electrocardiogram (ECG) monitoring; 6-minute walk test (6MWT); cycling ergometry; and coronary angiography, if necessary. After the inclusion, patients were examined every 2 weeks with HR and BP measurements. 6MWT was performed at the beginning of the follow-up, at 6 and 12 weeks. Electrocardiography, echocardiography and Doppler echocardiography, 24-hour ECG monitoring were performed before the study and at 12 weeks. ECGs were recorded in standard 12 leads on a Fucuda Denshi FX-7402 electrocardiograph. The 24-hour ECG monitoring was carried out on a Kardio–Tekhnika 04–3 device (Russia) using 5 leads. Echocardiography was carried out on a Vivid E9 (Germany) ultrasound device. Carotid arteries, major cerebral arteries, vertebral and subclavian arteries were examined on a MyLab 70 Easote ultrasound scanner.

During the 12-month prospective follow-up, bisoprolol and ivabradine effects within complex therapy on a composite primary endpoint (cardiovascular death, hospitalization for MI and CHF) were assessed in patients with CAD and HFpEF.

Quality of life (QoL) was assessed using the Minnesota questionnaire for patients with CHF developed by Hector et al. [18]. The study included a control group consisting

ISSN 0022-9040. Kardiologiia. 2020;60(10). DOI: 10.18087/cardio.2020.10.n1324

of 30 apparently healthy people without CVDs at the age of 52.5 ± 2.5 years.

Statistical analysis

The significance of differences was estimated using the Student t-test. A critical level of significance was 0.05<p<0.1, established a trend towards the statistical significance of differences. Differences were statistically significant at p<0.05. The Spearman rank correlation coefficient was used to identify and assess the relationship between two rows of comparable quantitative measures.

Results and discussion

The effects of the complex therapy, including ivabradine, on QoL of patients with HFpEF and stable CAD was evaluated within 12 weeks of follow-up, subject to attaining the target HR. The anti-ischemic effect was assessed by 24-hour Ecg monitoring. Exercise tolerance and functional status of CHF was estimated according to the 6MWT results.

The target HR was achieved within 12 weeks of treatment: HR decreased from 84±8 to 57±2 bpm (p<0.001) in group A; from 90±11 to 58±2 bpm (p<0.001) in group B; and in group C from 79±7 to 57±3 (p<0.001; Figure 1).

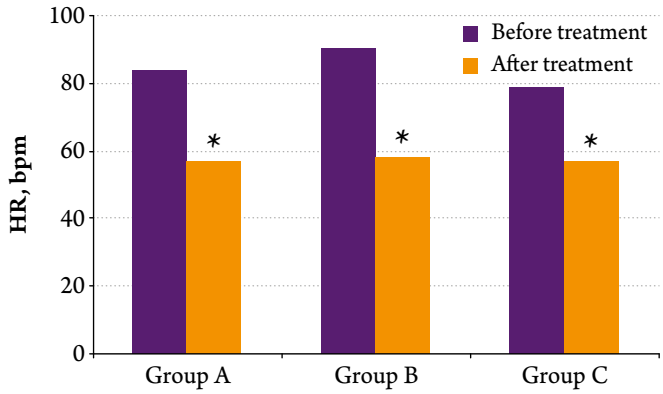
During the follow-up period, a statistically significant decrease in the duration of myocardial ischemia episodes from 20±3.7 to 6.8±5.7 hours (p<0.05) was observed in group B from combination therapy with bisoprolol and ivabradine, while only a trend towards the decreased in groups A and C when the target HR level was achieved. During treatment, all patients showed increased exercise tolerance according to the results of 6MWT after the 12-week follow-up (Table 1). There was a trend towards an increase in the 6-minute walk distance from 279±19 to 341±21 m (p>0.05) in group A; from 243±25 to 319±29 m (p<0.05) in group B; and from 268±21 to 323±22 m (p<0.05) in group C.

CHF FC decreased in 10 (19%) patients in group A, 185 (32%) in group B, and 16 (31%) in group C.

According to the findings of the Minnesota questionnaire, the most common symptoms were sluggishness, weakness (58.9%), difficulty climbing stairs (58.4%), and shortness of breath (54.5%). About 40% of patients complained of disturbed night sleep and anxiety, and an inability to exercise. Depression and lower leg and foot swelling were reported by 34.3% and 20,5% of patients, respectively.

