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HEART RATE IN PATIENTS WITH CORONARY ARTERY DISEASE IN LATVIA

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CONTENTS

ABBREVIATIONS USED

HDLC – high density lipoprotein cholesterol

ACEI – angiotensin converting enzyme inhibitors

ARB – angiotensin II receptor blockers

BEAUTIFUL – MorBiditymortality EvAlUation of The I_f inhibitor ivabradine in patients with coronary disease and left ventricULar dysfunction

BMI – body mass index

bpm – beats per minute

Ca – calcium

CABG – coronary artery bypass graft

CAD – coronary artery disease

CLARIFY – ProspeCtive observational LongitudinaAl RegIstry oF patients with stable coronary arterY disease

CV – cardiovascular

EHS – Euro Heart Survey

ECG – electrocardiogram

EUROASPIRE – a European Society of Cardiology survey of secondary prevention of coronary heart disease

Hb – hemoglobin

HR – heart rate

IQR – interquartile range

LDLC – low density lipoprotein cholesterol

M – mean

Me – median

mg/d – milligrams per day

n – number

p – confidence coefficient

PCI – percutaneous coronary intervention

r – Pearson correlation coefficient

REALITY Latvia – CurRent statE of Angina treatment in the outpatient popuLation and heart rate moITtoring survey in Latvia

r_s – Spearman rank correlation coefficient

SCORE – systematic coronary risk evaluation

SD – standard deviation

SHIFT – Systolic Heart failure treatment with the I_f inhibitor ivabradine Trial

SPSS – statistical package for the social sciences

vs – *versus*/compared to

Y – year

1. INTRODUCTION

1.1. Problem topicality

Coronary artery disease (CAD) is the top death reason worldwide and it is expected to preserve its stable leading position over the period of next 20 years as regards the causes of death among population [1].

In Latvia, the position of cardiovascular (CV) diseases is comparatively adverse. According to statistical data [2, 3, 4, 5], the mortality rate from CV diseases in Latvia is one of the highest in the European Union and CV diseases leave a very significant socio–economic impact on the overall Latvian society. CV diseases are the most frequent death cause in Latvia (56% of all deceased): 16 313 death cases (year 2012), from which ~10% have died in the age until 60 years. The standard premature mortality from CV diseases in Latvia is three times higher than on average in the European Union. CV diseases is the second most significant death cause group (following external causes of death), as a result of which most life years are potentially lost. Although during recent years, the mortality due to myocardial infarction and unstable angina among hospitalized patients is decreasing, CV diseases are still the leading cause of death in the country [2]**.** It makes us to conclude that the level of treatment of outpatients with CV diseases lacks behind the progressive, up–to–date and modern treatment in specialized centers and in combination with shortcomings in primary CV diseases prevention system, scarce understanding regarding CV risk factors and the necessity of adequate correction of them delays improvement of epidemiologic situation in Latvia. The same correlation can also be referred to CAD, if we look at it separately.

Although in patients with stable CAD the risk of CV events is comparatively lower as in patients with acute coronary syndrome, it is still high [6]. The number of CV events in patients with stable CAD is influenced both

by long–term treatment, as well as understanding of CV risk factors and effective control of them in longer sustainable period.

Increased heart rate (HR) is well known cause of ischemia accepted a long time ago. However, understanding of the prognostic role of HR in the context of CV events has created only in the recent years. If previously increased HR was perceived only as a marker of increased activity of sympathetic system, then during the recent years the world and also Latvia has increased thinking about accelerated HR as a fully independent risk factor of CV diseases, which together with well–known CV risk factors (such as increased blood pressure, dyslipidemia, etc.) impact the number of CV events. The information summarized already before permitted to mark a clear connection between HR and CV events both in the total population, as well as for patients with CAD [7]. New turn in the understanding about HR connection with CV events was marked by the BEAUTIFUL (Morbidity–mortality evaluation of the I_f inhibitor ivabradine in patients with coronary disease and left ventricular dysfunction), study published in 2008. BEAUTIFUL study for the first time in prospective way proved that HR $\geq$ 70 beats per minute (bpm) increases the number of CV events in patients with stable CAD [8]. The second prospective study, which analyzed relation between HR and risk of CV events, but this time for heart failure patients, was SHIFT (Systolic Heart failure treatment with the I_f inhibitor ivabradine Trial). SHIFT investigators concluded that in heart failure patients increased resting heart rate is a CV risk factor [9].

Increased HR as a CV risk factor was for the first time included in the guidelines comparatively recently (only in 2007, in the European guidelines [10] and Latvian [7] guidelines on CV diseases prevention of the same year). The fact that higher attention of medical community to HR as independent CV risk factor was paid only during the recent years, permits to think that Latvian practitioners, when treating CAD patients, HR may allegedly not perceive as

a treatment target, insufficiently evaluate it as an important hemodynamic CV parameter and thus improperly correct it.

There is scarce information about the situation how HR is controlled for patients with stable CAD in Latvia. EUROASPIRE (A European Society of Cardiology survey of secondary prevention of coronary heart disease) study acquired data about HR for CAD patients, however, in this study HR was not measured in standardized manner. No significant studies, focused on HR and which would fix it in standardized manner, have been made in Latvia.

Moreover, there are no data how this important CV hemodynamic parameter differs in total population compared to CAD patients. In Latvia there is acute coronary syndrome registry, however, these data refer to hospitalized patients. The lack of information regarding situation with stable CAD outpatients in Latvia should be acknowledged.

Such information would permit to understand better the habits of Latvian physicians in evaluation of HR and its control when treating CAD outpatients. This would permit to verify possible gaps between current practice and recommendations from guidelines. Diminishing of such gaps in the future would possibly help to improve symptoms as well as prognosis of CAD patients. This is the basis of topicality of current study.

1.2. Aim of the study

The aim of the study is to clarify the prevalence of increased HR as well as quality of treatment connected with HR control in outpatients with stable CAD.

1.3. Tasks

1. To clarify the level of HR, the prevalence of increased HR (≥ 70 bpm) as well as the dynamics of HR over three–year observational period in the sample of treated outpatients with stable CAD in Latvia created in 2010.
2. To evaluate changes in the proportion of patients with increased HR during 2006–2010 comparing the sample of CAD patients created in 2010 with historical CAD population from REALITY Latvia study in 2006.
3. To establish possible reasons for inadequate HR control in patients with CAD by analyzing usage of HR reducing agents (daily doses, combinations of different HR reducing agents, dynamics during period of time) as well as physicians' viewpoint regarding HR.
4. To evaluate prevalence of increased HR in general Latvia population in comparison with the sample of CAD patients created in 2010.

1.4. Hypothesis

HR in treated outpatients with stable CAD in Latvia is inadequately controlled, potential of HR reduction is not fully used by physicians and increased HR is frequent in general Latvia population.

1.5. Scientific and practical innovation of the study

Innovation of the study is related to the fact that nucleus of analysis is HR, to which so far no large attention was paid in research works in Latvia. The present study analyzes HR among other CV risk factors, by looking at

different aspects of this matter, i.e., by analyzing HR, its control and relation with other CV risk factors in CAD patients, by researching the dynamics of this and other CV risk factors' control over several years (both for the same sample of treated CAD patients in Latvia over three–years period, as well as by looking at two different CAD patients' populations observed in Latvia with a four years' interval), as well as comparing HR and other CV risks for CAD patients and for general population in Latvia.

When analyzing HR control rate for CAD patients, HR reducing agents, their doses and combinations, physicians' opinion about HR in different patients groups were analyzed. Also dynamics in the control of this CV risk factor over several years was evaluated as well as reasons for insufficient control of HR in treated CAD patients. Study shows so far unused potential for better control of HR. These findings would permit to control by practitioners HR as the CV risk factor more successfully in the future, thus decreasing the likeliness of CV events in Latvia.

1.6. Personal input

Author personally was involved in recruitment and briefing of practitioners who included patients. Author followed–up the whole process of data collection, controlled data quality, summarized and analyzed the information.

Author was involved also in REALITY Latvia (historical control group of CAD patients): in the development of questionnaire, recruitment of practitioners who investigated patients, summarization and analysis of the information.

Creation of questionnaire on HR for physicians, questioning of practitioners as well as analysis of collected data was done by the author.

Author also prepared all scientific publications reflecting study results and participated with oral presentations or posters communicating findings of the study in scientific conferences and congresses of Latvia as well as international scale.

1.7. Volume and structure of thesis

Thesis is written in Latvian and has the following structure: introduction, review of literature, materials and methods, results, discussion, conclusions, practical recommendations and list of literature. The volume of paper is 163 pages, including 54 tables, 17 figures and 1 appendix. List of references contains 168 publications' titles.

2. MATERIALS AND METHODS

Sample of treated outpatients with stable CAD was set up in the year 2010. It was the main researched population and it was analyzed at baseline, i.e., after inclusion of patients and later observed in the dynamics over three–year follow–up period. Data regarding HR, other CV risk factors, clinical condition and treatment of patients were recorded at baseline and annually. Thus four different assessments were acquired for each analyzed parameter.

In addition to the main researched sample of CAD patients, also other populations were analyzed: historical CAD population from REALITY Latvia study in 2006 and control group in general population. The baseline data of the main analyzed CAD population were compared both with the historical CAD control group from REALITY Latvia in order to assess changes in the control of HR and other CV risk factors during the time from 2006 to 2010, as well as with the control group in general Latvia population for evaluation of differences in HR and other CV risk factors for CAD patients and representatives of general population.

By means of a questionnaire, the opinion of practitioners about HR in patients with CAD as well as in patients with heart failure was clarified.

2.1. Analyzed population of CAD patients

One hundred twenty treated outpatients with established stable CAD were included in the study and later followed–up for three–year period. Approval of the Ethics Committee of the Research Institute of Cardiology, University of Latvia was obtained before enrollment of patients into study (23.09.2009). During the period from November 2009 to March 2010 twelve

physicians in Latvia (10 cardiologists and 2 general practitioners working in different regions of Latvia) included in the study six to 12 treated patients with stable CAD. The acquired data about patients were summarized in standardized forms completed by treating practitioners.

Physicians surveyed included patients in their places of practice and collected information regarding demographical characteristics, CV risk factors and lifestyle, medical history, results of physical examination, most recent measurements (including laboratory values), symptoms and treatment.

The resting HR was estimated by two methods: pulse palpation and electrocardiography (ECG). Pulse palpation was performed after sitting for at least 5 min in a quiet room with comfortable temperature, then HR was measured for 30 seconds, 2 measurements were taken, and the lowest was recorded. For ECG the most recent ECG within 6 months was analyzed.

After gaining of baseline data, included patients were followed–up for three–year period. Information about clinical events, demographical data, CV risk factors, lifestyle, physical examination data, laboratory values, as well as clinical symptoms and treatment was collected each year. HR was recorded for all patients (both by standardized palpation as well as ECG methods) each year. No special investigations, measurements or treatment changes took place during this observational study. In order to evaluate changes in the control of HR and other CV risk factors for the same population, comparison of data collected over a three–year observational period was carried out.

