Original paper

Mildronate improves the exercise tolerance in patients with stable angina: results of a long term clinical trial

Vilnis Dzerve[**, a,*], Dace Matisone [a], Yury Pozdnyakov [b], Rafael Oganov [c]

[a] *Research Institute of Cardiology, University of Latvia, Riga, Latvia*
[b] *Moscow Regional Cardiological Centre, Moscow, Russian Federation*
[c] *Science State Research Centre for Preventive Medicine, Moscow, Russian Federation*

Summary

The objective of the study was to assess the efficacy and safety of the treatment with Mildronate (1 g/day) in combination with a standard therapy for the exercise tolerance of patients with stable angina pectoris.

Design and methods: The study was a prospective, randomized, double-blind, placebo controlled phase III trial with two treatment groups. The study was carried out in 37 medical centres in 4 countries (Latvia, Lithuania, Russian Federation and Ukraine). The study group comprised 317 patients with chronic coronary heart disease (CHD, II–III according to the classification of the Canadian Cardiovascular Society (CCS)) who had ischemia as the limiting factor in the exercise test. The treatment period lasted for 12 months.

Results: The mean value of the change in the total exercise time in the mildronate group at month 12 was 55.05 ± 88.01 seconds (sec), while the placebo patients had the mean value 0.79 ± 68.21 sec. The difference between the treatment groups was highly significant ($p < 0.001$). The mean value of the change at the maximum achieved load in the mildronate group was 7.78 ± 13.90 W, while the placebo patients had the mean value 0.10 ± 12.40 W. The difference between the treatment groups was highly significant ($p < 0.001$). At month 12 the time to deviation of ST-segment to 1 mm at least in the mildronate group increased from 425.63 ± 160.97 sec to 483.83 ± 193.99 sec, whereas a decrease with respect to the visit 6 was observed in the placebo group: from 436.76 ± 177.66 to 425.98 ± 159.12 sec. The difference between the treatment groups at month 12 was significant ($p = 0.01$). At month 12 the time to the onset of angina in the mildronate group increased from 460.50 ± 155.51 sec to 490.50 ± 207.27 sec, whereas a slight decrease was observed in the placebo group. The difference between the treatment groups at month 12 was significant ($p = 0.044$).

Conclusions: This study has revealed the superiority of the treatment with Mildronate (1 g/day) in combination with a standard therapy for the exercise tolerance of patients with stable angina pectoris over the treatment with placebo in combination with a standard therapy.

Seminars in Cardiovascular Medicine 2010; 16: 3

Keywords: mildronate, stable angina, exercise tolerance

Introduction

Angina pectoris (AP) is one of the most common medical problems of the heart. Symptoms of angina are the first manifestation of CHD in about 50% of the patients. The prevalence of angina increases sharply with age in both sexes from 0.1–1% in women aged 45–54 to 10–15% in women aged 65–74 and from 2–5% in men aged 45–54 to 10–20% in men aged 65–74. Therefore, it can be estimated that in most countries, 30 000–50 000 individuals of the population per million suffer from angina [1–4].

More than in a half of the angina patients, the symptoms seriously limit the conventional day-to-day activities and often cause an early disablement [5,6].

The results of experimental studies and clinical experience suggest that adding an effective dose of mildronate to conventional antianginal therapy could significantly reduce the symptoms of angina. Mildronate is a structural asa-analogue of the carnitine precursor gamma-butyrobetaine (GBB). It inhibits carnitine biosyn-

* Corresponding address: Vilnis Dzerve, Research Institute of Cardiology, University of Latvia, Pilsonu iela 13, Riga LV-1002, Latvia.
E-mail: dzerve@lki.eunet.lv (V. Dzerve).

