Original Research

Heart Rate and B-Blockade in Stable Coronary Artery Disease in Greece

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CLARIFY registry, coronary artery disease, b-blockers, heart rate.

Introduction: Heart rate (HR) is a strong prognostic indicator in patients with coronary artery disease (CAD). However, there is only limited evidence on HR and the use of b-blockers in patients with CAD in contemporary clinical practice.

Methods: CLARIFY is an international, prospective, observational, longitudinal registry of outpatients with stable CAD, defined as prior myocardial infarction or revascularization procedure, evidence of coronary stenosis >50%, or chest pain associated with proven myocardial ischemia. A total of 33,283 patients from 45 countries were enrolled between November 2009 and July 2010; of these, 559 patients were enrolled in Greece (age 62.3 ± 10.6 years, 84.44% men).

Results: HR measured by pulse was 68.3 ± 10.2 bpm and by electrocardiogram 67.6 ± 10.9, with an excellent correlation (r=0.91, p<0.001). Overall, 42.8% had HR≥70 bpm. B-blockers were prescribed in 74.2% of patients. Resting HR by pulse on b-blocker was 67.8 bpm and without b-blocker 69.6 bpm (p=0.069). HR≥70 bpm was independently associated with a lack of physical activity, higher systolic blood pressure, and a higher prevalence of asthma or chronic obstructive pulmonary disease and carotid artery disease.

Conclusion: Despite the use of HR lowering agents, the percentage of patients with HR≥70 bpm was high. It is likely that we can further improve HR control in Greek patients with stable CAD by both increasing the prescription of b-blockers and up-titrating their dose, as well as by using and up-titrating other available HR lowering agents.

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Among cardiovascular diseases, coronary artery disease (CAD) remains the first cause of death, yet there is limited insight into improved care and better outcomes of patients with CAD.[1] Most of the available data on CAD come from clinical trials on acute coronary syndromes.[2] Heart rate (HR) is an independent predictor of cardiovascular and all-cause mortality in men and women with and without cardiovascular disease and represents a potential therapeutic target.[3-5] CLARIFY is a prospeCtive, observational LongtudinAl RegIstry of 33,283 outpatients with stable coronary arterY disease, receiving standard management, with broad geographic representation and followed up for 5 years.[6-8]

In this paper we report data on the Greek population, regarding resting HR and the determinants of HR as well as the use of b-blockers in the study cohort.

Methods

The rationale and design of CLARIFY have been published previously.[6] Eligible patients had at least one of the following: documented myocardial infarction (MI) >3 months before enrolment; coronary artery stenosis >50% on angiography; chest pain with positive stress test; coronary artery bypass surgery (CABG) or percutaneous coronary intervention (PCI) >3 months before enrolment. Exclusion criteria were hospital admission for cardiovascular reasons (including revascularization) in the past 3 months, planned revascularization, non-cardiovascular diseases hampering the 5-year follow-up (i.e. serious comorbidities interfering with life expectancy) and other severe cardiovascular diseases (advanced heart failure, severe valvular disease, valve repair/replacement). Patients' enrolment was restricted to a brief period between November 2009 and June 2010. The study was approved by national ethical committees and all patients gave informed consent. The study is registered with the number ISRRCTN43070564.

The investigators completed standardized electronic case report forms (eCRF) at baseline. Data were collected on baseline demographics, risk factors and lifestyle, physical condition, medical history, physical signs, current symptoms and treatments. Results of noninvasive and invasive procedures were recorded if available, but were not mandatory for inclusion.

Statistical analysis

Descriptive statistics are presented as mean ± standard deviation, or median [lower quartile (Q1), upper quartile (Q3)] for continuous variables, depending on whether the data are normally distributed or skewed, and as count (percentage) for categorical variables. A multivariable analysis of independent correlates of HR≥70 beats per minute (bpm) was performed using a logistic regression model. The cutoff of 70 bpm was selected based on the results of several studies showing that it is an important prognostic threshold across a variety of patient populations.[9-11] The multivariable model was built using a stepwise selection method applied to the significant univariate predictors.