Increased HR was defined $\geq$ 70 (bpm) in line with the taskforce of the Latvian Society of Cardiology [11]. According to the Latvian guidelines on CV diseases prevention 2007 [7], waist circumference was defined as increased when it was $\geq$ 80 cm for women, and $\geq$ 94 cm for men; height and weight were used to calculate body mass index (BMI) in kg/m^2 according to the formula BMI = body weight (kg)/height (m^2) and BMI was defined as increased when it

was ≥ 25 kg/m^2; systolic blood pressure ≥ 140 mm Hg and diastolic pressure ≥ 90 mm Hg was assessed as increased; the level of total cholesterol ≥ 5 mmol/l, low density lipoprotein cholesterol ≥ 3 mmol/l and triglycerides ≥ 1.7 mmol/l was defined as increased, but high density lipoprotein cholesterol level < 1.0 mmol/l and < 1.2 mmol/l for men and women, respectively, was assessed as too low; glucose level ≥ 5.6 mmol/l was assessed as increased. According to the Latvian guidelines on CV diseases prevention (2007) [7] and the European stable CAD guidelines of year 2013 [12] low density lipoprotein cholesterol level < 1.8 mmol/l was defined as the target. Doses of metoprolol, bisoprolol, nebivolol and carvedilol which according to the European Society of Cardiology experts' consensus document of year 2004 [13] and the European heart failure guidelines of year 2012 [14] are defined as target doses for treatment of heart failure patients, were assessed as maximal doses: for metoprolol – 200 milligrams per day (mg/d), for bisoprolol – 10 mg/d, for nebivolol – 10 mg/d, for carvedilol – 50 mg/d. For betaksolol, the maximal dose according to summary of product characteristics was assumed to be 20 mg/d [15].

2.2. Historical control group of CAD patients: REALITY Latvia

In order to assess the changes of HR and control of other CV risk factors during the time from 2006 to 2010, baseline data of the main analyzed CAD patients' population were compared with the data of historical CAD control group from REALITY Latvia. During REALITY Latvia study, 300 treated CAD outpatients with angina were investigated in 2006 [16] (approval of the Ethics Committee of the Research Institute of Cardiology, University of Latvia (March, 2006.)).

Thirty cardiologists practicing in Latvia included in the study 1–15 patients. No additional investigations were carried out and treatment was not changed.

Patients were investigated during one visit. Information about demographic data, medical history, physical examination data (including HR) angina symptoms, treatment and impact of symptoms on daily activities as well as satisfaction of patients with treatment was summarized in the case reporting form.

Resting HR was measured by standardized pulse palpation method: HR was measured for one minute after sitting for at least 10 min in a quiet room with comfortable temperature. Additionally, evaluation of the measured HR by physician was written down (whether the practitioner assesses it as normal/borderline high/high), as well as the physician' opinion regarding the target HR he would like to achieve when treating this patient.

2.3. Control group in general population

In order to assess the differences of HR and other CV risk factors for CAD patients and representatives of general population, baseline data of the main analyzed CAD patients' population were compared with the data of the control group in general population. For this comparison the data from Population–Based cross–Sectional study of Cardiovascular risk factors in Latvia carried out during the time from December 2008 to June 2009 and done in the Research Institute of Cardiology, University of Latvia with the approval of the Ethics Committee of the Research Institute of Cardiology, University of Latvia [17] were used. Within this study, by using the data of the Latvian Population Register, sample of Latvian inhabitants was created and information

regarding 3 807 investigated respondents was obtained. During the study, respondents were interviewed, they underwent taking of anthropometric measurements. The level of blood pressure as well as laboratory values of glucose and lipids' levels were recorded. Blood pressure and HR were measured in sitting position, after rest of 5 minutes with automatic device OMRON M6 Comfort. Three repeated measurements were made with two to three minutes' interval. Average ratio from the last two measurements was used for further analysis.

For the needs of current research in order to make HR and other CV risk factors comparison in CAD patients and general population from all 3 807 respondents surveyed during cross–sectional study individuals of both sexes were selected who were of proper age for the respective CAD population (≥ 45 years) about whom all information needed for comparison had been collected, namely: respondents were asked about smoking habits, their height and weight had been fixed, HR and blood pressure measured had been measured, as well as glucose and lipid levels laboratory were determined (fasting glucose level, total cholesterol, high and low density lipoprotein cholesterol, as well as level of triglycerides). Totally 1 474 of respondents corresponded to these characteristics. Data from cross–sectional study regarding respondents who were in improper age for CAD population (< 45 years) or those, for whom during the study fasting glucose level and/or some of the lipid levels was not determined, were not used for further comparison with CAD patients sample.

2.4. Physicians' questionnaire on heart rate

In order to gain insight how the practitioners in Latvia evaluate different levels of HR for different patients' groups with CAD and patients with heart failure, which level of HR physicians would like to achieve when treating patients and which HR reducing agents they would use for this purpose, 135 Latvian practitioners were questioned (13 cardiologists and 122 general practitioners and internists). From the questioned physicians, 102 completed questionnaires in electronic version, but 33 completed questionnaires in paper format. The questionnaire required answers about the fact how the practitioner evaluates different HR levels for CAD and heart failure patients and what HR level he or she would like to achieve, while treating these patients.

Data were processed with methods of descriptive and analytical statistics by using Statistical Package for the Social Sciences (SPSS), version 20.0.

As statistically significant was considered p value < 0.05.

3. RESULTS

3.1. Characteristics of treated outpatients with stable CAD in Latvia

All analyzed patients (n = 120) were with stable CAD: 73 persons (60.8%) were with documented myocardial infarction; documented coronary stenosis was presented in 106 patients (88.3%); 17 persons (14.2%) were with chest pain and percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) was observed in 105 cases (87.5%).

3.1.1. Demographical data

Mean age of patients was 64.2 ± 7.9 years and 87 (72.5%) of them were men. Mean age of women was significantly higher than that of men: 67.9 years compared to (vs) 62.8 years (independent t test, p = 0.001). Most of the patients, i.e., 107 persons (72.7%) lived together with another person: 24 (72.7%) women and 83 (95.4%) men. Fifty percent of patients were retired. Secondary education was in 57.7% of cases.

3.1.2. Heart rate

Resting HR of analyzed patients, when measured by pulse palpation, was within the range from 52 to 101 bpm. Median HR was 65.5[11.5] bpm. Mean HR in women and men was 69.6 ± 11.9 bpm and 67.0 ± 8.5 bpm, respectively and did not differ significantly (p = 0.195, independent t test). When analyzing HR (measured by pulse palpation) distribution in different levels (≤ 59; 60–64; 65–69; 70–74; 75–79; 80–84; ≥ 85 bpm), 39 persons

(32.5%) were with HR within the range from 60 to 64 bpm; HR ≥ 70 bpm was in 43 persons (35.8%).

Resting HR, measured by ECG method, was within the range from 46 to 105 bpm. Mean HR was 66.9 ± 9.9 bpm. Mean HR for women and men did not differ statistically significantly (68.7 ± 12.6 bpm vs 66.2 ± 9.9 bpm; independent sample test, p = 0.264). When analyzing HR (measured by ECG) distribution in different levels 27 persons (22.7%) had HR within the range from 60 to 64 bpm. In 40 (34%) cases HR (measured by ECG) was ≥ 70 bpm.

When comparing median HR measured by pulse palpation (65.5[11.5] bmp) and ECG (65.0[14.9] bpm), statistically significant difference was found (Wilcoxon Signed Rank test, p = 0.028). There was a close and statistically significant correlation between both HR measurements (with pulse palpation and ECG method) (r = 0.808; p = 0.001).

When analyzing HR correlation with other CV risk factors, a positive correlation was found between HR and diastolic blood pressure (measured by pulse palpation method: r = 0.270, p = 0.003; measured by ECG: r = 0.260, p = 0.004).

No worthy connection of HR with the use of simulating drinks and physical activities was found.

When analyzing HR level in relation with smoking status, it was noted that smokers have significantly higher HR than non–smokers. However, this was only in case for HR measured by pulse palpation, but not by ECG method (see Table 3.1).

Table 3.1

HR for smokers and non–smokers

Method of HR measurement	Statistical parameters	HR depending on smoking status (bpm)		p	Test
		smokers	non–smokers*		
Palpation	Me	69.0	65.0	0.048	Mann–Whitney test
	IQR	12.8	12.0		
	n	22	98		
ECG	M	70.7	66.0	0.068	Independent t test
	SD	9.6	10.8		
	n	22	97		

bpm – beats per minute; IQR – interquartile range; HR – heart rate; Me – median; n –number of patients; p – confidence coefficient; SD – standard deviation; * patients who had quit smoking and those who have never smoked

HR ≥ 70 bpm, when measured by pulse palpation, was present in 19 (33%) patients with angina attacks and in 25 (36.2%) patients with heart failure symptoms.

Mean HR in patients with symptoms (by analyzing separately angina and heart failure symptoms) did not differ significantly (independent t test, $p > 0.050$). No statistically significant correlation was found between HR and number of angina attacks ($r = 0.253$; $p = 0.057$) as well as between HR and heart failure symptoms ($r = 0.035$; $p = 0.706$).

3.1.3. Other cardiovascular risk factors and lifestyle

Breakdown of patients according to smoking status and use of alcohol differed significantly for men and women (Pearson Chi–Squared test, $p = 0.001$, $p = 0.005$, respectively). No one of the women was smoking, but 23% of men were smokers. In 56 cases (46.7%) recognized level of physical activity was “minor activities”.

Mean body weight differed for women (76.9 ± 15.8 kg) and for men (90.3 ± 11.8 kg), similarly also the height: it was 162.2 ± 4.8 cm and 175.6 ± 6.3 cm for women and for men, respectively ($p = 0.001$, independent t test). Mean BMI was 29.3 ± 4.4 kg/m^2 and it did not differ significantly for men and women (independent t test, $p = 0.824$). BMI group „overweight" (25.0–29.9 kg/m^2) was presented in 56 (46.7%) patients. Totally 103 (85.9%) patients were with BMI > 25 kg/m^2 and in 47 (39.2%) cases it was > 30 kg/m^2.

Waist circumference was increased in 106 (88.3%) cases: 30 (90.9%) women were with waist circumference ≥ 80 cm and 76 (87.4%) men were with waist circumference ≥ 94 cm.

Blood pressure did not differ between men and women (independent t test, $p > 0.050$). Blood pressure ≥ 140/90 mm Hg was presented in 68 cases (56.8%).

3.1.4. Laboratory values and measurements

The most important laboratory values are summarized in Table 3.2.

Mean left ventricular ejection fraction was 57.1 ± 8.7% and weak, negative statistically significant correlation was found between this ratio and HR.

For patients with positive exercise tolerance test HR was not higher than for those whose test was negative (Mann-Whitney test, $p > 0.050$).