** On behalf of the Study Group (full list of the names is given before References section).

thesis (reversibly competing for gamma-butyrobetaine hydroxylase). This results in reduced tissue [7] and plasma [8] concentrations of carnitine. Thereby, long-chain fatty acids transport through internal mitochondrial membranes is inhibited. That, in turn, further enhances the rehabilitation of the transport of entire ATP produced in cytosol. This induces delayed β-oxidation of fatty acids and prevents the accumulation of unoxidized fatty acids – acyl-carnitine and acyl-coenzyme A – into mitochondria. Increased cytosol concentration of fatty acids is a specific signal to cells that the fatty acid oxidation is not possible. The body responses to such a signal by the initiation of the glucose oxidation mechanisms [9].

Reduced body concentration of carnitine stimulates the synthesis of its precursor GBB [10], which activates NO-syntethase thus causing both vasodilatation and antivasospasmic effects. GBB's capability to selectively dilate spastic blood vessels is important, since this ensures blood supply to ischemic areas without provoking a steal effect for the healthy parts of the myocardium [11,12].

The efficacy of mildronate for the treatment of myocardial ischemia has been proved in experiments and clinics by: the improved systolic function of the myocardium; the inhibited hypertrophy and dilatation of the myocardium; the improved peripheral blood circulation – increased contractility of arteriole smooth muscles; the increased stress tolerance; the reduced anginal symptoms; the improved quality of life [13–17].

Up to now, the mildronate clinical trials of CHD have mostly been performed on a casual basis. They have usually been done in one centre involving a small number of patients, thus do not fully meet the principles of evidence based medicine.

The objective of the study was to assess the efficacy and safety of the treatment with mildronate (1 g/day) in combination with a standard therapy for the exercise tolerance of patients with stable angina pectoris. ***The aim*** of the study was to assess the efficacy of mildronate using the indices of exercise capacity for patients with stable angina. The study was designed to investigate whether statistically significant improvement in total exercise time of bicycle ergometry could be achieved by mildronate thus indicating its anti-ischemic properties compared to placebo in patients with stable effort angina (angina pectoris) as manifestation of CHD.

Design and Methods

The study was a prospective, randomized, double-blind, placebo controlled phase III trial with two treatment groups. The study was conducted in outpatients with justified stable effort angina due to myocardial ischemia with typical ST changes.

The study included totally 317 male and female patients (screened) with chronic CHD (II–III functional classes according to the CCS, who had ischemia as the limiting factor in the exercise test. Being found eligible, the patients were randomized in 1:1 ratio to receive either mildronate or placebo at visit 4, following the run-in period. Randomization was stratified by study sites. Overall, 278 patients completed the study, all of them were included into the statistical analysis (Table 1).

Both treatment groups were comparable with respect to their demographic characteristics. There were more males (80.3% in the mildronate group and 78.0% in the placebo group) than females (19.7% in the mildronate group and 22.0% in the placebo group).

The mean age at the date when a written informed consent was signed was 60.96 years in the mildronate group and 62.61 years in the placebo group ($p = 0.191$).

The follow-up time was planned for 13 months: the 4 weeks run-in period plus 12 months of the randomized therapy.

In order to investigate the study objective and document the findings, a bicycle ergometry testing – the standard examination method for patients with CHD (therefore not increasing the risk for the patients) – was used.

The study was conducted in accordance with the principles set forth in Good Clinical Practice (GCP), the International Conference of Harmonisation (ICH) *(CPMP/ICH/135/95)*, the Helsinki Declaration (1964, amended in 2002), the Guid-

Table 1.
Demographic characteristics of the patients

Variable		Treatment groups	
		Mildronate (*N* = 137)	Placebo (*N* = 141)
Male	*N*	110	110
Female	*N*	27	31
Premenopausal	*N*	1	2
Postmenopausal	*N*	26	29
Age	Mean	60.96	62.61
	SD	8.61	9.98
	Min	35.73	24.75
	Max	80.53	81.50

ance on the Clinical Investigation of Anti-Anginal Medicinal Products in Stable Angina Pectoris (CPMP/EWP/234/95/rev. 1) and any applicable national regulatory requirements.

