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Original Research Article

Insufficient control of heart rate in stable coronary artery disease patients in Latvia

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ABSTRACT

Background and objective: Heart rate (HR) ≥70 beats per minute (bpm) increases cardiovascular risk in coronary artery disease (CAD) patients. The objective of the analysis is to characterize HR as well as other clinical parameters in outpatients with stable CAD in Latvia.
Materials and methods: CLARIFY is an ongoing international registry of outpatients with established CAD. Latvian data regarding 120 patients enrolled in CLARIFY and collected at baseline visit during 2009–2010 were analyzed.
Results: The mean HR was 67.7 ± 9.5 and 66.9 ± 10.7 bpm when measured by pulse palpation and electrocardiography, respectively. HR ≤60 bpm and ≥70 bpm was observed in 25% and 35.8% of patients, respectively. When analyzing patients with angina symptoms, 22.8% had HR ≤60 bpm while HR ≥70 bpm was observed in 33.3% of the cases. HR ≥70 bpm was observed in 36.2% of patients with symptoms of chronic heart failure. Beta-blockers were used in 81.7% of the patients. Metoprolol (long acting succinate), bisoprolol, nebivolol and carvedilol in average daily doses 63.8, 5.3, 4.5, and 10.4 mg/d were used in 47, 37, 11 and 3 cases, respectively. Among patients with HR ≥70 bpm 79.1% were using beta-blockers. Medications did not differ significantly between the three groups according to HR level (≤60, 61–69 and ≥70 bpm).

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Conclusions: Despite the wide use of beta-blockers, HR is insufficiently controlled in the analyzed sample of stable CAD patients in Latvia. Target HR ≤60 bpm is achieved only in 25% of the patients while more than one third have increased HR ≥70 bpm.

1. Introduction

Coronary artery disease (CAD) is the main cause of mortality worldwide [1]. Cardiovascular mortality in Latvia is higher than in European Union on average [2]. The prospeCtive observational LongitudinAl RegIstry oF patients with stable coronary arterY disease (CLARIFY) registry was initiated to improve knowledge about outpatients with stable CAD: to describe this population in terms of demographics, risk factors, management as well outcomes; to find out discrepancies between evidence-based recommendations and routine treatment in practice as well as to identify long-term prognostic determinants in CAD outpatients [3]. Heart rate (HR) is important player in pathophysiology of CAD. Increased HR is associated with ischemia as it affects negatively the myocardial oxygen balance by increasing oxygen consumption and decreasing oxygen supply. Besides, large body of evidence suggests that high HR is associated with increased cardiovascular risk [4–6]. Several epidemiological studies underline relationship between increased HR and risk of total as well as cardiovascular mortality [4,5]. The prognostic value of high HR in stable CAD patients with left ventricular dysfunction has been confirmed also in a prospective way in the BEAUTIFUL trial. Analysis of a large cohort from the placebo arm in the BEAUTIFUL study showed strong association of HR ≥70 beats per minute (bpm) with higher risk of cardiovascular events [6]. Beta-blockers, agents providing efficient HR reduction, is well established class in treatment of stable CAD and clinical benefits of HR reduction with beta-blockers are well known. However, besides HR reduction beta-blockers have many other effects such us blood pressure reduction, negative inotropic effect etc. [7]. There is also an evidence of clinical improvement in angina symptoms with pure heart rate reducing agent [8,9]. BEAUTFUL study showed that pure HR lowering strategy in stable CAD patients may reduce coronary events [10,11]. By recognizing HR as the risk factor and defining reduction of HR <60 bpm as important goal of treatment CAD patients, the newest European guidelines on stable CAD (2013) establish role of HR control in management of stable CAD [12]. The objective of the current study is to analyze actually achieved HR level, to evaluate proportion of patients in whom HR targets are not reached despite treatment and to analyze other clinical parameters in routinely managed outpatients with stable CAD in Latvia.

2. Materials and methods

CLARIFY is an ongoing international, prospective, observational longitudinal registry of outpatients with established CAD in which patients are followed-up for 5 years. A total of 33,438 patients from 45 countries worldwide were included in the registry. The rationale of the registry was based on need to collect data on the current status of outpatients with stable CAD [3]. Worldwide baseline data of the registry have been published previously [13]. In Latvia, 120 patients with established CAD were included in CLARIFY registry during 2009 and 2010. Patients were managed according to usual clinical practice by treating physicians. No specific examinations or treatment changes were introduced.