Table 3.2

Laboratory values and measurements

Measurement	M ± SD or Me[IQR]	Different levels	n	%
Blood glucose (mmol/l)	5.7[1.2]	< 5.6	43	40.6
		≥ 5.6	63	59.4
		totally	106	100.0
Glycated Hb (%)	6.8 ± 0.9	< 6.5	15	75.0
		≥ 6.5	5	25.0
		totally	20	100.0
Total cholesterol (mmol/l)	4.5[1.3]	< 5	78	69.0
		≥ 5	35	31.0
		totally	113	100.0
High density lipoprotein cholesterol (mmol/l)	1.2[0.6]	low*	31	28.8
		others	73	71.2
		totally	104	100.0
Low density lipoprotein cholesterol (mmol/l)	2.7 ± 1.2	< 3	73	68.9
		≥ 3	33	31.1
		totally	106	100.0
		< 1.8	24	22.6
		≥ 1.8	82	77.4
		totally	106	100.0
Triglycerides (mmol/l)	1.4[1.0]	≥ 1.7	36	33.3
		the rest	72	66.7
		totally	108	100.0

Hb – hemoglobin; IQR – interquartile dispersion; M – mean; Me – median; n – number of patients; p – confidence coefficient; SD – standard deviation; * < 1,2 mmol/l for women un < 1 mmol/l for men

3.1.5. Symptoms and treatment

Angina symptoms and symptoms of heart failure were presented in 57 (47.5%) and 69 (57.5%) cases, respectively.

Usage of agents from most important CV classes is summarized in Table 3.3.

Table 3.3

Usage of agents from most important CV classes

CV classes	Number of patients receiving treatment	
	n	%
Antithrombotic agents	118	98.3
Lipid lowering agents	114	95.0
ACEI/ARB	102	85.0
β blockers	98	81.7
I_f inhibitors (ivabradine)	15	12.5
Ca antagonists	64	53.3
Nitrates	28	23.3
Other antianginal agents	15	12.5
Diuretics	31	25.8

ACEI – angiotensin converting enzyme inhibitors; ARB – angiotensin II receptor blockers; Ca – calcium; CV – cardiovascular; n – number of patients

From HR reducing agents patients received β blockers, ivabradine, digoxin and amiodarone. Most frequently used β blockers were metoprolol (long acting succinate) (used in 47 (39.2%) cases) and bisoprolol (used in 37 (30.8%) cases). From β blockers also nebivalol and carvedilol were used (in 10 (8.3%) and four (3.3%) cases, respectively).

Median daily doses for metoprolol, bisoprolol and nebivolol were 50.0[50.0] mg/d 5.0[0.0] mg/d and 5.0[0.0] mg/d, respectively. Mean daily dose for carvedilol was 8.4 ± 4.9 mg/d, Me = 9.4 mg/d. Five patients (5.1%) from all β blocker users received < 25% of maximal dose; 41 (41.8%) patient

received 25–49.9% of maximal dose; 50–74.9% of maximal dose was used in 45 (45.9%) cases; two (2%) patients received 75–99.9% of maximal dose and in five (5.1%) cases dose of β blockers was 100% of maximal dose. Totally 53 (53.1%) patients received at least half of maximal dose. For 23 patients (19.2%) there were β blocker contraindications or side–effects. Most frequently observed symptoms of intolerance of β blockers were weakness and bradycardia. For patients, to whom contraindications for β blockers' use were observed or there were symptoms of intolerance, in 12 (48%) cases the β blocker dose was decreased, for 15 (60%) patients treatment with β blocker was fully stopped (with or without decreasing of β blocker' dose before).

Ivabradine was received by 12.5% of all patients included in the study. Median dose of ivabradine was 5.0[5.0] (mg/d). One patient (6.7%) received 2.5 mg/d, nine patients (66.7%) received 5.0 mg/d, one (6.7%) patient was using ivabradine 7.5 mg/d, and two (13.3%) patients were using 10.0 mg/d and 15.0 mg/d. From all patients, for whom β blockers' treatment was stopped due to contraindications or symptoms of intolerance, 13 (86.7%) received ivabradine. Two patients (13.3% of all ivabradine users) received ivabradine, did not take β blocker and they previously did not have any β blockers' contraindications or side–effects. Ivabradine was received by 17.4% (n = 12) patients who had symptoms of heart failure, as well as 16.0% (n = 4) and 16.7% (n = 4) of patients, who had both heart failure symptoms, as well as HR of ≥ 70 bpm measured by pulse palpation and ECG, respectively. When analyzing the patients with angina symptoms, 17.5% (n = 10) received ivabradine, but from patients, who had both angina attacks, as well as HR ≥ 70 bpm, ivabradine was used in three cases (15.8%).

At least one HR reducing agent (β blocker, ivabradine, digoxin, amiodrone) was used by 111 patients (92.5%), 110 persons (91.7%) were using

either β blocker or ivabradine, but combination of β blocker and ivabradine was used by three (2.5%) patients.

When analyzing treatment with HR reducing agents for patients with HR ≥ 70 bpm (n = 45), it was noted that most frequently used β blockers in this patients' group were metoprolol (n = 19, 42.2%) and bisoprolol (n = 10, 22.2%). Six (13.3%) patients in this subgroup received ivabradine and two persons were using β blocker in combination with ivabradine. Doses of HR reducing agents in group of patients with HR ≥ 70 bpm did not differ from those, which were used for patients with HR < 70 bpm (see Table 3.4).

Table 3.4

Doses of HR reducing agents for patients with increased HR and the rest

Agent	Statistical parameters	HR (bpm)		p	Tests
		< 70 bpm	≥ 70 bpm		
Metoprolol	Me	50.0	50.0	0.173	Mann-Whitney test
	IQR	0.0	50.0		
	n	28	19		
Bisoprolol	Me	5.0	5.0	0.334	Mann-Whitney test
	IQR	0.0	3.7		
	n	27	10		
Ivabradine	M	6.1	8.3	0.284	independent t test*
	SD	3.6	4.1		
	n	9	6		

IQR – interquartile dispersion ; HR – heart rate; M – mean; Me – median; n – number of patients; p – confidence coefficient; SD – standard deviation; bpm – beats per minute; * used parametric statistics because of small sampling

Eight patients (17.6%) with HR ≥ 70 bpm were not treated neither with β blocker, nor ivabradine. From the patients with HR ≥ 70 bpm (measured by pulse palpation method) and angina attacks, 10 persons (66.7%) received ivabradine.

3.2. Analyzed population of treated CAD outpatients: results of three–year follow–up period

From the 120 patients initially included in the study, investigated during the first (Y1), second (Y2) and third (Y3) year of observation were 98.3% (n = 118), 95.8% (n = 115) and 95.0% (n = 114), respectively.

3.2.1. Heart rate

Median values of HR during the follow–up period are represented in Figure 3.1.

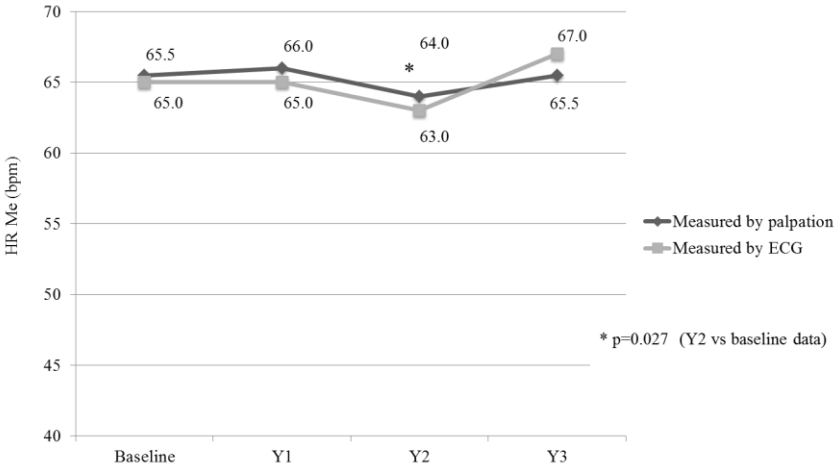


Figure 3.1 **Median HR values during follow–up period**

bpm – beats per minute ECG – electrocardiogram; Me – median; HR – heart rate; vs – *versus*; Y – year of follow–up

When comparing HR during follow–up period with HR at baseline, only at Y2, and only when HR was measured by pulse palpation method, a statistically significant difference was found: at Y2 HR was lower than at baseline (Wilcoxon Signed Rank test, p = 0.027).

Proportion of patients with increased HR (≥ 70 bpm) did not significantly change over the three–year follow–up period (McNemar's test, all p values > 0.050) (see Figure 3.2 and Figure 3.3).

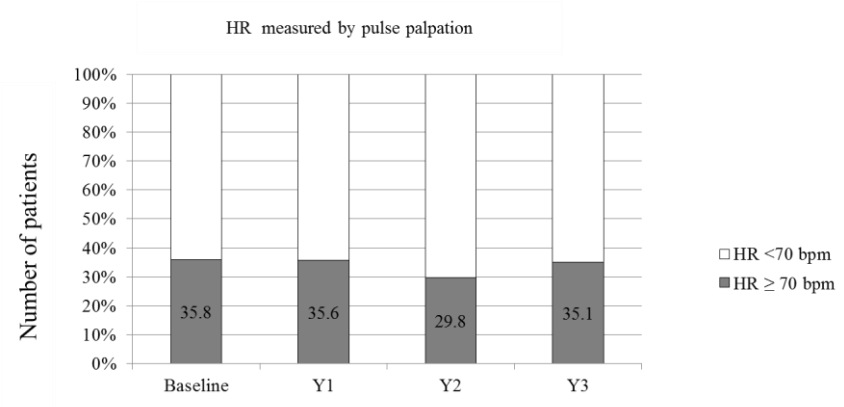


Figure 3.2 **Distribution of patients in two HR levels during follow–up period (by palpation method)**

bpm – beats per minute; HR – heart rate; Y – year of hollow–up

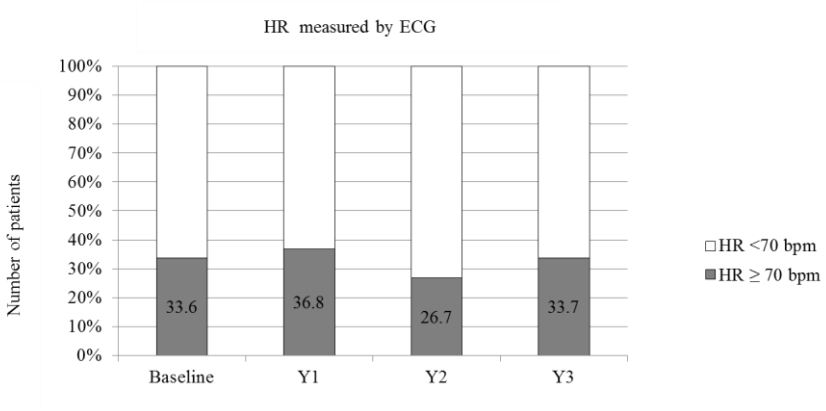


Figure 3.3 **Distribution of patients in two HR levels during follow–up period (by ECG method)**

bpm – times per minute; ECG – electrocardiogram; HR – heart rate; Y– year of follow–up

When analyzing HR relation with other CV risk factors, a correlation was found (Spearman correlation) between HR and diastolic blood pressure: for HR measured by pulse palpation method, at Y1 (r_s = 0.464; p = 0.002) and Y3 (r_s = 0.340; p = 0.029), but for HR measured by ECG, such correlation was observed only at Y1 (r_s = 0.340; p = 0.029).

