

CONTROL OF RESTING HEART RATE AND OTHER RISK FACTORS OVER A THREE-YEAR PERIOD IN OUTPATIENTS WITH STABLE CORONARY ARTERY DISEASE IN LATVIA

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The aim of the study was to evaluate control of heart rate (HR) and other risk factors (RF) over a three-year period in coronary artery disease (CAD) outpatients in Latvia. Patients (n = 120) were examined and questioned at baseline time and annually (four times in total). Increased resting HR (≥ 70 bpm) when measured by palpation was present in 35.8% of cases at baseline time, 35.6%, 29.8% and 35.1% of cases at Y1, Y2 and Y3, respectively; when measured by electrocardiography: in 33.6% (baseline), 36.8% (Y1), 26.7% (Y2), 33.7% (Y3) of cases. The proportion of patients with increased HR did not significantly change in Y1–Y3 vs baseline. Systolic blood pressure was lower in Y1 and Y3 vs baseline ($P = 0.005$ and $P = 0.003$, respectively). The proportion of patients with increased blood pressure ($\geq 140/90$ mmHg) was lower in Y1, Y2 and Y3 than at baseline ($P = 0.018$, $P = 0.030$ and $P = 0.017$, respectively). The proportion of patients with a decreased level of high density lipoprotein cholesterol (< 1.2 mmol/l for women and < 1.0 mmol/l for men) was lower in Y1–Y3 compared to baseline ($P < 0.001$). A substantial (about one-third) and stable proportion of patients with increased HR ≥ 70 bpm over the three-year period in the examined sample of treated CAD patients indicates that there is a need for better control of this RF.

Key words: increased resting heart rate, cardiovascular risk, coronary artery disease, heart rate reducing agents.

INTRODUCTION

Coronary artery disease (CAD) is a highly prevalent cardiovascular (CV) pathology and is the main cause of mortality worldwide and a major burden on public health (Leal *et al.*, 2006). It will remain the leading cause of death for coming years (Mathers and Loncar, 2006). CV mortality in Latvia is higher than in the European Union on average (Anonīms, 2011). Due to aging of the population and improved prognosis of coronary patients, the number of CAD patients in the future may increase (Tunstall-Pedoe *et al.*, 1999). Despite recent advances in management of CAD via more effective treatment for acute coronary syndrome, revascularisation and improved prevention, CAD remains a major public health concern and improvement in outcome of the disease continues to be a challenge.

Understanding of the cardiovascular (CV) risk factors (RFs) and treatment have markedly changed over the years. Dur-

ing the last decade, strong evidence has supported the concept about resting heart rate (HR) as an important prognostic RF (Diaz *et al.*, 2005; Fox *et al.*, 2008a; Bohm *et al.*, 2010). Both the BEAUTIFUL and SHIFT studies in a prospective way confirmed the prognostic value of increased resting HR. BEAUTIFUL showed an association of HR ≥ 70 beats per minute (bpm) with significantly increased CV risk in CAD patients with left ventricular dysfunction (Fox *et al.*, 2008a). Another prospective study, SHIFT, confirmed high HR as a RF and important target for treatment in heart failure (Bohm *et al.*, 2010).

Based on a large body of evidence, high resting HR as an independent CV RF is included in the European and Latvian guidelines on CV disease prevention (Ērglis *u.c.*, 2007; Graham *et al.*, 2007; Perk *et al.*, 2012).

Taking into account the evolving concept of high resting HR as an important correctable RF in CAD, there is increas-

ing demand for data regarding the level of HR control in clinical practice, particularly in outpatients.

The aim of the study was to evaluate control of resting HF as well as other RFs over three-year period in treated outpatients with established stable CAD, by annual collection and analysis of information about RFs (including increased HR), medical history, physical examination and clinical data, as well as the treatment. Following our previous publication on baseline data of the study (Balode *et al.*, 2011), the current paper focuses on three-year follow-up data.

MATERIALS AND METHODS

We surveyed 120 treated outpatients with established stable CAD. Ten cardiologists and two general practitioners working in different regions of Latvia took part in the study, by including 6 to 12 CAD patients each and observing them over a three-year period (from November 2009 to April 2013). CAD was confirmed by history of at least one inclusion criteria: documented myocardial infarction (more than three months ago), coronary stenosis more than 50% (confirmed by coronary angiography), chest pain in combination with myocardial ischemia (confirmed by stress ECG, stress echocardiography or myocardial imaging), coronary revascularisation (coronary artery bypass graft (CABG) or percutaneous coronary intervention (PCI)) more than three months ago. Exclusion criteria were hospitalisation due to CV disease within the last three months, planned revascularisation and limited cooperation of a patient. A case report form for baseline data contained the following parts: demographic information, RFs and lifestyle, medical history, physical examination, current symptoms, most recent measurements (glucose level, total cholesterol, high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), triglycerides, left ventricular ejection fraction (LVEF)), and current treatment. After the inclusion visit when baseline data were collected, patients were questioned and examined once per year during annual visits. During the whole follow-up period, four measurements per each parameter were collected (if available) for each patient. A case report form for annual data contained the following parts: clinical outcomes, RFs and lifestyle, physical examination, current symptoms, most recent measurements 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, two measurements were taken, and the second was recorded. For ECG the most recent ECG within six months was used. No special investigations, measurements or treatment changes took place during this observational study. Over the entire follow-up period, patients were managed in a normal manner by treating physicians.