Patients were eligible for enrollment if at least one of the inclusion criteria was presented: documented myocardial infarction (more than 3 months ago), coronary stenosis more than 50% on coronary angiography, chest pain in combination with myocardial ischemia (confirmed by stress electrocardiogram (ECG), stress echocardiography or myocardial imaging), coronary revascularization (coronary artery bypass graft (CABG) or percutaneous coronary intervention (PCI)) at least 3 months ago. Exclusion criteria were hospitalization due to cardiovascular disease within last 3 months, planned revascularization and conditions expected to interfere participation or 5-year follow-up.

Twelve physicians (cardiologists and general practitioners treating CAD outpatients) each enrolled 10 patients on average. During baseline visit the following data were collected: demographic information, medical history, risk factors and lifestyle, physical examination data (including HR), current symptoms, most recent laboratory values as well as information about current medical treatment. The resting HR was estimated by pulse palpation and electrocardiography (ECG). HR by pulse palpation was measured for 30 s after sitting for at least 5 min in a quiet room with comfortable temperature. Two different measurements were taken, and the second was recorded. For ECG the most recent 12-lead ECG within 6 months was analyzed. For evaluation of angina symptoms Canadian Cardiovascular Society (CCS) classification was used. New York Heart Association (NYHA) classification was used to assess severity of heart failure symptoms. Laboratory values (e.g. fasting blood glucose, cholesterol, triglycerides) were collected if given date were available. Patients were managed according to usual clinical practice at each institution with no specific tests defined in the protocol.

Data were collected by using standardized, international case report form translated into Latvian. Completed electronic case report forms using these data were sent to the data management center in Glasgow. Approval of the Ethics Committee of the Research Institute of Cardiology, University of Latvia was obtained before enrollment of patients into registry.

All CLARIFY data are stored and analyzed at the Robertson Center for Biostatistics, University of Glasgow, UK. Continuous

data are summarized using mean and standard deviation (SD), or median and interquartile range (IQR) depending on the distribution of the data. Categorical data are summarized using counts and percentages. Summaries are provided for the total CLARIFY Latvia data overall and split into three mutually exclusive groups of patients' according to HR (measured by palpation) level: with HR ≤60, 61–69 and ≥70 bpm. In order to analyze clinical characteristics and medications according to HR level, *P* values for differences between the groups were calculated using either the chi-square test or Fisher exact test for the categorical variables, depending on the data, and for the continuous variables using either one-way analysis of variance, or Kruskal–Wallis test, depending on the distribution of the data. The correlation between the different heart rate measurements was calculated using Pearson correlation. Statistical analyses were performed using the Statistical Analysis Software (SAS) (version 9.2). A significance level of 0.05 was used to test for statistical differences throughout and all tests used were two-sided.

HR ≥70 bpm was assessed as increased in accordance with recent evidence [10,14,15]. Target HR <60 bpm was defined in accordance with 2013 European stable CAD guidelines [12].

Height and weight were used to calculate body mass index in kg/m^2.

Permission to publish national data of CLARIFY registry was obtained from Les Laboratoires Servier (global sponsor of CLARIFY registry) and Servier Latvia (sponsor of CLARIFY registry on national level in Latvia) before publishing data.

3. Results

Characteristics of CLARIFY population in Latvia are summarized in Table 1. Mean age of patients was 64.2 ± 7.9 years; most of them were men (72.5%) (Table 1). Distribution of HR when measured by pulse palpation is shown in Fig. 1. Mean HR was 67.7 ± 9.5 bpm and 66.9 ± 10.7 bpm when measured by pulse palpation and ECG, respectively. A strong correlation between HR measured by pulse palpation and ECG-derived HR was found ($r = 0.848$, $P < 0.001$) (Fig. 2).

Ethnicity of all patients was Western descent, most of them were retired (50.8%) and most commonly the level of education was secondary school (57.5%). The median time since diagnosis of CAD was 4 (IQR 2–10) years. The most common risk factors were dyslipidemia (94.2%) and treated hypertension (78.3%); the majority of patients were nonsmokers (41.7%); most frequently alcohol intake was >0 and <20 drinks per week (65.0%); from stimulant drinks coffee was more consumed than tea (59.2% and 39.2% respectively) and regarding physical activity most of the patients had light physical activity most weeks (45.8%) (Table 1). Chronic heart failure symptoms were present more frequently than symptoms of angina (57.5% compared to 47.5%); most frequently coronary territories with stenosis >50% at coronary angiography or having required revascularization in the past were in left anterior descending (69.2%) and most of the patients were in sinus rhythm (95.8%) (Table 1). Patients were divided in to three groups according to baseline HR by pulse palpation: ≤60 bpm, 61–69 bpm and ≥70 bpm. The clinical characteristics of these three subgroups are summarized in Table 1. When analyzing clinical characteristics, only diastolic blood pressure and the presence of coronary stenosis >50% in right coronary artery at coronary angiography differed significantly between three HR groups (Table 1). Patients with higher HR had higher diastolic blood pressure (Table 1). Among all 57 patients with angina, 22.8% had HR ≤60 bpm, but HR ≥70 bpm was observed in 33.3% of cases while among patients with chronic heart failure ($n = 69$), HR ≤60 bpm was observed in 27.5% of cases, but in 29.0% of patients HR was ≥70 bpm.