Results

A total of 559 patients were available for analysis. The mean age was 62.3 ± 10.6 years and 84.44% were men. The median time [Q1, Q3] since initial diagnosis was 5 [2, 10] years. Regarding risk factors for CAD, 71.4% had hypertension, 27.9% diabetes, 89.3% hyperlipidemia, 35.1% a family history of CAD, while 53.5% were former smokers and 16.3% current smokers. Overall 57.1% patients had a history of prior MI; regarding revascularization procedures, 54.6% had prior PCI and 30.8% prior CABG. In addition to CAD, 10.2% patients had documented carotid artery disease, 10.9% peripheral arterial disease and 3.4% abdominal aortic aneurysm. In relation to the CAD diagnosis, 87.3% patients had been evaluated with a noninvasive test and 95.2% had undergone coronary angiography. Mean left ventricular ejection fraction (LVEF) was 56.0%; 95.8% of patients were in sinus rhythm. The distribution of HR based on palpation is shown in Figure 1. HR measured by pulse was 68.3 ± 10.2 bpm and by electrocardiogram (ECG) 67.6 ± 10.9, with an excellent correlation ($r=0.91$, $p<0.001$; Figure 2).

Patients were divided into three categories according to the HR based on palpation: HR ≤60 bpm (n=159, 28.4%), 61-69 bpm (n=161, 28.8%), and ≥70 bpm (n=239, 42.8%) (Table 1). Patients with higher HR more often had asthma/chronic obstructive pulmonary disease (COPD), carotid artery disease or peripheral arterial disease, were more often physically inactive, and had more anginal symptoms. Likewise, patients with higher HR had lower hemoglobin levels and higher total and low-density lipoprotein cholesterol. Furthermore, these patients had higher systolic and diastolic blood pressure and lower LVEF and were less often in normal sinus rhythm. In addition, patients with HR≥70 bpm were less often evaluated with either a noninvasive test ($p<0.001$) or coronary angiography ($p=0.027$). Interestingly, there was no

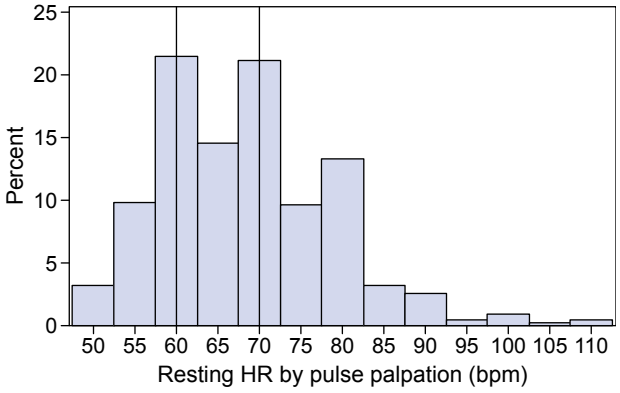

Figure 1. Heart rate distribution in patients in Greece with stable coronary artery disease.

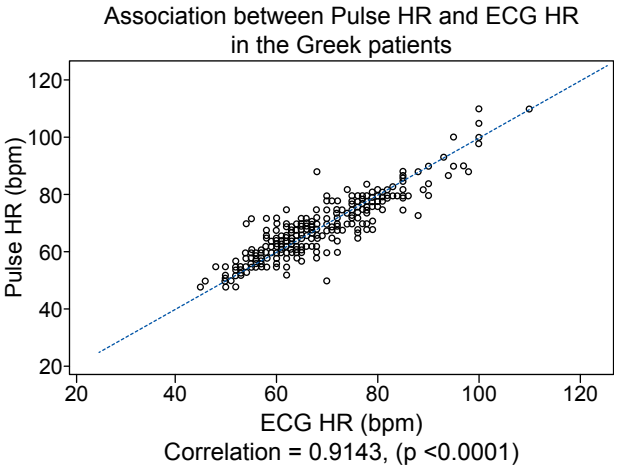

Figure 2. Association between heart rate measured by palpation and by electrocardiogram (ECG) in the Greek patients.

difference in the use of b-blockers between the three HR groups, although a symptom of b-blocker intolerance was found more often in the higher HR group. As expected, ivabradine was prescribed more often in the higher HR group. This was also the case for digoxin, amiodarone and dronedarone.

B-blockers were prescribed in three quarters of the patients (74.2%). Half of the patients off b-blocker had HR≥70 bpm whereas 40.2% on any b-blocker had HR≥70 bpm (p=0.041; Table 2). Resting HR on b-blocker was 67.8 bpm and without b-blocker 69.6 bpm, assessed by pulse palpation (p=0.069; Figure 3). LVEF was higher in patients off b-blockers (57.8%) than in those on any b-blockers (55.4%) (p=0.011). Patients on b-blockers were more often hypertensive and hyperlipidemic (p=0.012 and p=0.003, respectively). Patients with asthma/COPD were less often treated with b-blockers. Patients on b-blockers had marginally higher fasting blood glucose levels (p=0.041). As expected, patients without significant stenosis on coronary angiography were less often treated with b-blockers (p=0.048). Likewise, patients who were not treated with b-blockers more often had symptoms of b-blocker intolerance and were more often prescribed ivabradine and HR lowering calcium