High HR was defined as ≥ 70 (bpm) according to recent evidence (Fox *et al.*, 2008a). In accordance with Latvian guidelines on CV prevention (Ērglis *u.c.*, 2007): total cho-

lesterol ≥ 5 mmol/l, LDL-C ≥ 3 mmol/l, triglycerides ≥ 1.7 mmol/l, glucose level ≥ 5.6 mmol/l, body mass index (BMI) ≥ 25 kg/m², systolic blood pressure ≥ 140 mmHg and diastolic ≥ 90 mmHg were assessed as high; HDL-C level was defined as low at <1.2 mmol/l for women and <1 mmol/l for men. BMI was calculated by using height and weight in kg/m². Waist circumference ≥ 80 cm for women and ≥ 94 cm for men was defined as increased according to criteria of metabolic syndrome (Alberti *et al.*, 2005).

Target doses for β blockers were defined as follows: 200 mg daily (mg/d) for metoprolol, 10 mg/d for bisoprolol and nebivolol and 50 mg/d for carvedilol in accordance with the expert consensus document on β -adrenergic receptor blockers (Lopez-Sendon *et al.*, 2004) and the newest European heart failure guidelines (McMurray *et al.*, 2012). The target dose for betaxolol was defined as 20 mg/d according to SPC (Summary of Product Characteristics) (Anonims, 2013a).

Approval of the Ethics Committee of the Research Institute of Cardiology, University of Latvia, was obtained before enrollment of patients into study.

P values < 0.05 were considered as statistically significant.

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

RESULTS

Heart rate. HR values at baseline and during the follow-up period are summarised in Table 1. When compared, only HR values measured by palpation differed (were lower) from baseline data in Y2 (Wilcoxon test, $P = 0.027$). The proportion of patients with increased HR at baseline as well as during the follow-up period was about one-third (Table 2). When comparing Y1, Y2, Y3 values with baseline data, no significant changes in the proportion of patients with increased HR were found (McNemar's test, $P > 0.05$).

Clinical outcomes. During the three-year period, of 120 patients participating in the study, at least one clinical outcome was documented in 45 (37.5%) patients: 5 (4.2%) patients died and 40 (33.3%) had non-fatal clinical outcome. In the majority of cases ($n = 4$), death was due to CV reasons, one patient died from non-CV disease. In total, 88 non-fatal CV events were documented during follow-up. The most frequent were coronary angiography, unstable angina and percutaneous coronary intervention (PCI) (Table 3).

Mean baseline HR in patients with or without any clinical outcome was 66.1 ± 9.7 bpm (by pulse palpation), 65.5 ± 10.9 bpm (by ECG), 68.2 ± 8.9 bpm (by pulse palpation), and 67.4 ± 10.2 bpm (by ECG), respectively. No statistically significant differences were found between patients with or without clinical events in terms of baseline HR (independent t-test, $P > 0.050$ for both comparisons). Mean

Table 1

HEART RATE AT BASELINE AND DURING THREE-YEAR FOLLOW-UP

Period	HR measurement method	Statistical values	HR (bpm); n
Baseline	Palpation	M	67.7
		Me	65.5
		IQR	9.5
		n	120
	ECG	M	66.9
		Me	65.0
		IQR	14.0
		n	119
Y1	Palpation	M	67.9
		Me	66.0
		IQR	8.0
		n	118
	ECG	M	66.9
		Me	65.0
		IQR	15.3
		n	114
Y2	Palpation	M	66.0
		SD	±8.3
		Me	64.0
		n	114
	ECG	M	67.7
		Me	63.0
		IQR	12.0
		n	101
Y3	Palpation	M	68.5
		Me	65.5
		IQR	12.3
		n	114
	ECG	M	65.9
		Me	67.0
		IQR	14.5
		n	101

bpm, beats per minute; ECG, electrocardiography; HR, heart rate; IQR, interquartile range; M, mean; Me, median; n, number of patients with measured HR; SD, standard deviation; Y, year

Table 2

DISTRIBUTION OF PATIENTS OVER A THREE-YEAR PERIOD ACCORDING TO HEART RATE LEVEL

HR measurement method	HR levels	Period							
		baseline		Y1		Y2		Y3	
		n	%	n	%	n	%	n	%
Palpation	HRF bpm	77	64.2	76	64.4	80	70.2	74	64.9
	HR≥70 bpm	43	35.8	42	35.6	34	29.8	40	35.1
	Total	120	100	118	100	114	100	114	100
ECG	HRF bpm	79	66.4	72	63.2	74	73.3	67	66.3
	HR≥70 bpm	40	33.6	42	36.8	27	26.7	34	33.7
	Total	119	100.0	114	100.0	101	100.0	101	100.0