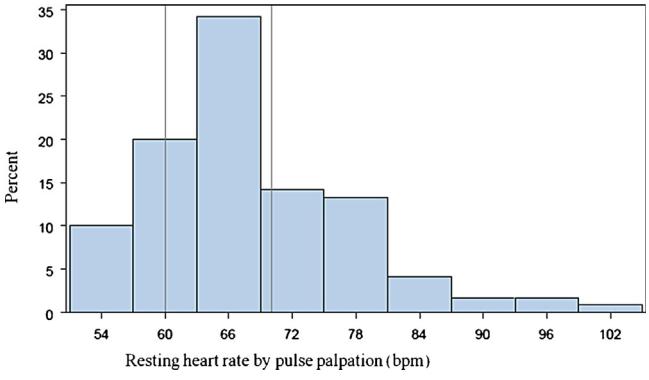

Fig. 1 – Distribution of Latvian patients with stable CAD by heart rate (cohort of Latvian patients, included in the worldwide registry CLARIFY).

The use of medication in total population as well as in three HR subgroups is summarized in Table 2. With respect of HR lowering agents, the most frequently used were beta-blockers (81.7%). Metoprolol (long acting succinate) and bisoprolol were used in 47 and in 37 cases, respectively. Nebivolol and carvedilol were used in 11 and 3 cases, respectively. Average daily dose used for metoprolol, bisoprolol, nebivolol and carvedilol were 63.8, 5.3, 4.5, and 10.4 mg/d, respectively. Ivabradine was used in 11.7% of the cases, while digoxin and amiodarone or dronedarone were used in 2.5% and 4.2% of the cases, respectively (Table 2). Calcium antagonists with HR-lowering effect (verapamil or diltiazem) were not used at all. No significant differences in terms of medications were found between three groups of patients with different resting HR level (Table 2). There was no difference between the median number of HR lowering agents and the IQR between the HR groups, or the number of antianginals (median number of HR lowering agents and the number of antianginals was 1 (IQR 1–1) and 2 (IQR 1–2), respectively).

Differences in HR level in groups of patients using or not beta-blockers are shown in Fig. 3. Mean HR when measured by pulse palpation in patients using beta-blockers and in those not receiving any beta-blocker was 67.3 ± 9.8 bpm and 69.4 ± 8.0 bpm, respectively; when measured by ECG HR was 66.2 ± 11.1 and 70.1 ± 8.4 in patients with and without beta-blockers, respectively. However, HR differences in patients with as opposed to without beta-blockers did not reach statistical significance (by palpation: $P = 0.356$; by ECG: $P = 0.131$). Proportion of patients with HR ≥70 bpm among patients using and not using beta-blockers was 34.7% and 40.9%, respectively ($P = 0.627$). Systolic as well as diastolic blood pressure was lower in patients using beta-blockers: systolic blood pressure with and without beta-blockers was 136.1 ± 16.4 mm Hg and 148.1 ± 17.2 mm Hg, respectively ($P = 0.003$); diastolic blood pressure with and without beta-blockers was 82.2 ± 8.4 mm

Table 1 – Baseline characteristics of the study population classified according to resting heart rate by palpation.