The primary endpoint of the study was the change in the exercise time during bicycle ergometry from the baseline up to 12 months of treatment.

The baseline was defined as the mean exercise time of the last two measurements (visit 3 and visit 4) of the run-in period. The exercise time after 12 months of treatment was defined as the mean of the measurements at visit 8 and visit 9.

Secondary endpoints concerning the exercise tolerance were:

- the change in the maximum achieved load (MAL) [W] from the baseline to month 12;
- the change in the time to ST segment depression of 1 mm at least in the left precordial leads in bicycle ergometry from baseline up to 12 months of treatment;
- the change in the time to the onset of angina from the baseline to month 12.

An exercise test had to be performed on a standard bicycle ergometer at least 12 hours since the intake of mildronate or placebo and the standard antianginal therapy (except the short acting nitrates). The initial load was 50 W, which was increased by 25 W at 3-minute intervals until a subjective maximum. Indications for stopping the exercise test were: severe exhaustion, severe dyspnoea, an anginal attack, dizziness, ST-depression over 1 mm, persistent drop in systolic blood pressure (below 90 mm Hg), serious ventricular arrhythmias, supraventricular tachycardia or AV-block.

During and before the termination of the test, a heart rate, blood pressure and the magnitude of changes of the ST-segment (at the end of each workload and upon the termination of the test) had to be measured. The total exercise time and the highest achieved workload had to be recorded. ST-depression had to be measured 80 ms from J-point.

It was requested that the antianginal medication of the patient should remain unchanged during the run-in period and 2 weeks before visits 6, 8 and 9.

Weighing up benefits and risks, placebo treatment for 12 months appeared acceptable, since the patients received an individually adjusted standard CHD treatment during the whole study period. Study medication (500 mg mildronate or placebo) was applied orally twice a day. The patients visited the study centre regularly for the investigator's evaluation of the efficacy, safety and tolerability, as outlined in the study flowchart (Table 2).

Results

Primary end point

At the baseline the mean value of the total exercise time in the mildronate group was 481.26 ± 159.52 seconds, and in the placebo group –457.50 ± 149.89 seconds in the study population. This difference between the treatment groups at the baseline was non-significant ($p = 0.226$).

During the treatment period, the total exercise time increased in both groups, but the mildronate group showed more pronounced values reaching the difference already after a 6-month treatment period.

So, the mean total exercise time increased to 525 ± 188 seconds in the mildronate group and to 478 ± 177 seconds in the placebo group at visit 6. The difference between the treatment groups was marked as significant ($p = 0.038$).

The difference grew during the further treatment period: at month 12 the mean total exercise time in the mildronate group increased to 529.22 ± 189.55 seconds, whereas a decrease with respect to visit 6 was observed in the placebo group: 468.01 ± 160.01 seconds. The difference between the treatment groups at month 12 was significant ($p = 0.009$).

Thus, the absolute values of the total exercise time sharply differ in the mildronate and placebo groups, as it is shown in Figure 1.

The mean value of the change in the total exercise time in the mildronate group was 55.05 ± 88.01 seconds, while the placebo patients had the mean value of 0.79 ± 68.21 seconds. The differ-

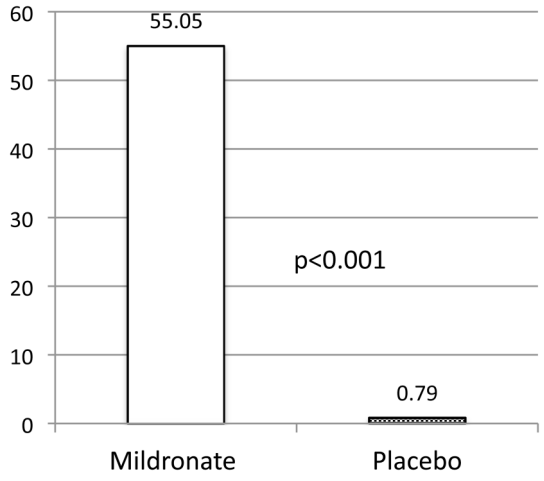

Figure 1. The change in the total exercise time from the baseline up to month 12 in the study groups.