For abbreviations see Table 1

Table 3

NON-FATAL CLINICAL OUTCOMES DURING FOLLOW-UP

Year	Clinical outcomes	Number of events	% from included 120 patients	% from patients with annual visit
Y1	Unstable angina	4	3.3%	3.4%
	Non fatal myocardial infarction	1	0.8%	0.8%
	Coronary angiography	10	8.3%	8.5%
	PCI	3	2.5%	2.5%
	Ischemic stroke	1	0.8%	0.8%
	Atrial fibrillation/flutter	3	2.5%	2.5%
	Carotid surgery/stenting	1	0.8%	0.8%
	Total	22		
	Number of events in Y1			
	Number of patients with events	15	12.5%	12.7%
Y2	Unstable angina	10	8.3%	8.7%
	Non fatal myocardial infarction	2	1.7%	1.7%
	Coronary angiography	16	13.3%	13.9%
	PCI	8	6.7%	7.0%
	Unknown stroke	1	0.8%	0.9%
	Transient ischemic attack	1	0.8%	0.9%
	Hospitalisation for chronic heart failure	1	0.8%	0.9%
	Implantation of pacemaker	1	0.8%	0.9%
	Implantation of cardiac defibrillator	1	0.8%	0.9%
	Atrial fibrillation/flutter	2	1.7%	1.7%
	Abdominal aorta surgery/stenting	2	1.7%	1.7%
	Total	45		
	Number of events in Y2			
	Number of patients with events	24	20.0%	20.9%
Y3	Unstable angina	3	2.5%	2.6%
	Non fatal myocardial infarction	1	0.8%	0.9%
	Coronary angiography	6	5.0%	5.3%
	PCI	3	2.5%	2.6%
	Hospitalisation for chronic heart failure	1	0.8%	0.9%
	Implantation of pacemaker	2	1.7%	1.8%
	Atrial fibrillation/flutter	4	3.3%	3.5%
	Periphery artery disease surgery	1	0.8%	0.9%
	Total	21		
	Number of events in Y3			
	Number of patients with events	16	13.3%	14.0%
Y1-Y3		88		
Number of events				
Number of patients with events		40	33.3%	

PCI, percutaneous coronary intervention; Y, year

baseline HR by pulse palpation and ECG in patients who died during the follow-up period were 72.6 ± 16.9 bpm and 71.4 ± 17.4 bpm, respectively. However, it did not differ significantly from patients who survived (67.5 ± 9.2 bpm by pulse palpation and 66.7 ± 10.4 bpm by ECG) (independent

t-test, $P > 0.05$). Mean baseline HR in patients with non-fatal events did not differ significantly from baseline HR in patients without any event; similarly HR in patients with coronary events did not differ from baseline HR in others (independent t-test, $P > 0.05$).

Other risk factors and lifestyle. Most patients were non-smokers. At Y1 and Y2 there were 19 (15.8%) smokers, while 18 (15.9%) patients smoked at Y3, compared with 22 (18.3%) at baseline (Wilcoxon test, $P > 0.05$). The mean number of cigarettes per day decreased significantly at Y1 vs at the baseline visit (7.8 ± 4.3 vs 8.3 ± 3.9 , respectively) (paired sample t-test, $P = 0.015$). Mean weight and BMI did not change during the three-year period (Wilcoxon test, $P > 0.05$). The proportion of patients with increased BMI as well as the proportion of patients with increased waist circumference did not change significantly (McNemar's test, $P > 0.05$). Mean waist circumference increased in women in Y1 vs baseline (96.5 ± 13.1 vs 94.6 ± 12.6 , paired sample test, $P = 0.048$). No other changes in waist circumference were found. Systolic blood pressure was significantly lower at Y1 and Y3 vs baseline data (at baseline: 138.3 ± 17.1 mmHg, Me = 140.0 mmHg; in Y1: Me = 130.0 mmHg, IQR (interquartile range) = 30.0 mmHg; at Y3: Me = 130.0 mmHg, IQR = 17.7 mmHg) (Wilcoxon test, $P = 0.005$ (Y1 vs baseline), $P = 0.003$ (Y3 vs baseline)). The number of patients with increased blood pressure ($\geq 140/90$ mmHg) at baseline, Y1, Y2 and Y3 was 68 (56.7%), 51 (43.2%), 48 (42.1%) and 47 (41.2%), respectively. The proportion of patients with increased blood pressure was significantly lower at Y1 ($P = 0.018$), at Y2 ($P = 0.030$) and at Y3 ($P = 0.017$) vs baseline (McNemar's test).

Other measurements. Regarding the most recently recorded measurements (Table 4), triglyceride level was significantly lower at Y3 vs baseline (Wilcoxon test, $P = 0.004$). The proportion of patients with increased total cholesterol (≥ 5 mmol/l) and with increased LDL-C (≥ 3 mmol/l) and increased level of triglycerides (≥ 1.7 mmol/l) did not differ significantly in comparison with baseline data (McNemar's test, $P > 0.05$), but the proportion of patients with decreased level of HDL-C (< 1.0 mmol/l for men and < 1.2 mmol/l for woman) significantly decreased at Y1, Y2 and Y3 vs baseline (McNemar's test < 0.001 in all cases).