Variable	Patients with data	Total population (n = 120)	Population according to palpation HR			P for differences between three HR groups
			≤60 bpm (n = 30)	61–69 bpm (n = 47)	≥70 bpm (n = 43)	
Age, mean ± SD, years	120	64.2 ± 7.9	64.7 ± 7.6	64.0 ± 7.3	64.1 ± 9.0	0.929
Men, n (%)	120	87 (72.5)	23 (76.7)	33 (70.2)	31 (72.1)	0.824
Body mass index, median (IQR), kg/m^2	120	28.8 (26.2–32.0)	29.9 (27.9–32.9)	28.1 (25.9–31.6)	29.1 (25.7–33.7)	0.114
Waist circumference, median (IQR), cm	120	101.0 (95.0–109.0)	101.5 (95.0–110.0)	100.0 (96.0–106.0)	102.0 (93.0–111.0)	0.869
Medical history, n (%)						
Myocardial infarction	120	76 (63.3)	17 (56.7)	29 (61.7)	30 (69.8)	0.498
PCI	120	89 (74.2)	26 (86.7)	35 (74.5)	28 (65.1)	0.117
CABG	120	29 (24.2)	8 (26.7)	10 (21.3)	11 (25.6)	0.834
ICD	120	0 (0)	0 (0)	0 (0)	0 (0)	–
Pacemaker	120	3 (2.5)	1 (3.3)	1 (2.1)	1 (2.3)	1.000
Hospitalization for CHF	120	2 (1.7)	1 (3.3)	0 (0)	1 (2.3)	0.520
Stroke	120	3 (2.5)	0 (0)	1 (2.1)	2 (4.7)	0.619
Atrial fibrillation/flutter	120	12 (10.0)	2 (6.7)	4 (8.5)	6 (14.0)	0.588
Asthma/COPD	120	7 (5.8)	2 (6.7)	3 (6.4)	2 (4.7)	1.000
Risk factors and life style, n (%)						
Family history of premature CAD[a]	120	29 (24.2)	5 (16.7)	12 (25.5)	12 (27.9)	0.523
Treated hypertension	120	94 (78.3)	24 (80.0)	38 (80.9)	32 (74.4)	0.736
Diabetes	120	25 (20.8)	6 (20.0)	12 (25.5)	7 (16.3)	0.554
Dyslipidemia	120	113 (94.2)	26 (86.7)	46 (97.9)	41 (95.3)	0.122
PAD	120	8 (6.7)	2 (6.7)	2 (4.3)	4 (9.3)	0.592
Smoking status, n (%)						
Current	120	21 (17.5)	2 (6.7)	9 (19.1)	10 (23.3)	0.194**
Former	120	49 (40.8)	16 (53.3)	15 (31.9)	18 (41.9)	
Never	120	50 (41.7)	12 (40.0)	23 (48.9)	15 (34.9)	
Alcohol intake (drinks/week), n (%)						
0	120	38 (31.7)	9 (30.0)	15 (31.9)	14 (32.6)	1.000**
>0 and <20	120	78 (65.0)	20 (66.7)	30 (63.8)	28 (65.1)	
20–40	120	4 (3.3)	1 (3.3)	2 (4.3)	1 (2.3)	
Stimulant drinks consumed, n (%)						
Coffee	120	71 (59.2)	16 (53.3)	25 (53.2)	30 (69.8)	0.320**
Tea	120	47 (39.2)	13 (43.3)	21 (44.7)	13 (30.2)	
Neither	120	2 (1.7)	1 (3.3)	1 (2.1)	0 (0)	
Physical activity						
None	120	8 (6.7)	4 (13.3)	2 (4.3)	2 (4.7)	0.418**
Light[b]	120	55 (45.8)	12 (40.0)	26 (55.3)	17 (39.5)	
1–2 times/week[c]	120	21 (17.5)	6 (20.0)	8 (17.0)	7 (16.3)	
≥3 times/week[c]	120	36 (30.0)	8 (26.7)	11 (23.4)	17 (39.5)	
Angina, n (%)	120	57 (47.5)	13 (43.3)	25 (53.2)	19 (44.2)	0.604
CCS class if angina, n (%)						
Class I	57	16 (28.1)	6 (46.2)	7 (28.0)	3 (15.8)	0.324**
Class II	57	36 (63.2)	7 (53.8)	16 (64.0)	13 (68.4)	
Class III	57	5 (8.8)	0 (0)	2 (8.0)	3 (15.8)	
CHF symptoms, n (%)	120	69 (57.5)	19 (6)	25 (53.2)	25 (58.1)	0.676
NYHA class if CHF, n (%)						
Class II	69	62 (89.9)	18 (94.7)	24 (96.0)	20 (80.0)	0.162**
Class III	69	7 (10.1)	1 (5.3)	1 (4.0)	5 (20.0)	
Creatinine, median (IQR), mmol/L	94	0.085 (0.073–0.100)	0.084 (0.074–0.102)	0.087 (0.072–0.099)	0.086 (0.074–0.112)	0.654
Blood glucose, median (IQR), mmol/L	107	5.7 (5.2–6.4)	5.8 (5.5–6.1)	5.7 (5.3–6.8)	5.6 (5.0–6.1)	0.119
Total cholesterol, median (IQR), mmol/L	113	4.5 (3.9–5.1)	4.4 (3.8–4.8)	4.6 (3.9–5.2)	4.5 (4.0–5.3)	0.329
HDL-C, median (IQR), mmol/L	102	1.2 (1.0–1.5)	1.3 (0.9–1.4)	1.2 (1.1–1.6)	1.2 (1.0–1.5)	0.572
LDL-C, median (IQR), mmol/L	104	2.6 (2.0–3.1)	2.5 (1.7–2.9)	2.7 (2.0–3.6)	2.5 (2.0–3.1)	0.365
Triglycerides, median (IQR), mmol/L	108	1.4 (1.0–2)	1.4 (1.1–1.9)	1.3 (1.0–1.8)	1.6 (1.1–2.1)	0.695