Seminars in Cardiovascular Medicine, 2010; 16:3
e-ISSN 1822-7767

Table 2.
Summary of primary and secondary end point data

Time	Index	Total exercise time		*p*-value	Maximum load		*p*-value	Time of ST dev. 1 mm		*p*-value	Time to onset of angina		*p*-value
		Mildronate	Placebo		Mildronate	Placebo		Mildronate	Placebo		Mildronate	Placebo	
BASELINE	Valid N	137	141		137	141		137	141		137	141	
	Minimum [sec]	220.5	200.5		75	75		105	167		167.5	200.5	
	Maximum [sec]	890.5	772		162.5	150		817.5	750		877.5	750.5	
	Mean [sec]	**481.26**	**457.5**	$p = 0.226$	**101.73**	**98.76**	$p < 0.001$	**425.63**	**398.98**	$p = 0.185$	**460.5**	**443.29**	$p = 0.34$
	Std deviation [sec]	159.52	149.89		21.66	20.77		160.97	145.75		155.51	148.23	
VISIT 6	Valid *N*	130	128		130	128		130	128		130	128	
	Minimum [sec]	156	176		50	50		108	120		0	0	
	Maximum [sec]	957	948		175	175		900	900		900	948	
	Mean [sec]	**525**	**478**	$p = 0.038$	**107**	**102**	$p = 0.06$	**473.84**	**436.76**	$p = 0.107$	**482.38**	**444.81**	$p = 0.114$
	Std deviation [sec]	188	177		21.66	24		188.07	177.66		213.29	189.32	
MONTH 12	Valid N	127	126		127	126		127	126		127	126	
	Minimum [sec]	165	185.5		50	50		104.5	122.5		0	0	
	Maximum [sec]	1154	888		187.5	150		1154	788		1154	815	
	Mean [sec]	**529.22**	**468.01**	$p = 0.009$	**108.56**	**100.3**	$p = 0.008$	**483.83**	**425.98**	$p = 0.01$	**490.5**	**443.06**	$p = 0.044$
	Std deviation [sec]	189.55	160.01		25.53	22.27		193.99	159.12		207.27	168.91	

Table 3.
Descriptive statistics for the change in the total exercise time from month 12 to the baseline [sec] by age groups and treatment groups

Age group	Difference: Month 12 - Baseline		*p*-value
Treatment	Valid *N*	Mean ± SD	
Younger than 60			
Mildronate	59	55.67 ± 99.52	0.045
Placebo	45	4.82 ± 77.71	
Older than 70			
Mildronate	15	21.57 ± 61.69	0.089
Placebo	31	–11.95 ± 52.28	

Table 4.
Descriptive statistics for the change in the total exercise time from the baseline to month 12 by CCS functional class at visit 4

		Treatment group	
	Mildronate	Placebo	
Class 2	Valid *N*	96	97
	Minimum [sec]	–66.00	–169.00
	Maximum [sec]	428.50	135.50
	Mean [sec]	57.31	0.04
	Std deviation [sec]	91.11	71.58
Class 3	Valid *N*	31	29
	Minimum [sec]	–62.50	–100.50
	Maximum [sec]	249.00	120.00
	Mean [sec]	48.06	3.33
	Std deviation [sec]	78.63	56.53

ence between the treatment groups was highly significant (p-value < 0.001).

The analysis of the dynamics of the total exercise time was performed in different patient subgroups depending on age (Table 3), class of CHD (Table 4), reason of stopping the exercise test (Table 5).

For patients younger than 60 years the mean value of the change in the total exercise time in the mildronate group was 55.67 ± 99.52 seconds, while the placebo patients had the mean value of 4.82 ± 77.71 seconds. The difference between the treatment groups was significant ($p = 0.045$).