3.2.2. Clinical events and association with the heart rate

Totally during three–year follow–up period 45 persons (37.5%) of initially included 120 patients had clinical events: five (4.2%) patients died, but 40 (33.3%) patients had non–fatal clinic events.

Mean HR for patients, who had clinic event during follow–up, did not differ significantly from those, who had no event documented (HR by palpation method: 66.1 ± 9.7 bpm vs 68.2 ± 8.9 bpm, p = 0.223; HR by ECG method: 65.5 ± 10.9 bpm vs 67.4 ± 10.2 bpm, p = 0.345, independent t test). The distribution of patients according to the level of HR (< 70 bpm or ≥ 70 bpm) for patients with clinical events during follow–up period did not differ from those, who had no clinic events (Pearson Chi–Squared test, p = 0.250 (for HR measured by palpation method) and p = 0.185 (for HR measured by ECG method)).

Mean HR at baseline for patients, who died during the follow–up period, was 72.6 ± 16.9 bpm (by palpation method) and 71.4 ± 17.4 bpm (by ECG method); for patients, who survived, HR was 67.5 ± 9.2 bpm and 66.7 ± 10.4 bpm, respectively. However, statistical significance was not found (independent t test, p = 0.246 (for HR measured by palpation method), p = 0.342 (for HR measured by ECG)). The distribution of patients according to the level of HR (< 70 bpm or ≥ 70bpm) for patients, who died during the follow–up period, did not differ significantly from those who survived (Fisher's exact test, p = 1.000 (for HR measured by palpation method) and p = 0.662 (for HR measured by ECG)).

3.2.3. Other CV risk factors and lifestyle

At Y1, compared to baseline data, mean number of smoked cigarettes decreased (7.8 ± 4.3 vs 8.3 ± 3.9, independent t test, p = 0.015).

Systolic blood pressure was significantly lower at Y1 and Y3 of follow–up in comparison with baseline data (Wilcoxon Signed Rank test) (see Figure 3.4). Proportion of patients with increased blood pressure (≥ 140/90 mm Hg) at all years of follow–up period was significantly lower in comparison with baseline data (see Figure 3.5) (McNemar's test).

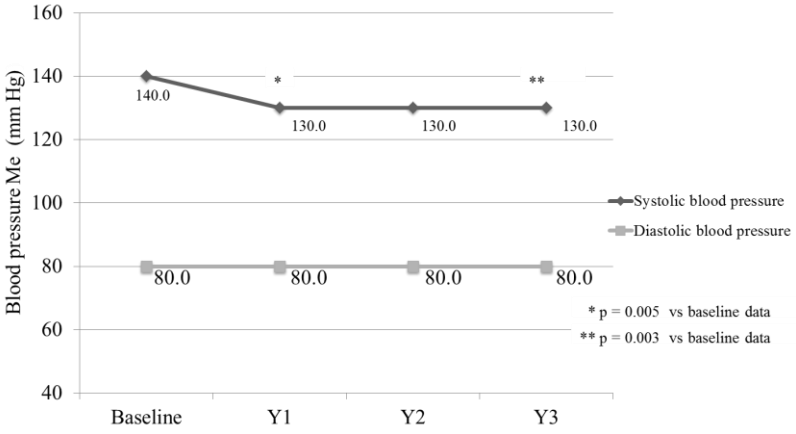


Figure 3.4 **Median blood pressures during follow–up period**

Me – median; p – confidence coefficient in Wilcoxon Signed Rank test; vs– *versus*; Y – year of follow–up

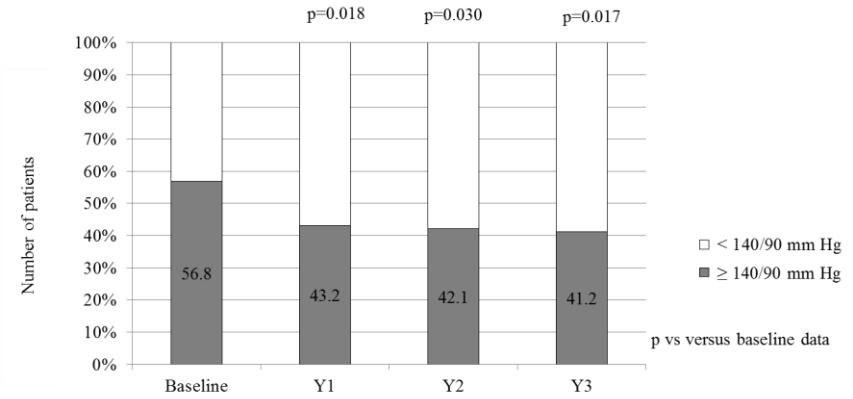


Figure 3.5 **Distribution of patients according to blood pressure level during follow–up period**

p – confidence coefficient in McNemar's test; vs – *versus*; Y – year of follow–up

3.2.4. Laboratory values and measurements

The level of triglycerides was significantly lower at Y3 of follow–up in comparison with baseline data (1.2[0.8] mmol/l vs 1.4[1.0], p = 0.004 Wilcoxon Signed Rank test test). The distribution of patients according to the level of total cholesterol (< 5 mmol/l or ≥ 5 mmol/l), low density lipoprotein cholesterol (< 3 mmol/l or ≥ 3 mmol/l and < 1.8 mmol/l or ≥ 1.8 mmol/l) as well as the level of triglycerides (< 1.7 mmol/l or ≥ 1.7 mmol/l) did not change significantly during follow–up period. While distribution of patients according to the level of high density lipoprotein cholesterol (decreased or not), differed significantly in comparison with baseline data: at Y1, Y2 and Y3 proportion of patients with decreased high

density lipoprotein cholesterol level was significantly lower than at baseline: in 28.8%, 27.3%, 28.3%, and 20.3% of patents at baseline, Y1, Y2 and Y3, respectively, low level of high density lipoprotein cholesterol was found (McNemar's test, all p values vs baseline data < 0.001). Significant changes in left ventricular ejection fraction during three–year follow–up period were not found (paired t test, $p > 0.050$).

3.2.5. Symptoms and treatment

The distribution of patients during the follow–up period according to the functional class of angina and heart failure is reflected in Figure 3.6 and Figure 3.7.

No significant changes in functional class of angina during the follow–up period were observed (Wilcoxon Signed Rank test, all p values > 0.050). Additionally, no significant correlation was found between changes of functional class of angina and changes of HR (paired t test, all p values > 0.050).

Functional class of heart failure significantly worsened in the third year of follow–up compared to baseline data (Wilcoxon Signed Rank test, $p = 0.013$). Correlation between changes of functional class of heart failure and changes of HR was not found (paired t test, all p values > 0.050).

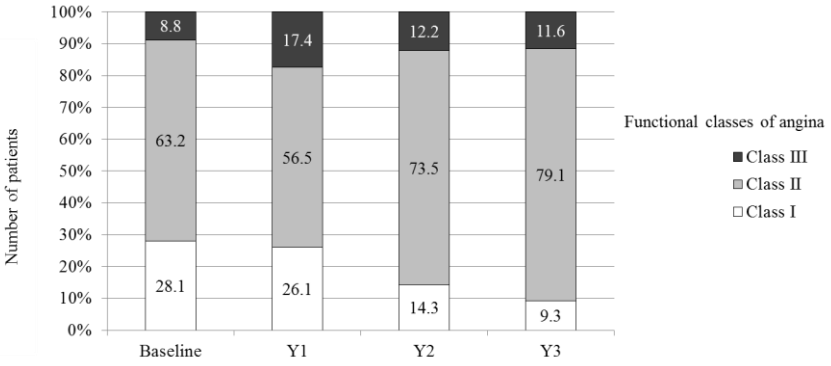


Figure 3.6. **Distribution of patients during the follow–up period according to the functional class of angina**

Y – year of follow–up

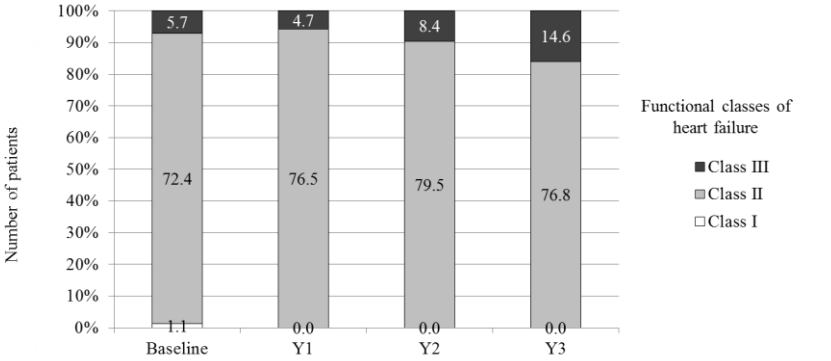


Figure 3.7. **Distribution of patients during the follow–up period according to the functional class of heart failure**

Y – year of follow–up

Usage of most important classes of CV agents during three–year follow–up period is reflected in Figure 3.8.

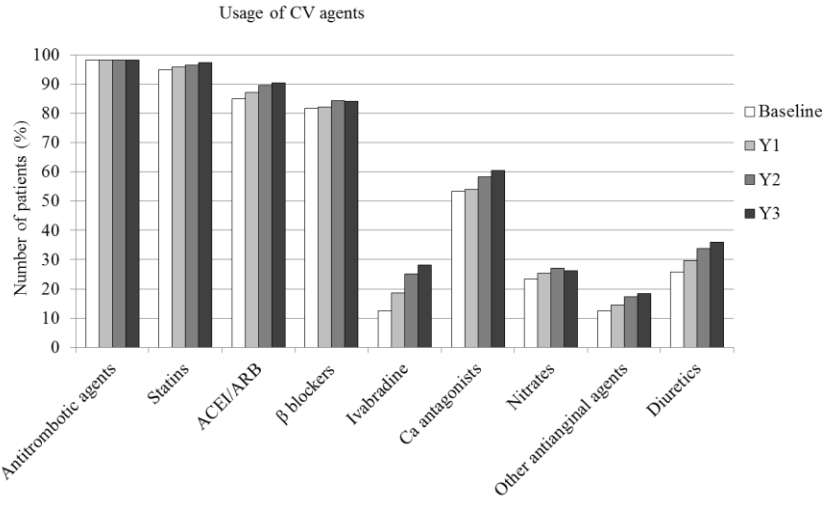


Figure 3.8 **Usage of most important classes of CV agents during three–year follow–up period**

ACEI – angiotensin converting enzyme inhibitors; ARB – angiotensin II receptor blockers; Ca – calcium; CV – cardiovascular; Y – year of follow–up

During the follow–up period, the number of patients receiving antiplatelet agents, ACEI/ARB and statins did not change significantly (McNemar's test, all p values > 0.050).

During whole follow–up period, the number of β blocker users was retained above 80% (see Figure 3.8). Most frequently used β blockers unchangeably were metoprolol (long activity succinate) and bisoprolol (see Figure 3.9).