Table 1 (*Continued*)

Variable	Patients with data	Total population ($n = 120$)	Population according to palpation HR			P for differences between three HR groups
			≤60 bpm ($n = 30$)	61–69 bpm ($n = 47$)	≥70 bpm ($n = 43$)	
Heart rate (palpation), mean ± SD, bpm	120	67.7 ± 9.5	57.4 ± 3.0	65.1 ± 2.1	77.8 ± 7.6	–
ECG heart rate, mean ± SD, bpm	119	66.9 ± 10.7	56.0 ± 4.5	65.7 ± 6.3	75.8 ± 10.1	–
SBP, mean ± SD, mm Hg	120	138.3 ± 17.1	136.0 ± 17.7	138.1 ± 14.7	140.0 ± 19.3	0.621
DBP, mean ± SD, mm Hg	120	83.0 ± 8.6	79.6 ± 7.7	83.9 ± 8.0	84.3 ± 9.2	0.043*
LVEF, mean ± SD, %	96	57.1 ± 8.7	58.4 ± 8.7	58.5 ± 8.2	54.6 ± 8.8	0.107
Presence of coronary stenosis >50%						
Left main stenosis[d], n (%)	120	13 (10.8)	4 (13.3)	6 (12.8)	3 (7.0)	0.609
LAD stenosis[d], n (%)	120	83 (69.2)	22 (73.3)	32 (68.1)	29 (67.4)	0.848
Cx stenosis[d], n (%)	120	56 (46.7)	13 (43.3)	24 (51.1)	19 (44.2)	0.739
RCA stenosis[d], n (%)	120	73 (60.8)	19 (63.3)	35 (74.5)	19 (44.2)	0.013*
CABG stenosis[d], n (%)	120	19 (15.8)	5 (16.7)	8 (17.0)	6 (14.0)	0.914
No stenosis, n (%)	120	1 (0.8)	0 (0)	1 (2.1)	0 (0)	1.000
Coronary angiography not done, n (%)	120	7 (5.8)	0 (0)	3 (6.4)	4 (9.3)	0.257
Test for myocardial ischemia[e], n (%)	120	108 (90.0)	26 (86.7)	44 (93.6)	38 (88.4)	0.543
Current evidence of ischemia, n (%)	120	8 (6.7)	3 (10.0)	4 (8.5)	1 (2.3)	0.372
ECG rhythm, n (%)						
Sinus rhythm	119	114 (95.8)	28 (93.3)	45 (97.8)	41 (95.3)	0.397**
Atrial fibrillation/flutter	119	3 (2.5)	1 (3.3)	0 (0)	2 (4.7)	
Paced rhythm	119	2 (1.7)	1 (3.3)	1 (2.2)	0 (0)	

bpm, beats per minute; CABG, coronary artery bypass graft; CAD, coronary artery disease; CCS, Canadian Cardiovascular Society; CHF, chronic heart failure; COPD, chronic obstructive pulmonary disease; Cx, circumflex; DBP, diastolic blood pressure; ECG, electrocardiogram; HDL-C, high-density lipoprotein cholesterol; HR, heart rate; ICD, internal cardiac defibrillator; IQR, interquartile range; LAD, left anterior descending; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; RCA, right coronary artery; SBP, systolic blood pressure.

[a] Myocardial infraction, sudden death, stable angina at age <55 years (men) or 65 years (women) in a first-degree relative.

[b] Light physical activity most weeks.

[c] At least 20-min vigorous physical activity.