For patients older than 70 years the mean value of the change in the total exercise time in the mildronate group was 21.57 ± 61.69 seconds, in the placebo group it was 11.95 ± 52.28 seconds. The difference between the treatment groups was non-significant ($p = 0.089$).

The data summarized in Table 3 revealed the effect of age on the total exercise time with a remarkable difference between the mildronate and placebo treatment in both age groups.

Table 5.
Descriptive statistics for the change in the total exercise time from the baseline to month 12 due to stopping the exercise test at visit 1

		Treatment group	
		Mildronate	Placebo
Severe exhaustion	Valid *N*	1	3
	Minimum [sec]	47.50	–97.50
	Maximum [sec]	47.50	–15.50
	Mean [sec]	47.50	–58.17
	Std deviation [sec]	0	41.10
Anginal attack	Valid *N*	88	90
	Minimum [sec]	–66.00	–169.00
	Maximum [sec]	263.50	135.50
	Mean [sec]	46.91	1.44
	Std deviation [sec]	79.95	68.86
ST depression over 1 mm	Valid *N*	28	23
	Minimum [sec]	–62.50	–147.50
	Maximum [sec]	428.50	126.50
	Mean [sec]	95.89	9.30
	Std deviation [sec]	108.99	68.51

The same correlation was observed between the total exercise time and severity of the disease (CCS class), though the in-group difference was essential as well (Table 4).

For the patients having the CCS functional class 2 at visit 4 the mean change in the total exercise time from the baseline to month 12 was 57.31 ± 91.11 seconds in the mildronate group and 0.04 ± 71.58 seconds in the placebo group. For the patients having the CCS functional class 3 at visit 4 the mean change in the total exercise time was 48.06 ± 78.63 seconds in the mildronate group and 3.33 ± 56.53 seconds in the placebo group.

The most common reason of stopping the exercise test was an anginal attack in both treatment groups. For these patients the mean change in the total exercise time from the baseline to month 12 was 46.91 ± 79.95 seconds in the mildronate group and 1.44 ± 68.86 seconds in the placebo group.

For the patients having severe exhaustion as the reason of stopping the exercise test the mean change in the total exercise time was 47.50 ± 0 seconds in the mildronate group and 58.17 ± 41.10 seconds in the placebo group. For the patients having ST depression over 1 mm as the reason of stopping the exercise test the mean change in the total exercise time was 95.89 ± 108.99 seconds in the mildronate group and 9.30 ± 68.51 seconds in the placebo group.

Secondary endpoints

Maximum achieved load

The dynamics of the maximum achieved load during the treatment period is shown in Figure 2.

At the baseline the mean value of the maximum achieved load in the mildronate group was 101.73 ± 21.66 W, and in the placebo group – 98.76 ± 20.77 W. The maximum achieved loads were quite similar for both treatment groups at the baseline ($p = 0.252$).

The maximum achieved load slightly increased at visit 6 in the mildronate group to 107 ± 21.66 W. For patients in the placebo group at visit 6 the maximum achieved load increased to 102 ± 24 W. The difference between the treatment groups was not significant ($p = 0.06$).

At month 12 the maximum achieved load in the mildronate group increased to 108.56 ± 25.53 W, whereas a slight decrease with respect to visit 6 was observed in the placebo group: 100.30 ± 22.27 W. The difference between the treatment groups at month 12 was significant ($p = 0.008$).

Therefore, the data analysis revealed, that the maximum achieved load in the placebo group did not change during the treatment period whereas in the mildronate group it gradually grew. This is demonstrated in Table 6, where the changes of the maximum achieved load are depicted.