The Minnesota questionnaire was used to evaluate QoL of patients with HFpEF during the treatment (Table 2). Repeat examination after 12 weeks of follow-up showed that the overall score decreased in patients with HFpEF from 44.5±2.6 to 38.4±2.1 in group A; from 45±2.9 to 38±2.2 in group B; and from 50.9±3.2 to 42.7±2.8 in group C (p<0.05). Thus, according to the Minnesota questionnaire, QoL improved in all three study groups.

Figures 1. Changes in HR in patients with HFpEF within the follow-up period



*, statistically significant differences from the pre-treatment values (p < 0.001). HR, heart rate; HFpEF, heart failure with preserved ejection fraction.

The Minnesota questionnaire comprises three factors of evaluating QoL: physical; social; and emotional (Table 3). In all three groups, the treatment had the most significant influence on the physical component that prevailed both before and after treatment. It was 31.5±1.0 (70.8%) and 26.3±0.6, respectively, in group A; 31.8±1.2 (70.6%) and 26.4±1.3, respectively, in group B; and 36.2±1.3 (71.1%); and 29.8±1.0, respectively, in group C.

The lowest scores in the study groups (A, B, and C) were observed for the social factor: 5.6±0.7 (12.6%); 3.9±0.9 (8.7%); and 6.3±0.9 (12.4%) before treatment. At 12 weeks this score was: 5.4±1.0; 3.6±0.4; and 6.0±1.0 respectively.

Large randomized trials demonstrated the positive effect of beta-blockers on the course of the disease and prognosis for patients with CHF [19, 20]. The BEAUTIFUL study showed that ivabradine could improve both QoL and the prognosis in patients with stable CAD complicated by HFpEF [21].

During the 12-month prospective follow-up, bisoprolol and ivabradine effects within complex therapy on a

Table 1. Changes in 6-minute walk distance in patients with HFpEF within the follow-up period

Follow-up group	Distance walked, m	
	Before treatment	After treatment
A (n=53)	279±19	341±21
B (n=56)	243±25	319±29*
C (n=51)	268±21	323±22*

*, statistically significant differences from the pre-treatment values at p < 0.05. HFpEF, heart failure with preserved ejection fraction

Table 2. Changes in quality of life in patients with HFpEF within the 12-week follow-up period

Follow-up group	Minnesota questionnaire scores of QoL	
	Before treatment	After treatment
A (n=53)	44,5±2,6	38,4±2,1*
B (n=56)	45±2,9	38±2,2*
C (n=51)	50,9±3,2	42,7±2,8*

*, statistically significant differences from the pre-treatment values ($p < 0.05$). QoL, quality of life.

Table 4. Effect of bisoprolol and ivabradine on the primary combined endpoint within the 1year follow-up period

Group	Number of hospitalizations about AMI	Number of hospitalizations for CHF
A (n=53)	3 (5.7%)	14 (26.4%)
B (n=56)	–	8 (14.3%)
C (n=51)	2 (3.9%)	12 (23.5%)

AMI, acute myocardial infarction; CHF, chronic heart failure.

Table 3. Results of intergroup analysis of the QoL scores using the Minnesota questionnaire (MLHFO) in patients with HFpEF within the 12-week follow-up period

Score	Group A (n=53)		Group B (n=56)		Group C (n=51)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Overall QoL	44.5±2.6	38.4±2.1*	45±2.9	38±2.2*	50.9±3.2	42.7±2.8*
Physical factor	31.5±1.0 (70.8%)	26.3±0.6	31.8±1.2 (70.6%)	26.4±1.3	36.2±1.3 (71.1%)	29.8±1.0
Social factor	5.6±0.7 (12.6%)	5.4±1.0	3.9±0.9 (8.7%)	3.6±0.4	6.3±0.9 (12.4%)	6.0±1.0
Emotional factor	7.4±0.9 (16.6%)	6.7±0.5	9.3±0.8 (20.7%)	8.0±0.5	8.4±1.0 (16.5%)	6.9±0.8

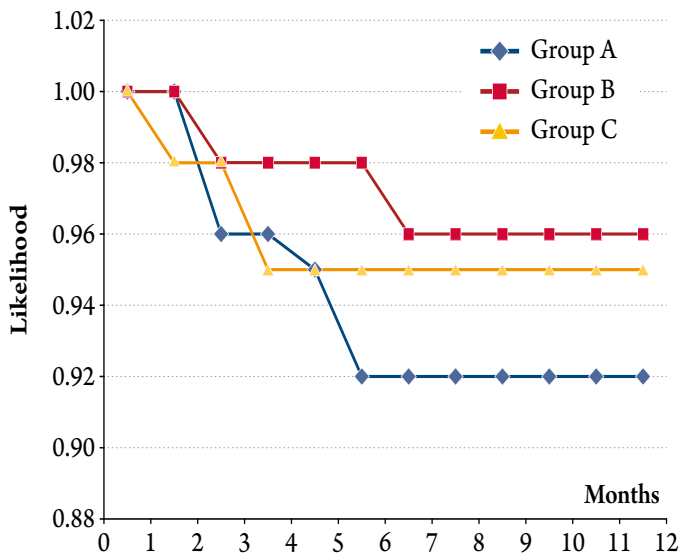
*, statistically significant differences from the pre-treatment values at $p<0.05$.

composite primary endpoint (cardiovascular death, hospitalization for acute MI and CHF) were assessed in patients with CAD and HFpEF (Table 4).