LVEF at baseline, at Y1, Y2 and Y3 was $57.1 \pm 8.7\%$, $58.0 \pm 7.8\%$, $57.8 \pm 8.4\%$, $56.9 \pm 10.2\%$, respectively. It did not differ at Y1–Y3 from baseline values (paired sample t-test, $P > 0.05$) and the proportion of patients with decreased LVEF (%) did not differ: 4 (4.2%) at baseline, 1 (1.9%) at Y1, 1 (1.8%) at Y2 and 3 (5.6%), $P > 0.05$, McNemar's test).

Current symptoms. Angina symptoms at baseline, Y1, Y2 and Y3 were present in 47.5% ($n = 57$), 39.0% ($n = 46$), 43.5% ($n = 50$) and 37.7% ($n = 43$) of patients, respectively. Significant improvement in angina symptoms was found at Y1 and Y3 vs baseline (Wilcoxon test, $P = 0.001$ in both cases). In patients with angina, average consumption of ni-

trates per month at baseline, Y1, Y2 and Y3 was 7.7 ± 5.2 , 4.4 ± 3.1 , 5.6 ± 3.2 and 5.1 ± 3.4 , respectively. Consumption of nitrates decreased significantly at Y1, Y2, Y3 vs baseline (paired sample t-test, $P = 0.001$, $P = 0.015$, $P = 0.004$, respectively).

The number of patients with heart failure at baseline and at Y1, Y2, Y3 was 69 (57.5%), 69 (68.5%), 73 (63.5%) and 75 (65.8%), respectively. Significant worsening in heart failure symptoms was found at Y3 vs baseline data (McNemar's test, $P = 0.022$).

Treatment. Treatment of patients with different classes of drugs is summarised in Table 5.

Preventive treatment. During the follow-up period, the number of patients receiving antithrombotic agents was invariably high (Table 5). The proportion of patients receiving antithrombotic agents and proportion of patients using statins and angiotensin-converting enzyme inhibitors (ACEI) or angiotensin-receptor blockers (ARB) did not differ at Y1–Y3 vs baseline data (McNemar's test, $P > 0.05$ in all cases).

HR reducing agents. Regarding heart rate reducing agents, patients were using β blockers and ivabradin (number of patients using these agents during the follow-up period are summarised in Table 5). No patient used digoxin or amiodaron as a single HR reducing agent without β blocker or ivabradin. Non-dihydropyridine Ca antagonists were not used at all. Among β blockers, metoprolol, bisoprolol, nebivolol and carvedilol were used. One patient at Y1 received betaxolol (10 mg/d). Most frequently, patients were receiving metoprolol and bisoprolol (Table 5). The proportion of patients using nebivolol significantly increased in Y2 and Y3 in comparison with baseline data (McNemar's test, $P = 0.031$ in both cases). Average daily dose (ADD) of metoprolol at baseline, in Y1, Y2 and Y3 was the same: Me = 50 mg/d, IQR = 50 mg/d. ADD of another most frequently used β blocker bisoprolol at baseline and in Y1–Y3 was the following: Me = 5.0 mg/d, IQR = 0.0 mg/d except Y1, when IQR = 2.5 mg/d. ADD of β blockers did not change over three-year period (Wilcoxon test, $P > 0.050$ in all cases). Distribution of patients according to used dose of β blocker is summarised in Table 6: no differences were found at Y1, Y2 and Y3 compared to baseline data (Wilcoxon test, $P > 0.050$ in all cases).

The proportion of patients using ivabradin significantly increased at Y1, Y2 and Y3 in comparison with baseline data (McNemar's test, $P = 0.016$, $P < 0.001$, $P < 0.001$, respectively). The median ADD of ivabradin at baseline and at Y1–Y3 was 5.0 (IQR = 5.0) mg/d and 15.0 (IQR = 5.0) mg/d, respectively. Doses of ivabradin at Y2, Y2 and Y3 significantly increased vs baseline values (Wilcoxon test, $P = 0.002$, $P = 0.002$ and $P = 0.001$, respectively). The number of patients using ivabradin in combination with β blocker was 3 (2.5%) at baseline and 9 (7.6%), 17 (14.8%) 20 (17.5%) at Y1, Y2 and Y3, respectively. The proportion of patients using this combination significantly increased at