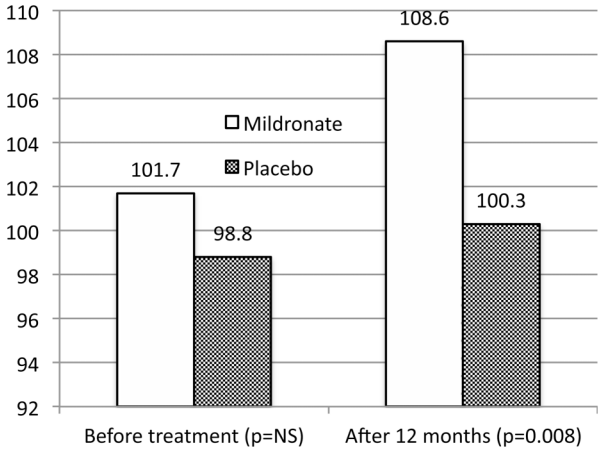

Figure 2. Maximum achieved load before the treatment and at month 12 (W).

Table 6.
Descriptive statistics for the change in the maximum achieved load [W] from the baseline to month 12

	Mildronate	Placebo
Valid N	127	126
Minimum	–25.00	–25.00
Maximum	50.00	25.00
Mean ± SD*	7.78 ± 13.90	0.10 ± 12.40

SD = standard deviation

The mean value of the change in the maximum achieved load in the mildronate group was 7.78 ± 13.90 W, while the placebo patients had the mean value of 0.10 ± 12.40 W. The difference between the treatment groups was highly significant (p-value < 0.001).

For the patients who were 70 years old and younger the mean changes in the maximum achieved load from the baseline to month 12 was 8.48 ± 14.06 W in the mildronate group and 1.05 ± 12.32 W in the placebo group. For the patients over 70 years old the mean changes in the maximum achieved load from the baseline to month 12 was 2.50 ± 11.76 W in the mildronate group and –2.82 ± 12.38 W in the placebo group.

Time to the deviation of the ST-segment to 1 mm at least

At the baseline the mean time to the deviation of the ST-segment to 1 mm at least in the mildronate group was 425.63 ± 160.97 sec, and in the placebo group – 398.98 ± 145.75 sec. The difference between the time to the deviation of the ST-segment to 1 mm at least between the treatment groups at the baseline was non-significant ($p = 0.185$).

The time to the deviation of the ST-segment to 1 mm at least increased at visit 6 in both treatment groups: in the mildronate group – to 473.84 ± 188.07 sec, in the placebo group – to 436.76 ± 177.66 sec. The difference between the treatment groups was not significant ($p = 0.107$).

At month 12 the time to the deviation of the ST-segment to 1 mm at least in the mildronate group increased to 483.83 ± 193.99 sec, whereas a decrease with respect to visit 6 was observed in the placebo group: 425.98 ± 159.12 sec. The difference between the treatment groups at month 12 was significant ($p = 0.01$).

Time to the onset of angina

At the baseline the mean time to the onset of angina in the mildronate group was 460 ±155 sec, and in the placebo group –443 ± 148 sec. The difference between the time to the onset of angina among the treatment groups at the baseline was non-significant ($p = 0.340$).

The time to the onset of angina increased at visit 6 in both treatment groups: in the mildronate group to 482.38 ± 213.29 sec, in the placebo group to 444.81 ± 189.32 sec. The difference between the treatment groups was not significant ($p = 0.114$).

At month 12 the time to the onset of angina in the mildronate group increased to 490.50 ± 207.27 sec, whereas a slight decrease was observed in the placebo group: 443.06 ± 168.91 sec.

The difference between the treatment groups at month 12 was significant ($p = 0.044$).

Discussion and Conclusions

For the primary efficacy evaluation the hypothesis of superiority in the change in the total exercise time in VEM (bicycle ergometry) from the baseline to month 12 was tested at the 5% level of significance in the study population.

The study showed that during a long-term treatment of CHD the mean increase of the total exercise time from the baseline to month 12 in the mildronate group was substantially higher than in the placebo group (55.05 seconds in the mildronate group versus 0.79 seconds in the placebo group). The difference between the treatment groups was highly significant (p-value <0.001).