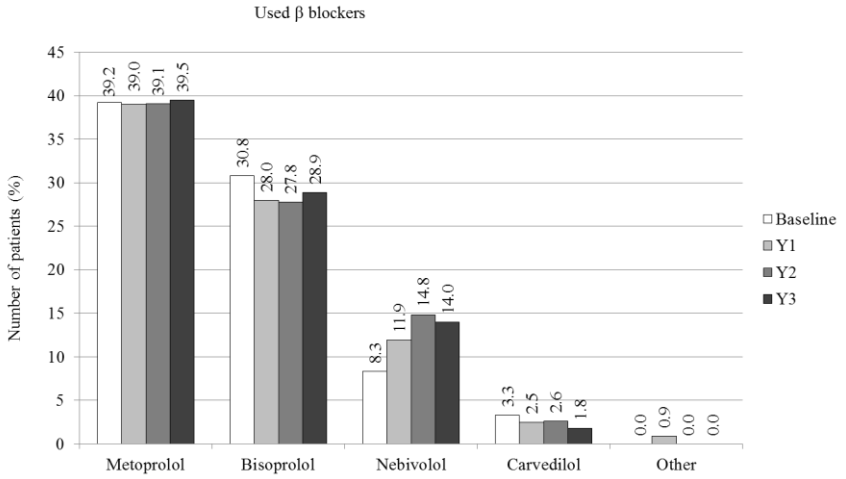


Figure 3.9 **Use of different β blockers during follow–up period**

Y – year of follow–up

During the follow–up period the distribution of patients according to β blocker used, changed only for nebivolol (there were significantly more users of nebivolol at Y2 and Y3 in comparison with baseline data (McNemar's test, in both cases $p = 0.031$).

Median doses of most frequently used β blocker doses are reflected in Figure 3.10.

The doses of used β blockers did not change significantly during three–year follow–up period (Wilcoxon Signed Rank, all p values > 0.050).

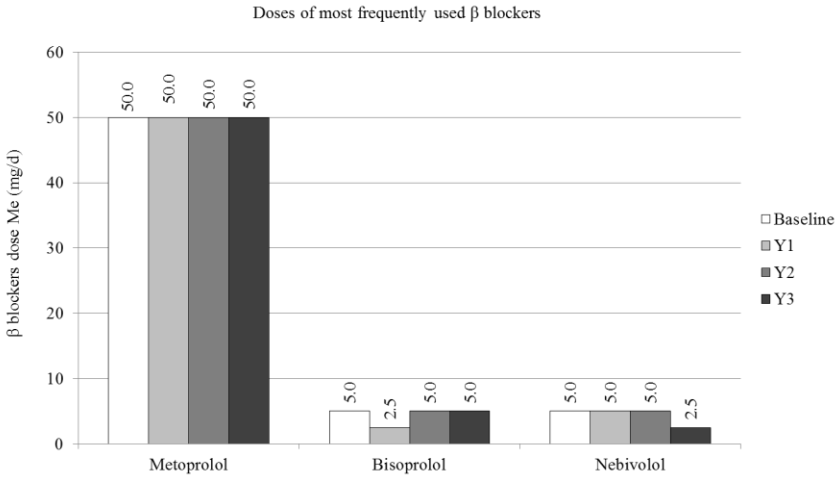


Figure 3.10 **Doses of most frequently used β blockers during the follow–up period**
Me – median; mg/d – milligrams per day; Y – year of follow–up

At baseline, Y1, Y2 and Y3 of follow–up 52 (53.1%), 47 (48.5%), 50 (51.5%) and 47 (49.0%) patients, respectively, from all using β blockers, received at least half of the maximal dose. From all patients using β blockers proportion of patients, using at least half of the maximal dose, did not change significantly compared to baseline data (McNemar's test, all p values > 0.050). During the whole three–year follow–up period, β blockers' contraindications or symptoms of intolerance were observed in 36 (32.1%) patients. When comparing to baseline data, the number of β blockers' side–effects significantly increased at Y2 ($p = 0.004$) and Y3 ($p = 0.011$) (McNemar's test). From for patients with β blockers' contraindications or side–effects, ivabradine was used in 20 (55.6%), 21 (58.3%) and 22 (61.1%) cases at Y1, Y2, Y3, respectively. Compared to baseline data, when the number of such patients was 15 (41.7%),

proportion of them significantly increased at Y2 (p = 0.031) and Y3 (p = 0.016) (McNemar's test).

The number of patients using ivabradine increased significantly during follow–up period in comparison with baseline data (McNemar's test: p = 0.016 (Y1 vs baseline data); p < 0.001 (Y2 and Y3 vs baseline data)). Median dose of ivabradine significantly increased (see Figure 3.11) compared to baseline data (Wilcoxon Signed Rank test).

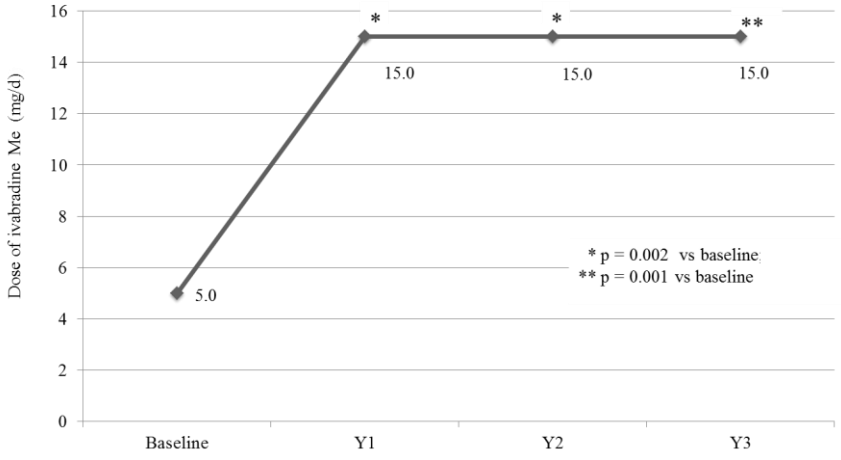


Figure 3.11 **Median dose of ivabradine during the follow–up period**

Me – median; mg/d – milligrams per day; p – confidence coefficient; vs – *versus*; Y – year of follow–up

The proportion of patients receiving any HR reducing agent as well as the number of patients receiving either β blocker, or ivabradine did not change significantly during follow–up period (McNemar's test, p values > 0.050). What about patients receiving combination of β blocker and ivabradine,

proportion of them increased significantly during follow–up period in comparison with baseline data (see Figure 3.12).

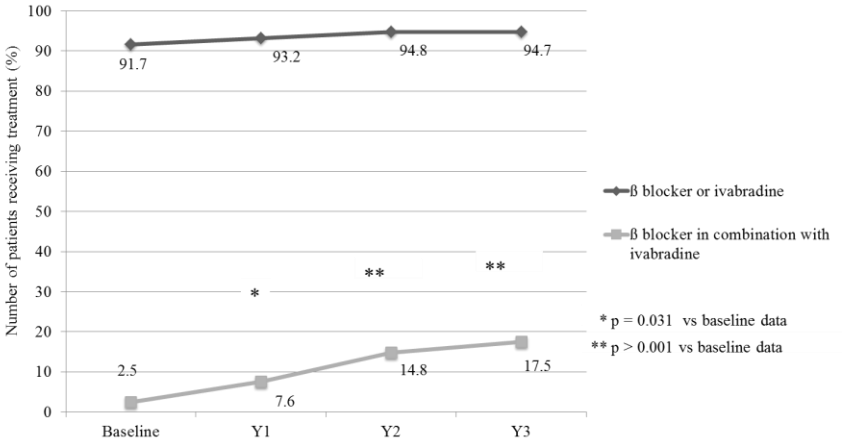


Figure 3.12 **Usage of HR reducing agents during three–year follow–up period**

HR – heart rate; p – confidence interval in McNemar's test; vs – *versus*; Y – year of follow–up

Most of the patients (> 90%), who had increased HR (≥ 70, ≥ 75, ≥ 80 and ≥ 85 bpm) at least in one of the visits, were using β blocker or ivabradine. However, 6–8% of the patients with increased HR (≥ 70 bpm) did not use any HR reducing agent: from all patients with HR (measured by pulse palpation) ≥ 70, ≥ 75, ≥ 80 or ≥ 85 bpm in at least one the visits 6.9%, 6.4% 6.3% and 5.0%, respectively; from the patients, whose increased HR (≥ 70, ≥ 75, ≥ 80 or ≥ 85 bpm) was measured by ECG, 6.8%, 6.7%, 9.7% and 8.3%, respectively, did not use any HR reducing agent.

When dividing the patients with increased HR in four categories (70–74 bpm (the first category), 75–79 bpm (the second category), 80–84 bpm (the third category) and ≥ 85 bpm (the fourth category)) and analyzing the usage of

HR reducing agents, statistically significant parabolic correlations were found between the category of increased HR and usage of ivabradine, as well as the frequency of usage β blocker in combination with ivabradine (see Figure 3.13 and Figure 3.14).

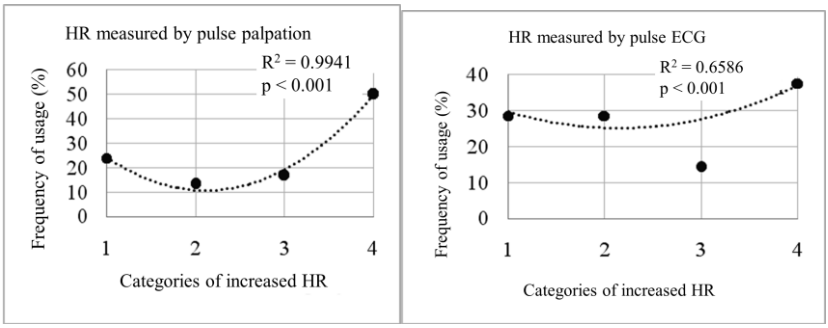


Figure 3.13 **Usage of ivabradine according to increased HR category**

HR – heart rate; categories of increased HR: 70–74 bpm (1), 75–79 bpm (2), 80–85 bpm (3), ≥ 85 bpm (4); R^2 – determination coefficient (shows likeliness that all points are on parabola); p–confidence coefficient for parabolistic regression

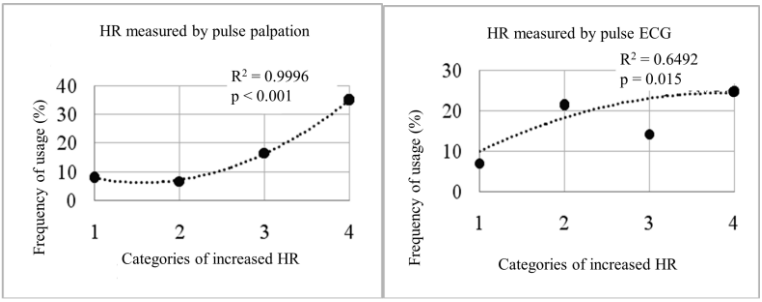


Figure 3.14 **Usage of β blocker in combination with ivabradine according to increased HR category**

HR – heart rate; increased HR categories: 70–74 bpm (1), 75–79 bpm (2), 80–85 bpm (3), ≥ 85 bpm (4); R^2 – determination coefficient (shows likeliness that all points are on parabola); p – confidence coefficient for parabolic regression

Usage of ivabradine as well as usage of β blocker in combination with ivabradine decreased or slightly increased in the second (74–79 bpm) and the third (80–84 bpm) category of increased HR compared to the first (70–74 bpm), but it significantly increased in the fourth category of increased HR (≥ 85 bpm) (see Figure 3.13 and Figure 3.14). In the similar manner, parabolic, statistically significant correlation was found between the category of increased HR and usage of β blockers in higher doses (≥ 50% of the maximal dose) as well as frequency of β blockers' contraindications or side–effects. Compared to the first increased HR category (70–74 bpm), the frequency of higher β blocker doses increased in the second category (75–79 bpm) and in the third category (80–85 bpm), but decreased in the fourth category (≥ 85 bpm) (see Figure 3.15), but the frequency of β blocker contraindications or side–effects increased when HR was higher (see Figure 3.16).