Table 4

MOST RECENT MEASUREMENTS DURING THE FOLLOW-UP PERIOD

Measurement	Period	Statistical parameters and values			Levels	n	%
Glucose level (mmol/l)	Baseline	M	Me	IQR	< 5.6	43	40.6
		6.1	5.7	1.2	≥ 5.6	63	59.4
					total	106	100.0
	Y1	M	Me	IQR	< 5.6	44	43.6
		6.2	5.7	1.4	≥ 5.6	57	56.4
					total	101	100.0
	Y2	M	Me	IQR	< 5.6	47	43.9
		6.2	5.8	1.2	≥ 5.6	60	56.1
					total	107	100.0
	Y3	M	Me	IQR	< 5.6	42	42.0
		5.9	5.7	1.2	≥ 5.6	58	58.0
					total	100	100.0
Total cholesterol (mmol/l)	Baseline	M	Me	IQR	< 5	78	69.0
		4.7	4.5	1.3	≥ 5	35	31.0
					total	113	100.0
	Y1	M	SD	Me	< 5	80	70.8
		4.6	±1.1	4.5	≥ 5	33	29.2
					total	113	100.0
	Y2	M	SD	Me	< 5	80	71.4
		4.6	±1.1	4.4	≥ 5	32	28.6
					total	112	100.0
	Y3	M	SD	Me	< 5	83	79.0
		4.4	±0.9	4.2	≥ 5	22	21.0
					total	105	100.0
HDL-C (mmol/l)	Baseline	M	Me	IQR	low*	30	28.8
		1.4	1.2	0.5	others	74	71.2
					total	104	100.0
	Y1	M	SD	Me	low*	30	27.3
		1.3	±0.4	1.2	others	80	72.7
					total	110	100.0
	Y2	M	SD	Me	low*	28	28.3
		1.3	±0.4	1.3	others	71	71.7
					total	99	100.0
	Y3	M	SD	Me	low*	19	20.0
		1.3	±0.3	1.2	others	76	80.0
					total	95	100.0
LDL-C (mmol/l)	Baseline	M	Me	IQR	< 3	73	68.9
		2.7	2.6	1.1	≥ 3	33	31.1
					total	106	100.0
	Y1	M	Me	IQR	< 3	83	75.5
		2.7	2.5	1.0	≥ 3	27	24.5
					total	110	100.0
	Y2	M	Me	IQR	< 3	83	77.6
		2.7	2.5	1.1	≥ 3	24	22.4
					kopā	107	100.0
	Y3	M	SD	Me	< 3	79	79.0
		2.5	±0.8	2.4	≥ 3	21	21.0
					kopā	100	100.0
Triglycerides (mmol/l)	Baseline	M	Me	IQR	≥ 1,7	36	33.3
		1.7	1.4	1.0	others	72	66.7
					total	108	100.0
	Y1	M	Me	IQR	≥ 1,7	28	25.2
		1.5	1.2	0.8	others	83	74.8
					total	111	100.0
	Y2	M	Me	IQR	≥ 1,7	26	25.7
		1.5	1.3	0.7	others	75	74.3
					total	101	100.0
	Y3	M	Me	IQR	≥ 1,7	27	27.3
		1.5	1.2	0.8	others	72	72.7
					total	99	100.0

HDL-C, high density lipoprotein cholesterol; IQR, interquartile range; LDL-C, low density lipoprotein cholesterol. For other abbreviations see Table 1

* < 1.2 mmol/l for women and < 1.0 mmol/l for men

Table 5

USE OF THE MOST IMPORTANT CLASSES OF CARDIOVASCULAR DRUGS OVER THE THREE-YEAR PERIOD

Classes	Number of patients receiving drugs							
	baseline		Y1		Y2		Y3	
	n	%	n	%	n	%	n	%
Antithrombotic agents	118	98.3	116	98.3	113	98.3	112	98.2
Statins	113	94.2	113	95.8	111	96.5	111	97.4
ACEI/ARB	103	85.5	103	87.3	103	89.6	103	90.4
β blockers (total)	98	81.7	97	82.2	97	84.3	96	84.2
metoprolol	47	39.2	46	39.0	45	39.1	45	39.5
bisoprolol	37	30.1	33	28.0	32	27.8	33	28.9
nebivolol	10	8.3	14	11.9	17	14.8	16	14.0
carvedilol	4	3.3	3	2.5	3	2.6	2	1.8
betaksolol	0	0.0	1	0.9	0	0.0	0	0.0
I _f inhibitors (ivabradin)	15	12.5	22	18.6	29	25.2	32	28.1
Ca antagonists	64	53.3	66	53.9	67	58.3	69	60.5
Nitrates	28	23.3	30	25.4	31	27.0	30	26.3
Other antianginal agents	15	12.5	17	14.4	20	17.4	21	18.4
Diuretics	31	25.8	35	29.7	39	33.9	41	36.0

ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin-receptor blockers; n, number of patients; Y, year

Y1, Y2, Y3 comparing to baseline values (McNemar's test, $P = 0.031$, $P < 0.001$, $P < 0.001$, respectively).