Within the 12 months of follow-up no deaths were reported in groups A, B and C. The 12-month incidence of acute IM was 5.7% and 3.9% in groups A and C, respectively. No cases of MI were reported in group B. The rate of repeat hospitalizations for decompensated CHF was 26.4% in group A, 14.3% in group B, and 23.5% in group C.

Figure 2 contains an estimate of the probability of repeat hospitalizations for CHF in groups A, B, and C. The improved QoL and the reduced risk of hospitalizations for acute MI and CHF were demonstrated within the first 12 months of follow-up in the group of patients treated with biosprolol and ivabradine within the complex therapy.

Figures 2. Likelihood of rehospitalization of the followed-up patients for CHF within a year



CHF, chronic heart failure.

Conclusion

Given the above points, achieving the target heart rate in patients with chronic heart failure with preserved left ventricular ejection fraction and type I and II diastolic dysfunctions, who receive composite therapy including bisoprolol with dose titration from 2.5 to 10 mg/day and ivabradine from 10 to 15 mg/day, contributes to a better quality of life.This is in accordance with the results of the Minnesota questionnaire after 12 weeks of follow-up. Inclusion of the combination of selective beta-blocker bisoprolol and sinoatrial f-channel blocker ivabradine in the background therapy of patients with chronic heart failure with preserved left ventricular ejection fraction and stable coronary artery disease reduces the risk of hospital admissions for acute myocardial infarction and chronic heart failure within 12 months.

No conflict of interest is reported.