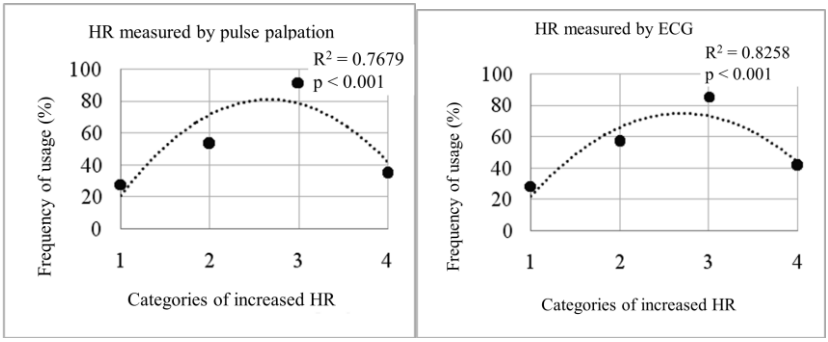


Figure 3.15 **Usage of higher β blocker doses (≥ 50% of the maximal dose) according to increased HR category**

HR – heart rate; HR categories: 70–74 bpm (1), 75–79 bpm (2), 80–85 bpm (3), ≥ 85 bpm (4); R^2 – determination coefficient (shows likeliness that all points are on parabola); p – confidence coefficient for parabolic regression

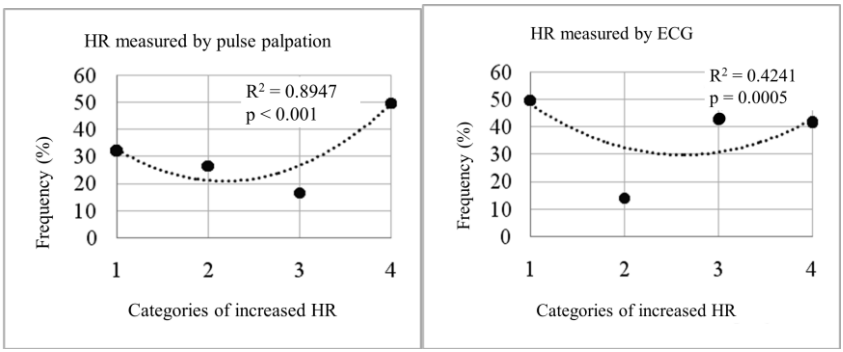


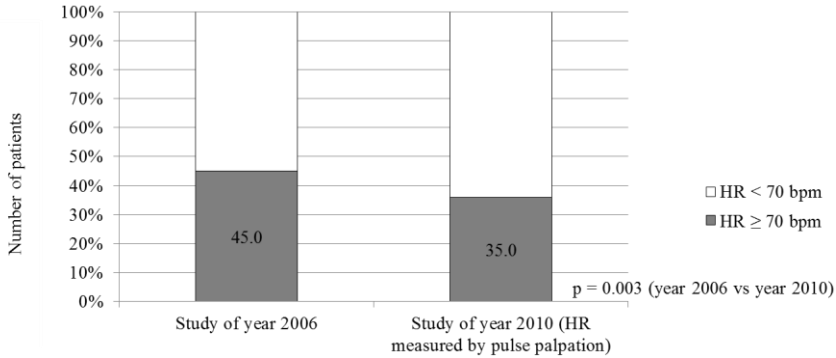
Figure 3.16 **Frequency of ß blocker contraindications or side–effects according to category of increased HR**

HR – heart rate; HR categories: 70–74 bpm (1), 75–79 bpm (2), 80–85 bpm (3), ≥ 85 bpm (4); R^2 – determination coefficient (shows likeliness that all points are on parabola); p – confidence coefficient for parabolic regression

3.3. Comparison of heart rate and other cardiovascular risk factors in two different CAD patients' populations with four years' interval

Median HR in the study of year 2006 was significantly higher than in the study of CAD population in the year 2010 (70.0 bpm vs 65.5 bpm, Mann-Whitney test, p = 0.034).

Increased HR (≥ 70 bpm) in the study of year 2006 was more frequent in comparison with study done in 2010 (45% vs 35.8%, Pearson Chi–Squared test, p = 0.003) (see Figure 3.17).



Picture 3.17 **Distribution of patients according to HR in studies of 2006 and 2010**

bpm – beats per minute; HR – heart rate; p – confidence coefficient

BMI in both studies did not differ significantly (independent t test, $p = 0.149$). Neither systolic, nor diastolic blood pressure differed ($p = 0.745$) (Mann-Whitney test, $p = 0.961$), nor the distribution of patients according to the level of blood pressure (above or below 140/90 mm Hg) (Pearson Chi–Squared test, $p = 0.703$).

The number of smokers and non–smokers did not differ significantly (Pearson Chi–Squared tests, $p = 0.399$), however, the number of smoked cigarettes on average per day differed: in the study of 2006 it was significantly higher (15.0 ± 9.4 vs 8.3 ± 3.9, independent t test, $p < 0.001$). The level of total cholesterol and low density lipoprotein cholesterol in the study of year 2010 was statistically significantly lower in comparison with study of year 2006. But the level of high density lipoprotein cholesterol and the level of triglycerides did not differ significantly.

In the study of year 2010 patients more often received statins and ARB, but long–acting nitrates, β blockers and ACEI were used by these patients more rarely than in the year 2006 study (see Table 3.5).

Table 3.5

Use of CV agents in the studies of year 2006 and year 2010

Classes of CV agents	Year when study was done				p
	2006		2010		
	n	%	n	%	
Antiplatlets	289	96.3	118	98.3	0.365*
Nitrates	197	65.7	28	23.3	< 0.001**
ß blockers	273	91.0	98	81.7	< 0.001**
Ca antagonists	170	56.7	64	53.3	0.534**
Statins	250	83.3	114	95.0	0.001**
ACEI	246	82.0	85	70.8	0.011**
ARB	8	2.7	17	14.2	0.001**

ACEI – angiotensin converting enzyme inhibitors; ARB – angiotensin receptor blockers; Ca – calcium; CV – cardiovascular; n – number of patients; p – confidence coefficient; * Fisher's exact test; ** Pearson Chi–Squared test

In both studies, the most frequently used β blockers were metoprolol (long acting succinate) and bisoprolol, and used doses of β blockers did not differ significantly. At least half of the β blocker maximal dose was used by 156 (52%) and 52 (43.3%) patients, in the studies of year 2006 and 2010, respectively. Proportions of patients using at least half of the β blocker maximal dose did not differ significantly in both studies (Pearson Chi–Squared test, $p = 0.109$).

3.4. Comparison of heart rate and other cardiovascular risk factors in CAD patients' and general populations

When comparing the data of study 2010 where CAD patients' group was analyzes with the general Latvia population, CAD patients had higher BMI, higher level of triglycerides, higher level of glucose and lower level of high

density lipoprotein cholesterol. Diastolic blood pressure, HR, the average number of smoked cigarettes, the total and low density lipoprotein cholesterol was lower in CAD population (see Table 3.6). The distribution of patients according to BMI, HR, blood pressure, the total, high and low density lipoprotein cholesterol, triglycerides, glucose level and smoking status differed significantly in both groups (see Table 3.7).

Table 3.6

Comparison of different parameters in CAD patients' and general populations

Analyzed characteristics Me[IQR]	Compared groups		p*
	CAD	general population	
Age (years)	64.5[13.0]	60.0[15.0]	< 0.001
BMI	29.0[5.9]	27.3[6.5]	< 0.001
SBS (mm Hg)	140.0[22.0]	139.0[30.0]	0.418
DBS (mm Hg)	80.0[10.0]	90.0[18.0]	< 0.001
HR (bpm)	65.5[12.0]	70.0[14.0]	< 0.001
Average number of cigarettes	10.0[5.0]	15.0[15.0]	< 0.001
Total cholesterol (mmol/l)	4.5[1.2]	6.0[1.7]	< 0.001
HDLC (mmol/l)	1.2[0.6]	1.5[0.6]	< 0.001
LDLC (mmol/l)	2.6[1.1]	4.0[1.5]	< 0.001
Triglycerides (mmol/l)	1.4[0.9]	1.3[0.9]	< 0.001
Glucose (mmol/l)	5.7[1.1]	5.4[0.8]	< 0.001

BMI – body mass index; bpm – beats per minute; CAD – coronary artery disease; DBS – diastolic blood pressure; HDLC – high density lipoprotein cholesterol; HR – heart rate; IQR – interquartile range; LDLC – low density lipoprotein cholesterol; Me – median; p – confidence coefficient; SBS – systolic blood pressure;
*Mann-Whitney test

Table 3.7

Distribution of patients in CAD and general populations according to different parameters

Parameters	Groups	Compared groups				P*
		CAD patients		general population		
		n	%	n	%	
BMI	< 18.5	0	0.0	8	0.5	< 0.001
	≥ 18.5 < 25.0	17	14.2	434	29.4	
	≥ 25.0 < 30.0	55	45.8	593	40.2	
	≥ 30.0 < 35.0	36	30.0	297	20.1	
	≥ 35.0 < 40.0	9	7.5	97	6.6	
	≥ 40.0	3	2.5	45	3.1	
	totally	120	100.0	1474	100.0	
Blood pressure (mm Hg)	≤ 140/90	76	63.3	684	46.4	< 0.001
	> 140/90	44	36.7	790	53.6	
	totally	120	100.0	1474	100.0	
HR (bpm)	< 70	77	64.2	667	45.2	< 0.001
	≥ 70	43	35.8	807	54.8	
	totally	120	100.0	1474	100.0	
Smoking	yes	22	18.3	509	34.5	< 0.001
	no	98	81.7	965	65.5	
	totally	120	100.0	1474	100.0	
Total cholesterol (mmol/l)	< 5,0	78	69.0	293	19.9	< 0.001
	≥ 5,0	35	31.0	1181	80.1	
	totally	113	100.0	1474	100.0	
HDLC (mmol/l)	decreased**	30	28.8	164	11.1	< 0.001
	the rest	74	71.2	1310	88.9	
	totally	104	100.0	1474	100.0	
LDLC (mmol/l)	< 3,0	74	69.2	269	18.2	< 0.001
	≥ 3,0	33	30.8	1205	81.8	
	totally	107	100.0	1474	100.0	
Triglyceri–des (mmol/l)	> 1,7	35	32.4	423	28.7	0.412
	≤ 1,7	73	67.6	1051	71.3	
	totally	108	100.0	1474	100.0	
Glucose (mmol/l)	< 5,6	43	40.6	919	62.3	< 0.001
	≥ 5,6	63	59.4	555	37.7	
	totally	106	100.0	1474	100.0	

BMI – body mass index; bpm – beats per minute; CAD – coronary artery disease; HDLC – high density lipoprotein cholesterol; HR – heart rate; LDLC – low density lipoprotein cholesterol; n – number; p* – confidence coefficient in Pearson Chi-Squared test; ** for men < 1.0 mmol/l and for women < 1.2 mmol/l

3.5. Physicians' questionnaire on heart rate

When surveying the physicians to know how they evaluate different HR levels for patients with CAD, 23 practitioners (17.0%) noted that HR within the range from 70 to 74 bpm is considered as normal, 11 (8.2%) physicians perceived a normal rate also the HR within the range 75–79 bpm and 5 (3.7%) surveyed practitioners answered that normal is the HR within the range 80–84 bpm. When asked what level of HR they would like to achieve, when treating four different groups of CAD patients (CAD with the history of myocardial infarction; CAD with angina/ischemia; CAD with revascularization, without ischemia and without the history of myocardial infarction; CAD with left ventricular dysfunction (left ventricular ejection fraction > 40%), 97.7%, 97.1%, 94.0%, 97.1% of the physicians, respectively, marked the HR, which is < 70 bpm.