HR reducing agents in the group of patients with increased resting HR ≥ 70 bpm. Regarding patients with increased HR (documented at least in one visit), more than 90% of patients with HR ≥ 70 bpm, ≥ 75 bpm, ≥ 80 bpm and ≥ 85 bpm were using β blocker or ivabradin. However, HR reducing agents were not used at all in 6–8% of patients with increased HR: in 5 (6.9%), 3 (6.4%), 2 (6.3%) and 2 (5.0%) cases of patients with HR ≥ 70 bpm, ≥ 75 bpm, ≥ 80 bpm and ≥ 85 bpm, respectively (when HR was documented by pulse palpation) and in 4 (6.8%), 3 (6.7%), 2 (9.7%) and 2 (8.3%) cases of patients with HR ≥ 70 bpm, ≥ 75 bpm, ≥ 80

Table 6

DISTRIBUTION OF PATIENTS USING β BLOCKERS ACCORDING TO DOSE

Dose of β blocker (% from target dose*)	Baseline		Y1		Y2		Y3	
	n	%	n	%	n	%	n	%
< 25	5	5.1	6	6.2	8	8.2	7	7.3
25–49,9	41	41.8	44	45.4	39	40.2	41	42.7
50–74,9	45	45.9	41	42.3	45	46.4	43	44.8
75–99,9	2	2.0	1	1.0	1	1.0	1	1.0
100	5	5.1	5	5.2	4	4.1	3	3.1
> 100	0	0.0	0	0.0	0	0.0	1	1.0
Total	98	100.0	97	100.0	97	100.0	96	100.0

n, number of patients; Y, year; * target dose for metoprolol – 200 mg/d, for bisoprolol – 10 mg/d, for nebivolol – 10 mg/d, for carvedilol – 50 mg/d, for betaksolol – 20 mg/d

bpm and ≥ 85 bpm, respectively (when HR was documented by ECG).

The number of patients using ivabradin, β blockers and ivabradin in combination with β blockers according to HR are summarised in Table 7. Dividing patients in four categories according to HR (70–74 bpm, 75–79 bpm, 80–84 bpm and ≥ 85 bpm), parabolic regression analysis showed a significant parabolic relationship with a high determination coefficient between HR category and use of ivabradin, as well as frequency of β blockers in combination with ivabradin: decrease or slight increase when HR was 75–79 bpm and 80–85 bpm in comparison with HR level 70–74 bpm and significant increase when HR was ≥ 85 bpm (Table 8). Use of higher doses of β blockers ($\geq 50\%$ from target dose) and frequency of β blockers contraindications/side effects also changed parabolically: use of $\geq 50\%$ of β blockers target dose increased when HR was 70–74 bpm, 75–80 bpm and decreased when HR was ≥ 85 bpm; frequency of β blockers contraindications/side effects increased when HR was higher (Table 9).

Other CV agents. All patients receiving Ca antagonists used dihydropyridine type Ca antagonists. At Y2 and Y3,

Table 7

USE OF BRADICARDIC AGENTS IN PATIENTS WITH INCREASED HEART RATE

HR* (bpm)	Method	n	β blocker or ivabradin**		β blocker**				Ivabradin**		β blocker and ivabradin**	
					all doses		≥50% from target dose					
			n	%	n	%	n	%	n	%	n	%
≥70	palpation	72	67	93.1	59	81.9	33	49.3	20	27.8	12	16.7
≥75	palpation	47	44	93.6	40	85.1	26	55.3	14	29.8	10	21.3
≥80	palpation	32	30	93.7	27	84.4	18	56.3	12	37.5	9	28.1
≥85	palpation	20	19	95.0	16	80.0	7	35.0	10	50.0	7	35.0
≥70	ECG	59	55	93.2	48	81.4	28	47.5	18	30.5	11	18.6
≥75	ECG	45	42	93.4	38	84.4	24	53.3	14	31.1	10	22.2
≥80	ECG	31	28	90.3	25	80.7	16	51.6	10	32.3	7	22.6
≥85	ECG	24	22	91.7	19	79.2	10	41.6	9	37.5	6	25.0

bpm – beats per minute. For other abbreviations see Table 1; *documented at least in one visit; **used at least one year

Table 8

USE OF IVABRADIN AND β BLOCKERS IN COMBINATION WITH IVABRADIN ACCORDING TO INCREASED HEART RATE CATEGORY

HR* category (bpm)	Palpation									ECG								
	n	ivabradin**				β blocker in combination with ivabradin**				n	ivabradin**				β blocker in combination with ivabradin**			
		n	%	p	R ²	n	%	p	R ²		n	%	p	R ²	n	%	p	R ²
70–74	25	6	24.0	\wedge 0.001	0.994	2	8.0	\wedge 0.001	1.000	14	4	28.6	\wedge 0.001	0.659	1	7.1	0.015	0.649
75–79	15	2	13.3			1	6.7			14	4	28.6			3	21.4		
80–85	12	2	16.7			2	16.7			7	1	14.3			1	14.3		
≥ 85	20	10	50.0			7	35.0			24	9	37.5			6	25.0		

bpm, beats per minute; p, significance coefficient for parabolic regression; R², determination coefficient. For other abbreviations see Table 1; *documented at least in one visit; **used at least one year