The same relationship concerning the mean change in the maximum achieved load, the mean time to the deviation of the ST-segment to 1 mm at least and the time to the onset of angina during VEM was found. The difference between the treatment groups at month 12 was highly significant.

It should be stressed that the mean age of the patients at the visit for randomization was 61–62 years, their heart health condition was serious (2–3 class CCS) and the process of atherosclerosis was likely to be ongoing. In spite of this baseline exercise tolerance and the quality of life in the mildronate group the patients were not only maintained on the same level but also remarkably improved during the treatment period, whereas the best result in the placebo group was that the values remained very similar throughout the treatment.

Therefore, this study has revealed the advantage of the treatment with mildronate (1 g/day) in combination with a standard therapy for the exercise tolerance of patients with stable angina pectoris over the treatment with placebo in combination with a standard therapy.

Therefore, the results of MILSS II completely confirmed mildronate as a corrector of metabolism improving the exercise tolerance und quality of life of CHD patients.

These clinical consequences are supported by the theoretical considerations, experimental data and previous clinical findings about the impact of mildronate.

List of Principal Investigators

Dr. Archil Gersamija, Daugavpils, Latvia;
Prof. Ivars Silins, Riga, Latvia;
Dr. Baiba Anshmite, Riga, Latvia;
Dr. Janina Romanova, Riga, Latvia;
Dr. Silvija Hansone, Riga, Latvia;
Dr. Maija Keisha, Valmiera, Latvia;
Dr. Maruta Priedite, Mezotne, Latvia;
Dr. Jūratė Anusauskienė, Klaipėda, Lithuania;
Dr. Roma Kavalauskienė, Klaipėda, Lithuania;
Dr. Romualdas Stankevičius, Šiauliai, Lithuania;
Prof. Rima Steponenienė, Vilnius, Lithuania;
Dr. Sigita Aidietienė, Vilnius, Lithuania;
Dr. Gintarė Šakalytė, Kaunas, Lithuania;
Prof. Irena Milvidaitė, Kaunas, Lithuania;
Dr. Virgilijus Grinius, Kaunas, Lithuania;
Prof. Rimvydas Šlapikas, Kaunas, Lithuania;
Prof. Virginija Grabauskienė, Vilnius, Lithuania;
Prof. Loreta Ivaškevičienė Vilnius, Lithuania;
Prof. Valentin Shumakov, Kiev, Ukraine;
Prof. Leonid Voronkov, Kiev, Ukraine;
Prof. Vladimir Kovalenko, Kiev, Ukraine;
Prof. Viktor Lizogub, Kiev, Ukraine;
Prof. Jekaterina Amosova, Kiev, Ukraine;
Prof. Ivan Vihovanyk, Kiev, Ukraine;
Prof. Vera Celuiko, Kharkov, Ukraine;
Prof. Igor Bereznyakov, Kharkov, Ukraine;
Dr. Igor Kraiz, Kharkov, Ukraine;
Prof. Vladimir Volkov, Kharkov, Ukraine;
Prof. Inna Homazjuk, Kiev, Ukraine;
Prof. Alexander Legkonogov, Simferopol, Ukraine;
Prof. Maria Orinchak, Ivano-Frankovsk, Ukraine;
Prof. Nestor Seredyk, Ivano-Frankovsk, Ukraine;
Prof. Jury Grishkin, St. Petersburg, Russian Federation;
Dr. Zinovy Smolin, St. Petersburg, Russian Federation;
Dr. Sergey Bondarev, St. Petersburg, Russian Federation;
Prof. Tatjana Tjurina, St. Petersburg, Russian Federation;
Prof. Alexander Konjakhin, Moscow, Russian Federation.