For heart failure patients with systolic dysfunction, 43 (31.9%) practitioners perceived as normal the HR within the range from 70 to 74 bpm, 17 (13.0%) physicians perceived as normal also HR within the range from 75 to 79 bpm and 18 (13.6%) practitioners as normal marked HR within the range from 80 to 84 bpm.

When asked a question what HR they would like to achieve, when treating heart failure patients with systolic dysfunction, 88.7% of the physicians marked HR rate, which is < 70 bpm.

4. DISCUSSION

Analysis of different aspects related to HR control in patients with CAD done during the study confirms hypothesis that HR in treated outpatients with stable CAD in Latvia is inadequately controlled, potential of HR reduction is not fully used by physicians and increased HR is frequent in general Latvia population. Despite wide use of β blockers, for more than one third of the patients HR retained ≥ 70 bpm which is the level associated with the increased CV risk (35.8% and 33.6% when HR is measured by pulse palpation and ECG method, respectively). Irrespective of the fact that compared to the data from REALITY Latvia study carried out four years ago, there is an improvement (in REALITY Latvia study 45% patients had HR ≥ 70 bpm), when studying changes in HR control for the same CAD patients group over three–year follow–up period, there are no significant improvements marked. Actually for all the observational period for more than one third of the patients HR is increased (≥ 70 bpm) and the proportion of these patients does not change statistically significant. At the same time, control of several other important CV risk factors (increased blood pressure, smoking, dyslipidemia) improves with time. As revealed by the study, incompletely used potential of treatment with HR reducing agents and the specific characteristics of physicians' point of view regarding HR level, which should be achieved by treatment, are the possible reasons of insufficient HR control. Results show that β blockers are used in insufficient doses and get rarely combined with ivabradine. Almost a half of the patients, who use β blockers, receive them in doses, which are lower than 50% of the β blocker maximal dose [13, 14]. Proportion of patients using β blockers at the doses lower than 50% of the maximal dose, as well as median doses of β blockers used are not changing over the time. Whereas, ivabradine is preferred by the practitioners

not for the patients with HR ≥ 70 bpm, but in those cases when β blockers cannot be used due to side–effects or contraindications and treatment with β blocker is supported by ivabradine in cases when HR is already extremely increased (≥ 85 bpm). The results of physicians' questionnaire shows that the practitioners have no common view which level of HR should be considered as normal and which one as increased. Physicians' point of view regarding HR differs from the conception manifested in the guidelines. Moreover, the practitioners admit as a target HR the level, which is lower by the one, which is perceived as the normal. It confirms that the physicians' conception about HR does not stimulate achieving of target HR, even if it is formally acknowledged and decreasing of HR is not considered by the practitioners as a serious goal of treatment. Increased HR in general population is often met in Latvia, i.e., HR of ≥ 70 bpm is for more than a half of the studied respondents of Latvian general population and it is even more frequent than for the analyzed CAD patients. However, the study brought forward also good news – irrespective of the fact that more than a third of the treated patients with stable CAD HR is still increased, comparison with general population indicates that HR in the same way as many other CV risk factors, which can be modified by treatment (increased blood pressure, total and low density lipoprotein cholesterol), are overall effectively corrected for the analyzed treated CAD patients compared to the general population.

Increased HR as the CV risk factor is included in CV diseases prevention guidelines already for several years [7, 10, 18], and recently recognized as the CV risk factor by the European stable CAD guidelines [12]. Reduction of HR below 60 bpm is emphasized by European stable CAD guidelines as an important goal of treatment [12]. In the Latvian stable angina guidelines the target HR 55–60 bpm [19] is pointed out. It makes clear that HR for CAD patients should be evaluated every day and reaction should be taken

by using HR reducing agents if it is ≥ 70 bpm. Such recommendations are given also in the taskforce on evaluation and correction of increased heart rate in CAD patients with sinus rhythm [11]. The study elucidates how HR is controlled in real life, whether and what dynamism can be observed over several years' period in this area and how practitioners in Latvia treat HR with HR reducing agents, as well as reveals possible reasons of insufficient HR control.

Several important CV risk factors, which can be influenced by treatment, are not fully controlled for the analyzed CAD population. For example, 56.8% of patients have blood pressure ≥ 140/90 mm Hg, for 31.0% of patients the total cholesterol level is ≥ 5 mmol/l, low density lipoprotein cholesterol level is ≥ 3 mmol/l for 31.1% of patients, but low density lipoprotein cholesterol target [12] of < 1.8 mmol/l is achieved in only 22.6% of patients. On this background it may seem that HR control is still comparatively good, but it should be taken into account that HR is one of the simplest CV parameters to be measured, i.e., in order to measure it, it is not necessary to have any equipment, the patient himself can count his pulse at any moment and due to this cause HR control in everyday circumstances is simpler than for other CV risk factors.

If we compare the data of analyzed CAD population with the situation in the world and in Europe, we can conclude that in Latvia HR for CAD patients is better controlled. For example, the data of world register CLARIFY (ProspeCtive observational LongitudinaAl RegIstry oF patients with stable coronary arterY disease), which summarizes information regarding 33 177 treated CAD patients from 44 countries, shows that HR ≥ 70 bpm is in 44.14% of patients [20]. Whereas, EHS (Euro Heart Survey) study of angina patients, which surveyed 3 779 patients from different European countries, shows that for more than a half (52.3%) of the patients with stable angina treated by

cardiologists HR is above 70 bpm [21]. Comparatively, the proportion of patients with increased HR in the analyzed Latvian CAD population may give certain optimism, unless there was no adverse situation in Latvia in respect to CV mortality, as it is on average in Europe [5]. The relatively high morbidity and mortality rate from CV diseases in Latvia [2, 3, 4, 5] places a moral duty on the physicians to take an especially serious attitude towards control of CV risk factors (including increased HR) for CAD patients.

The latest European stable CAD guidelines define as the target HR the level < 60 bpm. For the analyzed CAD patients' population, that level is only in 13.3% of the cases when HR is measured by pulse palpation method and in 21.8% of the cases when measured by ECG. It is in line with the European data from EHS, which proved that HR for only 19.4% of treated patients with stable angina is ≤ 62 bpm [21] and the worldwide data from CLARIFY where HR of ≤ 60 bpm was 27.9% for CAD patients and only 22.1% for patients with angina [20]. It illustrates that insufficient HR control for CAD patients is a general problem.

For decreasing HR, the practitioners mainly use β blockers. They are used widely as 81.7% of analyzed patients receive β blockers. However, doses of β blockers are substantially behind the maximal doses. Thus, for example, the doses of two most frequently used β blockers metoprolol and bisoprolol mainly correspond to 25% – 50% of the maximal doses (median dose of metoprolol is 64.4 mg/d (corresponding to 32.3% of the maximal dose); median dose of bisoprolol is 5.3 mg/d (corresponding to 53% of the maximal dose)). These data are not contrary to the overall situation in Europe. Also in EHS average doses of β blockers used is below the maximal doses: for metoprolol it is 75.3 mg/d (37.7% of the maximal dose), for carvedilol it is 18.6 mg/d (37.2% of the maximal dose), for bisoprolol – 5.9 mg/d (59.0% of the maximal dose) [21, 13]. Also meta–analysis, where 55 315 patients with a history of

myocardial infarction are analyzed, shows that the use of insufficient β blockers' doses is a widely met phenomenon as the doses, which the patients really receive, are less than 50% of those used in studies [22]. Authors relate it to compliance problems [22]. Also in the analyzed CAD patients' population 19.1% of the patients have β blockers' intolerance signs or contraindications. Possibly β blocker side–effects are the reasons why also in Latvia full β blockers' doses are almost not used in the practice and the β blockers' doses for patients with increased HR $\geq$ 70 bpm does not differ from those, which are used for the whole analyzed patients. However, it may also be connected with the insufficient understanding of the negative impact of increased HR on the CAD patients' prognosis by physicians. Ivabradine, agent acting in sinus node and lowering HR without influence on other heart functions, is chosen by the practitioners mainly in situations when they are forced to stop treatment with β blockers due to side–effects or contraindications. From the analyzed population, 86.7% of the patients, in whom β blockers' therapy was stopped due to intolerance or contraindications, receive ivabradine. Practitioners rare use options to combine β blockers with ivabradine, therefore possibilities to achieve better HR control are not used.

The comparison of historical CAD population from REALITY Latvia with the CAD patients' population from the study of year 2010, although carried out for two different samples, gives insight about HR rate and changes in its control over the time and makes to think that during four years a positive dynamics has been observed. The patients' group analyzed in the year 2010 study (comparing to the group of coronary patients surveyed in the year 2006) showed lower median HR, as well as smaller proportion of patients whose HR is increased $\geq$ 70 bpm. The doses of β blockers used in both studies are similar and far from the maximal doses. It makes us to think that the use of insufficient β blockers' doses is a constant problem, which over the time does

not lessen. But practitioners' possibilities to correct increased HR have, however, improved because differently from the year 2006, in the year 2010 ivabradine was already available for decreasing HR. Possibly the use of ivabradine by the analyzed CAD population in the year 2010 permits to explain why in the year 2010 study HR was lower as well as the proportion of patients with increased HR than in the year 2006 REALITY Latvia study.