[d] Coronary territories with stenosis >50% at coronary angiography or having required revascularization in the past.

[e] Noninvasive test for myocardial ischemia (stress ECG, stress echocardiography, myocardial imaging).

* Statistically significant.

** P value calculated for distribution of patients according to HR level into different groups of given variable.

Hg and 86.6 ± 8.5 mm Hg, respectively ($P = 0.030$). Patients using beta-blockers less frequently had family history of premature CAD (17.3% vs. 54.5%, $P < 0.001$) and more frequently had medical history of PCI (80.6% vs. 45.5%, $P < 0.001$) than those not using beta-blockers. In patients not using beta-blockers, coronary angiography was not done more frequently compared with those who were using beta-blockers (22.7% vs. 2%, $P = 0.002$). Comparison of patients using and not using beta-blockers also showed that of those not on beta-blockers, symptoms indicative of intolerance or contraindication to beta-blockers as well as the usage of ivabradine was more frequent than for those patients who were on beta-blockers (59.1% vs. 12.2%, $P < 0.001$ for intolerance of beta blockers and 50.0% vs. 3.1%, $P < 0.001$ for usage of ivabradine, respectively). The median number of HR-lowering agents in group of patients using and not using beta-blockers was 1 (IQR 1–1) and 1 (IQR 0–1), respectively ($P < 0.001$). Number of antianginal agents and number of antianginal or HR lowering agents also differed significantly between two groups according to beta-blockers usage: median number of antianginal agents was higher in group of patients using beta-blockers (2 [IQR 1–2] vs. 1 [IQR 0–2], $P < 0.001$) as well as median number of antianginal or HR lowering agents (2 [IQR 2–2] vs. 1 [IQR 1–2], $P < 0.001$).

4. Discussion

By giving description of HR in the analyzed sample of stable CAD patients, this study elucidates insufficient control of HR in treated stable CAD population. Despite the fact, that absolute majority of patients receive beta-blockers, more than one third still have increased resting HR ≥70 bpm which is the level associated with higher risk of cardiovascular events in CAD patients [11]. According to European guidelines on management of stable CAD 2013, target HR in stable CAD patients is <60 bpm [12]. In the analyzed sample proportion of patients with HR

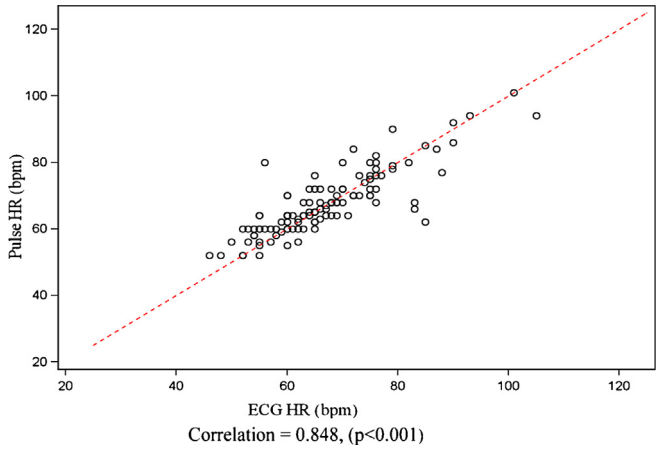

Fig. 2 – Association between pulse HR and ECG HR in Latvian patients (cohort of Latvian patients, included in the worldwide registry CLARIFY).

≤60 bpm is smaller than proportion of patients with increased HR ≥70 bpm. Increased HR in angina patients not only has negative impact on prognosis but also is pathophysiologically linked with ischemia. That is why situation with HR control in analyzed CAD patients with angina symptoms seems even worse. One third of angina patients are with increased HR ≥70 bpm and only in 22.8% of cases HR level ≤60 bpm is reached. Proportion of patients with increased HR among CHD patients with present symptoms of chronic heart failure is also around one third despite the fact that increased HR has been proved to be risk factor in heart failure patients [16]. Even among patients on beta-blockers proportion of patients with increased HR ≥70 bpm was more than one third and did not differ significantly from those not on beta-blockers. CLARIFY data from Latvian population are fully comparable to worldwide CLARIFY data [13]. A total 33,177 CAD patients from 45 countries have been analyzed in the CLARIFY registry. In Latvian population proportion of patients with increased HR ≥70 bpm is smaller than in global CLARIFY population (35.8% vs. 44.0%) as well as proportion of patients with HR ≥70 bpm among patients on

Table 2 – Medications of the study population classified according to resting heart rate by palpation.