The article was received on 16/08/2020

ISSN 0022-9040. Kardiologiia. 2020;60(10). DOI: 10.18087/cardio.2020.10.n1324

REFERENCES

1. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. European Heart Journal. 2016;37(27):2129–200. DOI: 10.1093/eurheartj/ehw128
2. Mosterd A, Hoes AW. Clinical epidemiology of heart failure. Heart. 2007;93(9):1137–46. DOI: 10.1136/hrt.2003.025270
3. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. Russian Cardiology Journal. 2017;22(1):7–81. [Russian: Рекомендации ESC по диагностике и лечению острой и хронической сердечной недостаточности 2016. Российский Кардиологический Журнал. 2017;22(1):7–81]
4. Filippatos G, Parissis JT. Heart failure diagnosis and prognosis in the elderly: the proof of the pudding is in the eating. European Journal of Heart Failure. 2011;13(5):467–71. DOI: 10.1093/eurjhf/hfr036
5. Van Riet EES, Hoes AW, Limburg A, Landman MAJ, van der Hoeven H, Rutten FH. Prevalence of unrecognized heart failure in older persons with shortness of breath on exertion: Unrecognized HF in older persons with shortness of breath on exertion. European Journal of Heart Failure. 2014;16(7):772–7. DOI: 10.1002/ejhf.110
6. Maggioni AP, Dahlström U, Filippatos G, Chioncel O, Crespo Leiro M, Drozdz J et al. EURObservational Research Programme: regional differences and 1-year follow-up results of the Heart Failure Pilot Survey (ESC-HF Pilot). European Journal of Heart Failure. 2013;15(7):808–17. DOI: 10.1093/eurjhf/hft050
7. Oshchepkova E.V., Lazareva N.V., Satlykova D.F., Tereshchenko S.N. The first results of the Russian register of chronic heart failure. Kardiologiia. 2015;55(5):22–8. [Russian: Ощепкова Е.В., Лазарева Н.В., Сатлыкова Д.Ф., Терещенко С.Н. Первые результаты Российского регистра хронической сердечной недостаточности. Кардиология. 2015;55(5):22–8]
8. Van Riet EES, Hoes AW, Wagenaar KP, Limburg A, Landman MAJ, Rutten FH. Epidemiology of heart failure: the prevalence of heart failure and ventricular dysfunction in older adults over time. A systematic review: Prevalence of heart failure and ventricular dysfunction. European Journal of Heart Failure. 2016;18(3):242–52. DOI: 10.1002/ejhf.483
9. Boonman-de Winter LJM, Rutten FH, Cramer MJM, Landman MJ, Liem AH, Rutten GEHM et al. High prevalence of previously unknown heart failure and left ventricular dysfunction in patients with type 2 diabetes. Diabetologia. 2012;55(8):2154–62. DOI: 10.1007/s00125-012-2579-0
10. Magaña-Serrano JA, Almahmeed W, Gomez E, Al-Shamiri M, Adgar D, Sosner P et al. Prevalence of Heart Failure With Preserved Ejection Fraction in Latin American, Middle Eastern, and North African Regions in the I PREFER Study (Identification of Patients With Heart Failure and PREserved Systolic Function: An Epidemiological Regional Study). The American Journal of Cardiology. 2011;108(9):1289–96. DOI: 10.1016/j.amjcard.2011.06.044
11. Böhm M, Swedberg K, Komajda M, Borer JS, Ford I, Dubost-Brama A et al. Heart rate as a risk factor in chronic heart failure (SHIFT): the association between heart rate and outcomes in a randomised placebo-controlled trial. The Lancet. 2010;376(9744):886–94. DOI: 10.1016/S0140-6736(10)61259-7
12. Perepech N.B. Why reduce heart rate in patients with chronic heart failure? Medical Council. 2013;9:82–91. [Russian: Перепеч Н.Б. Зачем надо уменьшать частоту сердечных сокращений у больных хронической сердечной недостаточностью? Медицинский Совет. 2013;9:82–91]
13. Flannery G, Gehrig-Mills R, Billah B, Krum H. Analysis of Randomized Controlled Trials on the Effect of Magnitude of Heart Rate Reduction on Clinical Outcomes in Patients With Systolic Chronic Heart Failure Receiving Beta-Blockers. The American Journal of Cardiology. 2008;101(6):865–9. DOI: 10.1016/j.amjcard.2007.11.023
14. Borer JS, Böhm M, Ford I, Robertson M, Komajda M, Tavazzi L et al. Efficacy and Safety of Ivabradine in Patients With Severe Chronic Systolic Heart Failure (from the SHIFT Study). The American Journal of Cardiology. 2014;113(3):497–503. DOI: 10.1016/j.amjcard.2013.10.033
15. Böhm M, Borer J, Ford I, Gonzalez-Juanatey JR, Komajda M, Lopez-Sendon J et al. Heart rate at baseline influences the effect of ivabradine on cardiovascular outcomes in chronic heart failure: analysis from the SHIFT study. Clinical Research in Cardiology. 2013;102(1):11–22. DOI: 10.1007/s00392-012-0467-8
16. Ageev F.T. Diastolic heart failure: 10 years of knowlege. Russian Heart Failure Journal. 2010;11(1):69–76. [Russian: Агеев Ф. Т. Диастолическая сердечная недостаточность: 10 лет знакомства. Журнал Сердечная Недостаточность. 2010;11(1):69–76]
17. Vasyuk Yu.A. Guidelines for functional diagnostics in cardiology. Modern methods and clinical interpretation. –M.: Practical medicine;2012. – 162 p. [Russian: Васюк Ю.А. Руководство по функциональной диагностике в кардиологии. Современные методы и клиническая интерпретация. – М.: Практическая медицина, 2012. –162 с]. ISBN 978-5-98811-223-4
18. Rector TS, Kubo SH, Cohn JN. Patients self-assessment of their congestive heart failure. Part 2: content, reliability and validity of a new measure, the Minnesota living with heart failure questionnaire. Heart failure. 1987;10:198–209
19. Zhoubrina E.S., Ageev F.T. Beta-blockers – opportunities of therapy optimization in patients with chronic heart failure in out-patient setting. Lechaschi Vrach Journal. 2013;3:80. [Russian: Жубрина Е.С., Агеев Ф.Т. Бета-адреноблокаторы - возможности оптимизации терапии хронической сердечной недостаточности в амбулаторных условиях Лечащий врач. 2013;3:80]
20. McMurray JJV, Adamopoulos S, Anker SD, Auricchio A, Bohm M, Dickstein K et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. European Heart Journal. 2012;33(14):1787–847. DOI: 10.1093/eurheartj/ehs104
21. Fox K, Ford I, Steg PG, Tendera M, Ferrari R. Ivabradine for patients with stable coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): a randomised, double-blind, placebo-controlled trial. The Lancet. 2008;372(9641):807–16. DOI: 10.1016/S0140-6736(08)61170-8