However, it should be taken into account that the analyzed CAD group in 2010 is not the same, which was studied in 2006 within the REALITY Latvia project. Better view regarding the situation what is the CV risk factors' distribution and control dynamics, is provided by the analysis of the same CAD patients' group over several years' period. It shows positive trends in the control of such important CV risk factors as smoking, high blood pressure and dyslipidemia, however, there are no improvements in the control of increased HR. During the relatively short three–year follow–up period, the mean number of smoked cigarettes for smokers has significantly decreased, systolic blood pressure as well as the proportion of patients with increased blood pressure (> 140/90 mm Hg) has significantly decreased, in the same manner dyslipidemia ratios have improved as the triglycerides level has significantly decreased and the number of patients with normal high density lipoprotein cholesterol level has increased. It looks optimistic and indicates to a link between regular CAD patients' medical care and improvements in CAD risk factors control. However, it is not really the same in respect to HR because during three–year follow–up period the proportion of patients with increased HR (≥ 70 bpm) has not changed. During the whole follow–up period it was unchangeably high and met for a third part of the patients. Three–year follow–up of CAD patients' group shows that potential to decrease HR by using HR reducing agents is not fully used in practice. Firstly, it refers to β blockers. The use of ß blockers during the whole follow–up period is wide (more than

80%), but insufficient doses of β blockers over the time do not grow in the same manner, as the proportion of patients using at least 50% of the β blocker's maximal dose (during the whole three–year follow–up period it is about 50% and does not change with the time). It is worrying that during the three–year follow–up period 6–8% patients with increased HR (≥ 70 bpm) did not receive any of HR reducing agents. Nevertheless, the progress of using HR controlling agents shows also positive tendencies. During three years the practitioners most frequently started to use ivabradine and more frequently also to combine it with β blockers. The use of ivabradine in monotherapy or in combination with β blockers is considered to be a modern option to lower the increased HR for CAD patients in more efficient way. Analysis of CAD patients' group during three–year period shows that the option to combine β blocker with ivabradine is mainly used in cases when HR is very high. The physicians combine β blocker with ivabradine for patients whose HR is ≥ 85 bpm. These are patients who more rarely are using higher doses of β blockers (≥ 50% of the maximal dose) (most likely due to side–effects as symptoms of β blockers' intolerance in this group are fixed most frequently). It evidences that ivabradine therapy is added rather than in cases of taking a look at HR and making a decision to use it if increased HR is above 70 bpm, but in situations when side–effects or contraindications appear and therefore usage of β blockers is limited and HR is already substantially high. Here are the possibilities to control HR better for CAD patients. The first rule would be strict HR monitoring for CAD patients. It is necessary for the practitioners to be aware of the patients who require decreasing HR, respectively, the patients whose HR is increased ≥ 70 bpm. In addition, it is necessary to spread understanding among practitioners that according to the latest stable CAD European guidelines, reduction of HR to > 60 bpm is an important goal of treatment of CAD patients [12]. The next step would be wide use of β blockers and the use of these agents in higher

doses than up to now (if possible). The third step would be adding of ivabradine to the treatment with the purpose to reach better HR control for CAD patients whose HR is ≥ 70 bpm (not ≥ 85 bpm, as it is now) and most frequent combination of β blocker and ivabradine. Most likely it would permit to control better the increased HR as a CV risk factor and in longer sustainable period would improve both the symptoms as well as prognosis of CAD patients.

Analysis of Latvian general populations shows that increased HR is widely met and HR of ≥ 70 bpm is for more than a half of the analyzed individuals. Due to the fact that increased HR is a CAD risk factor, it might be expected that HR is higher for CAD population and there are more patients with increased HR than in general population, however, the study clearly indicates to the contrary, i.e., HR of ≥ 70 bpm in general population is most frequently met than for the analyzed CAD patients. It shows that for treated CAD patients HR is effectively decreased. It is very positive. In addition, the comparison of CAD group with general population shows, that also other CV risk factors, which can be modified by the treatment, are indeed effectively corrected. For example, diastolic blood pressure, the levels of total cholesterol and low density lipoprotein cholesterol for CAD patients are significantly lower than for representatives of general population.

The physicians' questionnaire about perception of different HR levels for different patient profiles highlights that practitioners hold no one integral opinion about the fact what HR level for CAD and heart failure patients should be considered as normal and what level should be considered as increased one. HR of ≥ 70 bpm by part of the physicians is perceived both as „normal", as well as „borderline high", as well as „high". A part of the practitioners even HR of 80–85 bpm perceive as normal, irrespective of the fact that already the recommendations of year 2010 made by Latvian Society of Cardiology clearly indicate that HR for CAD patients being ≥ 70 bpm should be considered as

increased as it raises CV risk [11] and the HR target mentioned in the Latvian stable angina guidelines is 55–60 [19]. This manifests that practitioners' point of view regarding HR does not agree with the conception written in the guidelines and they do not properly recognize this CV risk factor. This largely helps to explain why HR for CAD patients is not sufficiently controlled. Similar view was also in the year 2006 when within the REALITY Latvia project the practitioners' point of view regarding various HR levels was evaluated. Also at that time, the results of the study indicated that HR within the range from 70 to 80 bpm may be perceived by the physicians both as „normal", as well as „borderline high", as well as „high" [16]. The very fact that one and the same HR level could be perceived by the practitioners differently may not be material, unless it were not most closely related to the practitioners' decision to decrease HR, or not. REALITY Latvia showed that if a physician does not perceive HR as high, then there is neither the decision coming to decrease HR. In the opposite, if the HR rate for the given patient seems „high" for the practitioner's point of view, then in 100% of the cases the physician wants to reduce it [16]. Therefore not the HR level *per se* being high or low determines whether the practitioner will try to reduce HR or not. It is determined by the physician's opinion that the given HR rate is „high". In such a case the proper action follows [16]. The physicians' questionnaire carried out within the scope of this thesis shows that practitioners admit as the target HR the rate, which is lower than the one that they themselves perceive as normal. This indicates that the practitioners do not see decreasing of HR as an important goal of treatment (it is most likely because they insufficiently recognize this CV risk factor) and are not really ready to achieve HR target, even if they seem to know what it should be like. Accordingly, given the correlations found by REALITY Latvia study, we may not hope that practitioners will try to decrease HR in situations when it does not

seem high for them, even it will be significantly above the formally defined target.

Thereby, in order to hope of more successful control of increased HR for CAD patients in the future, it is decisive that Latvian practitioners hold integral point of view that HR ≥ 70 bpm for CAD patients is considered as increased and it should be lowered by using HR reducing agents [11], that decreasing of HR for patients with stable CAD is an important goal of treatment [12] and that the target HR for CAD patients is < 60 bpm, as defined by the latest European stable CAD guidelines [12]. Education of physicians on principles disclosed in the European stable CAD guidelines regarding HR [12], and wide communication about the need to regularly following one's HR would certainly improve the understanding of practitioners about the necessity to control HR rate for CAD patients and promote adequate action from physicians' side in situations when it is increased. This would permit to decrease the number of patients with increased HR rate and would serve as a significant step in fighting increased HR as a CAD risk factor.

Also more detailed communication with community is needed that increased HR along with increased blood pressure, increased cholesterol level, smoking and other well–known CV risk factors plays role in the development of CAD. That would help to form the opinion of medical community, as well as the understanding of the whole society about HR as a CV risk factor. A good tool in enforcement of this target could be a risk calculation table developed by the SCORE (Systematic Coronary Risk Evaluation) researchers, according to which any individual at home is able to evaluate 10 years' death risk by knowing only his/her age, gender, HR and BMI without any additional expenses [23]. Currently the use of this table is not popular in primary prevention. Promotion of its wider application could be useful as it could increase the society's attention paid to HR as CV risk factor. Taking into

account the simplicity and cheapness of the method, by using it, possibly higher number of Latvia residents would evaluate their CV risk and would be ready to correct it under the supervision of practitioners in case of need. In longer sustainable period this would give feedback in the total hard fight against morbidity due to CV diseases and improvement of the existing patients' prognosis in Latvia.

The interpretation of the results of this study has several limitations, i.e., the analyzed CAD patients' group is relatively small and may not reflect the total insight into the CAD patients care in Latvia, also the follow–up period is relatively short. Moreover, selection bias may also have taken place. The historical CAD patients' group from REALITY Latvia study, which was used for comparison with the main CAD patients' sample, is the different one CAD population, analyzed according to different methodology. What about general Latvia population, to which the analyzed CAD group was compared, it is considerably larger. In order to understand better the incidence of increased HR and other CV risk factors, interrelation between them and dynamics in the control of CV risk factors, larger studies with longer follow–up period are needed.

5. CONCLUSIONS

1. Analysis of treated CAD outpatients' sample in Latvia shows that HR control for patients with stable CAD is not sufficient. Despite of wide use of β blockers, for more than a third of the patients analyzed in 2010, HR is increased (≥ 70 bpm) and proportion of patients with increased HR does not change over three–year follow–up period.
2. Comparison of CAD patients' group of year 2010 with the REALITY Latvia population (year 2006) shows improvement in HR control during the time from 2006 to 2010 as CAD patients of year 2010 have by four bpm lower median HR value and lower proportion of patients with increased HR (≥ 70 bpm).
3. Possible reasons of weak HR control are the use of β blockers in insufficient doses, rare combination of these agents with ivabradine, a habit to add ivabradine not in cases when HR is ≥ 70 bpm, but for patients with β blocker side–effects or contraindications and expressively high HR.

   Physicians do not sufficiently recognize HR as a CV risk factor. Their views about HR are not in line with the conception of guidelines and do not promote reaching of target HR, even it is formally admitted. The HR, which is perceived as normal, is higher than the formal target, defined by practitioners.

   Improvement of HR control during the time between 2006 and 2010 is likely to be connected with the use of ivabradine, which was not yet available in 2006.
4. Incidence of increased HR in Latvian general population is high, i.e., for more than a half of analyzed respondents of general Latvia population HR is ≥ 70 bpm and it is even more frequent than for analyzed CAD patients.

6. PRACTICAL RECOMMENDATIONS

Based on the data obtained in the study, practitioners may be advised the following:

1. Regularly control HR rate for all CAD patients in order to identify whose HR is increased (≥ 70 bpm).
2. In order to decrease the proportion of CAD patients with increased HR and thus better control HR as a CAD risk factor, which impacts prognosis as well as symptoms of patients:
   a. when treating CAD patients, pay attention to increasing the dose of β blockers;
   b. if additional reduction of HR is needed, use a combination of β blocker and ivabradine.
3. Try to achieve an HR target for CAD patients, which in the latest European Stable CAD guidelines 2013 is defined as < 60 bpm.
4. To encourage CAD patients for regular measurement and follow–up of resting HR at home.

In order to increase understanding of practitioners, patients and society about HR as a CV risk factor, medical specialists and lecturers can be advised the following:

1. To educate the existing and forthcoming physicians, as well as society about increased HR as a CV risk factor and its interrelation with prognosis.
2. To communicate with the existing and forthcoming medical specialists, as well as the whole society about the fact that HR ≥ 70 bpm for CAD patients should be considered as increased as it is connected with higher risk of CV events.

3. To educate the existing and forthcoming medical specialists about the HR target for CAD patients < 60 bpm as it is defined by the European Stable CAD guidelines 2013.
4. In order to draw the attention of society to HR as a CV risk factor, to encourage society (also the healthy persons) to follow–up regularly the resting pulse at home.

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