Parameter (all data available for 120 patients)	Total population (n = 120)	Population according to palpation HR			P
		≤60 bpm (n = 30)	61–69 bpm (n = 47)	≥70 bpm (n = 43)	
Aspirin, n (%)	117 (97.5)	29 (96.7)	45 (95.7)	43 (100)	0.468
Thienopyridine, n (%)	18 (15.0)	7 (23.3)	7 (14.9)	4 (9.3)	0.256
Other antiplatelets, n (%)	1 (0.8)	1 (3.3)	0 (0)	0 (0)	0.250
Oral anticoagulants, n (%)	4 (3.3)	1 (3.3)	0 (0)	3 (7.0)	0.130
Beta-blockers, n (%)	98 (81.7)	26 (86.7)	38 (80.9)	34 (79.1)	0.699
Symptoms indicative of intolerance or contraindication to beta-blockers, n (%)	25 (20.8)	8 (26.7)	8 (17.0)	9 (20.9)	0.597
Ivabradine, n (%)	14 (11.7)	1 (3.3)	7 (14.9)	6 (14.0)	0.257
Calcium antagonists, n (%)[a]	65 (54.2)	20 (66.7)	26 (55.3)	19 (44.2)	0.162
Angiotensin-converting enzyme inhibitors, n (%)	86 (71.7)	25 (83.3)	34 (72.3)	27 (62.8)	0.158
Angiotensin II receptor blockers, n (%)	17 (14.2)	3 (10.0)	7 (14.9)	7 (16.3)	0.738
Lipid-lowering drug, n (%)	114 (95.0)	27 (90.0)	47 (100)	40 (93.0)	0.070
Long-acting nitrates, n (%)	28 (23.3)	4 (13.3)	10 (21.3)	14 (32.6)	0.147
Other antianginal agents, n (%)	15 (12.5)	5 (16.7)	7 (14.9)	3 (7.0)	0.383
Diuretics, n (%)	31 (25.8)	10 (33.3)	9 (19.1)	12 (27.9)	0.355
Other antihypertensive agents, n (%)	11 (9.2)	4 (13.3)	3 (6.4)	4 (9.3)	0.565
Digoxin and derivatives, n (%)	3 (2.5)	1 (3.3)	0 (0)	2 (4.7)	0.352
Amiodarone/dronedarone, n (%)	5 (4.2)	2 (6.7)	1 (2.1)	2 (4.7)	0.631
Other antiarrythmics, n (%)	4 (3.3)	1 (3.3)	2 (4.3)	1 (2.3)	1.000
Antidiabetic agents, n (%)	23 (19.2)	5 (16.7)	12 (25.5)	6 (14.0)	0.349

HR, heart rate.
[a] Dihidropiridine calcium antagonists.

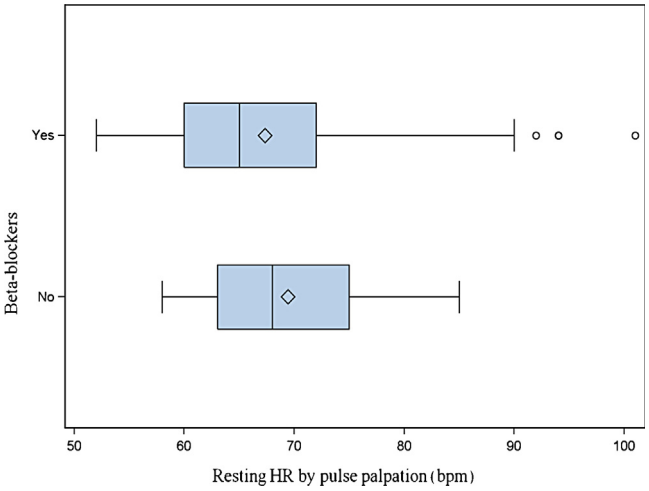

Fig. 3 – Distribution of Latvian patients with and without beta-blockers use by heart rate (cohort of Latvian patients, included in the worldwide registry CLARIFY). The vertical lines represent the minimum and maximum values. The box represents the lower (25th percentile) and upper (75th percentile) quartiles. Within the box, the vertical line is the median and the diamond the mean. Values 1.5 times the interquartile range were considered outliers and are shown as individual circles.