Table 9

USE OF HIGHER DOSES OF β BLOCKERS AND FREQUENCY OF β BLOCKERS INTOLERANCE ACCORDING TO INCREASED HEART RATE CATEGORY

HR* category (bpm)	Palpation									ECG								
	n	$\geq 50\%$ of β blocker dose**				β blockers contraindications/side effects**				n	$\geq 50\%$ of β blocker dose**				β blockers contraindications/side effects**			
		n	%	p	R ²	n	%	p	R ²		n	%	p	R ²	n	%	p	R ²
70–74	25	7	28.0	\wedge 0.001	0.768	8	32.0	\wedge 0.001	0.895	14	4	28.6	\wedge 0.001	0.826	7	50.0	0.005	0.4241
75–79	15	8	53.3			4	26.7			14	8	57.1			2	14.3		
80–85	12	11	91.7			2	16.7			7	6	85.7			3	42.9		
≥ 85	20	7	35.0			10	50.0			24	10	41.7			4	41.7		

For abbreviations see Table 8; *documented at least in one visit; **at least in one year

the proportion of patients using Ca antagonists significantly increased in comparison with baseline data (McNemar's test, $P = 0.039$ and $P = 0.012$, respectively). The proportion of patients using nitrates did not change vs baseline data (McNemar's test, $P > 0.050$). The number of patients using other antianginal agents (trimetazidin in all cases, except one patient at Y2 and Y3 using ranolazin) was: 15 (12.5%) at baseline 17 (14.4%) at Y1, 20 (17.4%) and 21 (18.4%) at Y3 and it increased at Y3 vs baseline (McNemar's test, $P = 0.031$). The proportion of patients using diuretics increased at Y1, Y2 and Y3 vs baseline (McNemar's test, $P = 0.031$, $P = 0.004$ and $P < 0.001$, respectively).

DISCUSSION

Observed clinical outcomes in our study are typical for CAD patients, with domination of non-fatal coronary events (coronary angiography, unstable angina, PCI). The documented fatal events were connected with progression or complications of CV disease, as in the majority of deceased patients, cause of death was CV. Our data did not show the well known relationship between increased HR and CV events (including mortality) (Diaz *et al.*, 2005; Fox *et al.*, 2008a). Although HR in deceased patients was higher than in patients who survived, the difference does not reach statistical significance. This is probably connected with a low sample size of observed patients and too short follow-up period.

In our study, the proportion of patients using preventive treatment (Fox, 2006) was high, indicating a favourable

trend to follow guidelines and consider CV prevention by treating CAD patients. However, the high mortality rate from CV diseases in Latvia (Anonims, 2011) indicates a need to use all possibilities by practitioners to control CV RFs when treating CAD patients.

Data from analysed sample indicates a good tendency for better control of several important RFs over the three-year period: mean number of smoked cigarettes per day in smokers decreased, systolic blood pressure as well as number and proportion of patients with increased blood pressure decreased significantly. Also, control of dyslipidemia improved, as the level of triglycerides decreased, and proportion of patients with normal HDL-C increased. This seems encouraging and shows a connection between regular control of CAD patients by practitioners and progress in management of RFs, even during the relatively short period of time. However, this is not the case with HR. In our sample the percentage of CAD patients with increased HR (≥ 70 bpm) was lower than in the Euro Heart Survey (EHS) and REALITY Latvia (Daly *et al.*, 2008; Balode *et al.*, 2010), but the proportion of patients with increased HR (≥ 70 bpm) did not change over the three-year period. EHS analysed information from 156 cardiology clinics in 34 countries with 3031 patient included, on the basis of a new clinical diagnosis of stable angina by a cardiologist (Daly *et al.*, 2006). In EHS, the proportion of patients with increased HR (≥ 70 bpm) was 53% (Daly *et al.*, 2008). REALITY Latvia results are particularly interesting, as this study reflects the situation in Latvia with stable angina management four years before the start of our study. That study analysed 300 stable

angina outpatients treated by cardiologists and highlighted increased HR and its management (Balode *et al.*, 2010). The proportion of patients with increased HR ≥ 70 bpm in REALITY Latvia was 43%. In our study the proportion of patients with increased HR was lower (36% by pulse palpation and 34% by ECG at the beginning of study). This suggests that HR management has improved, as REALITY Latvia was performed seven years ago. However, the patients in REALITY Latvia and in our study are not the same. Examination of HR control in our study during a three-year follow-up period of the same population suggests lack of improvement in HR. The proportion of patients with increased HR was high (around one-third) and stable over the three-year period, indicating a need for better control of this RF. HR is one of the most frequently assessed clinical parameters, which can be easily followed even by patients, and should be better controlled, especially taking into account the strong association of increased HR with CV events (Fox *et al.*, 2008a) in CAD patients.

The current study does not indicate movement of patients from the group with increased HR to the group with normal HR or vice versa, over the follow-up period. It does not answer the question if patients did not respond to treatment with HR reducing agents. That type of analysis would be very useful in further studies.