References

[1] Guidelines on the management of stable angina pectoris: executive summary. The Task Force on the Management of Stable Angina Pectoris of the European Society of Cardiology. *Eur Heart J* 2006; 27 (11): 1341–1381.
[2] Sorlie PD, Cooper L, Schreiner PJ, Rosamond W, Szklo M. Repeatability and validity of the Rose questionnaire for angina pectoris in the Atherosclerosis Risk in Communities Study. *J Clin Epidemiol* 1996; 49: 719–725.
[3] Ford ES, Giles WH, Croft JB. Prevalence of nonfatal coronary heart disease among American adults. *Am Heart J* 2000; 139: 371–377.
[4] Cosin J, Asin E, Marrugat J, Elosua R, Aros F, de los Reyes M, et al. Prevalence of angina pectoris in Spain. *Eur J Epidemiol* 1999; 15: 323–330.
[5] Arornaa A, Heliovaara M, Impivaara O, Knekt P, Klaukka T, Joukamaa M. Health, functional limitations and need for care in Finland. Basic results from the Mini-Finland Health Survey. Helsinki and Turku 1989; Kansanel Kkelailoksenjulkaisuja AL; 32.
[6] Royal College of General Practitioners, Office of Population Censuses and Surveys. *Morbidity statistics from general practice 1981–1982 (third national study) 1986;* London: HMSO, (Series MB5, No 1:23).
[7] Hayashi Y, Muranaka Y, Kirimoto T, Asaka N, Miyake H, Matsuura N. Effects of MET-88, a γ-butyrobetaine hydroxylase inhibitor, on tissue carnitine and lipid levels in rats. *Biol Pharm Bul* 2000; 23 (6): 770–773.

[8] Spaniol M, Brooks H, Lucas A, Zimmerman A, Solioz M, Stieger B, Krahenbuhl S. Development and characterization of an animal model of carnitine deficiency. *Eur J Biochem* 2001; 268, 1876–1887.
[9] Kalviņsh I. Mildronate. The mechanisms of action and perspectives of use. Riga, *Grindex,* 2002: 36.
[10] Liepinsh E, Vilskersts R, Loca D, Kirjanova O, Pugovichs O, Kalvinsh I, et al. Mildronate, an inhibitor of carnitine biosynthesis, induces an increase in gamma-butyrobetaine contents and cardioprotection in isolated rat heart infarction. *J Cardiovasc Pharmacol* 2006; 48 (6): 314–319.
[11] Veveris M, Kalvins I. Cardioprotective effect of γ-butyroretaine on experimental myocardial infarction on dogs. *19-th Congress of the European Society of Cardiology* 1997; Abstr., Stockholm.
[12] Veveris M, Atare Z, Kimenis A, Kalvins I. Results of pharmacologic investigation of mildronate. *Experim Klin Pharmacother 1991; Riga, Zinatne*, 1991; 19: 15–22.
[13] Sesti C, Simkhovich BZ, Kalvinsh I, Kloner R. Mildronate, a novel fatty acid oxidation inhibitor and antianginal agent, reduces myocardial infarct size without affecting hemodynamics. *J Cardiovasc Pharm* 2006; 47(3): 493–499.
[14] Teplyakov AT, Sankevitch TV, Stepatcheva TA, Mamchur SE. The use of fatty acid beta-oxidation inhibitor mildronate as monotherapy or in combination with atenolol in patients with left ventricular dysfunction after myocardial infarction. *Kardiologiia* 2003; 43(12): 15–18.
[15] Kutishenko NP, Dmitrieva NA, Lukina JV, Kozireva MP, Semyonova YE, Deev AD, et al. Influence of mildronate on efficiency of antianginal therapy in patients with stable burden angina. *Rational Pharmacother Cardiol* 2005; 2: 37–47.
[16] Sergienko IV, Bugriy ME, Balahonova TV, et al. The possibility of usage of metabolic correction therapy in patients with ischemic heart disease and heart failure. *Rational Pharmacother Cardiol* 2007; 4: 25–31.
[17] Dzerve V, Matisone D, Kukulis I, Romanova J, Putane L, Grabauskienė V et al. Mildronate improves peripheral circulation in patients with chronic heart failure: results of clinical trial (I st report). *Semin Cardiol* 2005; 11(2): 56–64.