beta-blockers (34.7% vs. 41.1%). The Latvian sample studied CLARIFY is also comparable to EuroHeart Survey population where 156 cardiology clinics from 34 countries participated and more than 3000 patients with diagnosis of stable angina were analyzed [17]. Investigators of EuroHeart Survey showed that proportion of patients with HR >70 bpm in analyzed angina population is 52.3% despite treatment [18]. On one hand it seems encouraging and likely showing that HR control in analyzed Latvian CAD patients is better than in other countries. On the other side we should take into account that situation in Latvia with cardiovascular mortality is not favorable and is higher than in European Union on average [2]. Therefore all signs of insufficient control of CAD risk factors (including HR) should be seriously analyzed. Proportion of angina patients with HR ≤60 bpm in our sample is similar to worldwide CLARIFY data [13] (22.8% vs. 22.1%) and is in line with observations in the EuroHeart Survey where only 19% of angina patients had HR ≤62 bpm [18]. These findings are a warning and have important clinical implications. HR remains above the level associated with higher risk of cardiovascular events in CAD patients in a substantial proportion of CAD patients. This indicates need for further improvement of HR control in CAD patients. Education of physicians regarding negative impact of increased HR on prognosis as well as wide communication about statement of guidelines [12] that the target HR in stable CAD is <60 bpm could be an important part in further improvement of HR control in Latvia.

Usage of beta-blockers does not fully solve the problem of increased resting HR as most of the analyzed CLARIFY Latvian patients were on beta-blockers. It is in line with global CLARIFY data [13] and could be explained by insufficient dosage of beta-blockers as underdose of these agents is typical in community and associated with poor long-term compliance [19]. Combination of beta-blockers with ivabradine could be a step further toward a better HR control in CAD patients. Our findings show a potential for better control of HR and encourage use of available tools in order to improve control of this risk factor for further improvement of symptoms and prognosis in CAD patients in Latvia.

Limitations for interpretation of our data should be acknowledged as the analyzed sample of CAD patients includes relatively small number of patients. Selection bias may also have taken place during the enrollment of patients into CLARIFY and therefore the study population may not fully reflect the situation for the total population of stable CAD patients in Latvia. For a better understanding of the situation with HR control in CAD patients in Latvia, studies with larger number of included patients are needed. Long term observations with follow-up period are preferable to evaluate changes in management of HR over a period of time.

5. Conclusions

Despite the wide use of beta-blockers, HR is insufficiently controlled in analyzed sample of stable CAD patients in Latvia. HR ≤60 bpm is achieved only in 25% of analyzed CAD patients and 22.8% of patients with angina symptoms while more than one third has increased HR ≥70 bpm. The findings elucidate underusage of HR controlling agents and a great potential for targeting HR as the risk factor and determinant of symptoms.

Conflict of interest

Inga Balode is employed by Servier Latvia. Iveta Mintāle has received lecturer's fees or research grants from Pfizer, Astra-Zeneca, Servier Laboratories, Abbott Laboratories, Berlin Chemie, Bayer, Boehringer Ingelheim, Merck Sharp and Dohme. Gustavs Latkovskis has received lecturer's fees or research grants from Pfizer, Astra-Zeneca, Servier Laboratories, Abbott Laboratories, GlaxoSmithKline, Berlin Chemie, Novo Nordisk, Bayer, Boehringer Ingelheim, Sanofi Aventis, Merck Sharp and Dohme. Advisory board: Boehringer Inghelheim, Pfizer, Berlin Chemie/Menarini. Sanda Jēgere has received Speaker's Bureau: Abbott Laboratories, AstraZeneca, Berlin Chemie, Pfizer, Sanofi Aventis, Servier Laboratories. Inga Narbute states no conflict of interest. Iveta Bajāre states no conflict of interest. Nicola Greenlaw states no conflict of interest. Philippe Gabriel Steg has received compensation from Amarin, Astrazeneca, Bayer, BristolMyersSquibb, Boehringer-Ingelheim, Daiichi-Sankyo, GlaxoSmithKline, Merck, Novartis, Otsuka, Pfizer, Roche, Sanofi, Servier; The Medicines Company and Vivus for steering committees, data monitoring committees, event committees and consulting activities; Research grants (to institution) from Sanofi and Servier. Roberto Ferrari: Speaker's Bureau: Servier, Roche and Boehringer Ingelheim; Research Grant: Servier, Boehringer Ingelheim and Roche; Advisory Board: Servier, Bayer, Roche and Boehringer Ingelheim. Andrejs Ērglis has research contracts: Abbott Vascular, Boston Scientific; Consulting, Speaker's Bureau: Abbott Laboratories, Abbott Vascular, AstraZeneca, Berlin Chemie,

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