Our data indicate unused potential for better control of HR. The most commonly used agents with HR reducing effect are β blockers. The proportion of patients using β blockers was high (more than 80%), but the used doses were far from β blocker target doses. Long-term compliance and underdosing of β blockers is typical, as in real life patients are using significantly less dosages than those used in clinical trials (Gislason, 2006). Around 50% of patients on β blockers in our study were using 2% of the target dose and our data did not show any change in doses of β blockers used over the three-year period. Use of nebivolol, a β blocker with relatively weak HR reducing effect, increased during the follow-up period. Also, in 6–8% of cases, despite increased HR, patients did not use any HR reducing agent. In our study, patients were mainly treated by cardiologists. In real life, stable CAD patients are more frequently treated by general practitioners. As understanding of increased HR as an independent CV RF and important target for treatment can be significantly lower among general practitioners, in comparison with cardiologists, HR control in patients treated by general practitioners is likely even weaker.

However, there are some positive tendencies in management of HR — practitioners are starting to use ivabradin more frequently, as well as more commonly combining β blockers with ivabradin. Ivabradin is good HR lowering agent without influence on other cardiac functions and provides antianginal and antiischemic efficacy in case of angina (Anonymous, 2013b). There is also evidence about ability of ivabradin to reduce risk of events (Fox *et al.*, 2008b; Fox *et al.*, 2009; Swedberg *et al.*, 2010). Our data show that use of ivabradin is more frequent when HR is significantly higher than 70 bpm — at the level ≥ 85 bpm. In those patients, higher doses of β blockers (≥ 50 from target dose)

were less frequently used, probably due to side effects, as incidence of β blocker intolerance was higher in this group. Insufficient reduction of HR is indication for combination of β blocker with ivabradin. However, our data suggest that ivabradin is added to treatment not because of HR, but because of intolerance of β blockers. Newest European as well as Latvian heart failure guidelines recommend adding ivabradin when HR is ≥ 70 bpm (McMurray *et al.*, 2012). Use of higher doses of β blockers and more frequent combination with ivabradin in patients with ≥ 70 bpm could be potentially beneficial for better control of HR in CAD patients.

Limitations for interpretation of the results should be acknowledged, as the number of patients involved was relatively small and the follow-up period was rather short. Selection bias may also have taken place. For better understanding of how management of increased HR and other RFs in stable CAD patients is changing, studies with a bigger number of patients and a longer follow-up period are needed. The results of the study indicate improvement over the three-year period in the management of several important RFs, like smoking, increased blood pressure as well as dyslipidemia, in the analysed sample of treated outpatients with established CAD.

However, prevalence of patients with increased HR (≥ 70 bpm) remained high (around one-third) and stable, indicating a need for better control.

Use of higher doses of β blockers and more frequent combination of β blockers with ivabradin in patients with HR ≥ 70 bpm could be an unused potential for better control of increased HR and an additional step towards reduction of coronary events and improvement of symptoms in CAD patients.

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SIRDSDARBĪBAS FREKVENCES UN CITU RISKĀ FAKTORU KONTROLE TRĪS GADU PERIODĀ LATVIJĀ AMBULATORI ĀRSTĒTIEM PACIENTIEM AR STABILU KORONĀRO SIRDIS SLIMĪBU

Pētījuma mērķis bija novērtēt palielinātas sirdsdarbības frekvences (SF) un citu riska faktoru (RF) kontroli trīs gadu ilgā novērošanas periodā ambulatori ārstētiem pacientiem ar stabilu koronāro sirds slimību (KSS). Pacienti ($n = 120$) tika iztaujāti un izmeklēti kopumā četras reizes — sākotnēji un ik gadu trīs gadus pēc kārtas. Palielināta sirdsdarbības frekvence (≥ 70 x/min), nosakot to ar palpācijas metodi, sākotnēji un trijos novērošanas gados attiecīgi bija 35,8%, 35,6%, 29,85 un 35,1%; nosakot ar elektrokardiogrāfijas metodi, 33,6%, 36,8%, 26,75% un 33,7%. Šo pacientu īpatsvars trīs gadu novērošanas periodā statistiski ticami nemainījās. Sistoliskais asinsspiediens pirmajā un trešajā novērošanas gadā bija ticami zemāks nekā sākotnēji (attiecīgi, $P = 0,005$ un $P = 0,003$). Pacientu ar palielinātu asinsspiedienu ($\geq 140/90$ mmHg) īpatsvars statistiski ticami samazinājās pirmajā (43,2%), otrajā (42,1%) un trešajā (41,2%) novērošanas gadā salīdzinājumā ar sākotnējiem datiem (56,7%) (attiecīgi, $P = 0,018$, $P = 0,030$ un $P = 0,017$). Tāpat pirmajā, otrajā un trešajā novērošanas gadā bija būtiski mazāks to pacientu īpatsvars, kuriem bija pazemināts augsta blīvuma lipoproteīnu holesterīna līmenis ($< 1,2$ mmol/l sievietēm un $< 1,0$ mmol/l vīriešiem) (27,3%, 28,3%, 20,0% vs 28,8%, $P < 0,001$ visos gadījumos). Fakts, ka, neraugoties uz ārstēšanu, nozīmīgam analizēto KSS pacientu skaitam (apmēram trešajai daļai) saglabājas palielināta SF un šādu pacientu proporcija laika gaitā būtiski nemainās, norāda, uz nepieciešamību labāk kontrolēt šo nozīmīgo RF.