Table 1. Baseline characteristics and medications of the Greek population classified according to resting heart rate by palpation

Parameter	Total (n= 559)	HR≤60 bpm (n=159)	HR 61-69 bpm (n=161)	HR ≥70 bpm (n=239)	p
Carotid artery disease, n (%)	57 (10.2)	13 (8.2)	9 (5.6)	35 (14.6)	0.008
Peripheral arterial disease, n (%)	61 (10.9)	13 (8.2)	12 (7.5)	36 (15.1)	0.024
Stroke, n (%)	13 (2.3)	8 (5.0)	1 (0.6)	4 (1.7)	0.037
Asthma/COPD, n (%)	36 (6.4)	4 (2.5)	7 (4.3)	25 (10.5)	0.003
No physical activity weekly, n (%)	72 (12.9)	11 (6.9)	10 (6.2)	51 (21.3)	<0.001
Light physical activity most weeks, n (%)	318 (56.9)	86 (54.1)	97 (60.2)	135 (56.5)	
Vigorous physical activity once or twice a week, n (%)	104 (18.6)	35 (22.0)	29 (18.0)	40 (16.7)	
Vigorous physical activity three or more times a week, n (%)	65 (11.6)	27 (17.0)	25 (15.5)	13 (5.4)	
Angina, n (%)	89 (15.9)	23 (14.5)	18 (11.2)	48 (20.1)	0.048
Hb, mmol/L, median [Q1, Q3]	8.69 [8.19, 9.25]	8.72 [8.32, 9.31]	8.69 [8.38, 9.31]	8.69 [8.07, 9.06]	0.013
TC, mmol/L, median [Q1, Q3]	4.6 [4.1, 5.1]	4.4 [3.9, 4.9]	4.4 [3.9, 4.8]	4.7 [4.3, 5.2]	<0.001
LDL, mmol/L, median [Q1, Q3]	2.60 [2.24, 3.12]	2.55 [2.08, 2.89]	2.54 [2.15, 3.02]	2.76 [2.34, 3.38]	0.0006
SBP, mmHg, mean ± SD	127.9 (14.2)	122.2 (11.3)	126.9 (11.9)	132.2 (15.8)	<0.001
DBP, mmHg, mean ± SD	78.1 (9.2)	74.9 (8.4)	78.3 (7.6)	80.1 (10.2)	<0.001
LVEF (%), mean ± SD	56.0 (9.1)	57.6 (8.6)	57.0 (8.5)	53.9 (9.6)	0.0002
Non-invasive test for ischemia, n (%)	488 (87.3)	148 (93.1)	149 (92.5)	191 (79.9)	<0.001
Coronary angiography not done, n (%)	27 (4.8)	3 (1.9)	6 (3.7)	18 (7.5)	0.027
ECG sinus rhythm, n (%)	388 (95.8)	126 (98.4)	104 (96.3)	158 (93.5)	0.011
ECG atrial fibrillation/flutter, n (%)	14 (3.5)	0 (0)	4 (3.7)	10 (5.9)	
ECG paced rhythm, n (%)	3 (0.7)	2 (1.6)	0 (0)	1 (0.6)	
B-blocker, n (%)	415 (74.2)	124 (78.0)	124 (77.0)	167 (69.9)	0.122
Symptoms of b-blocker intolerance, n (%)	129 (23.1)	33 (20.8)	23 (14.3)	73 (30.5)	0.0006
Ivabradine, n (%)	230 (41.1)	55 (34.6)	51 (31.7)	124 (51.9)	<0.001
Digoxin, n (%)	10 (1.8)	0 (0)	2 (1.2)	8 (3.3)	0.035
Amiodarone/dronedarone, n (%)	15 (2.7)	3 (1.9)	1 (0.6)	11 (4.6)	0.047
Verapamil or diltiazem	33 (5.9)	5 (3.1)	8 (5.0)	20 (8.4)	0.08

COPD – chronic obstructive pulmonary disease; Hb – hemoglobin; TC – total cholesterol; LDL – low density lipoprotein; SBP – systolic blood pressure; DBP – diastolic blood pressure; LVEF – left ventricular ejection fraction.

Table 2. Differences in baseline characteristics of the Greek population classified according to b-blocker usage.

Parameter	Any b-blocker (n=415, 74.2%)	No b-blocker (n=144, 25.8%)	p-value
Resting heart rate, bpm, mean ± SD	67.8 ± 10.1	69.6 ± 10.1	0.069
Heart rate ≥70 bpm, n (%)	167 (40.2)	72 (50.0)	0.041
LVEF (%), mean ± SD	55.4 (9.3)	57.8 (8.3)	0.011
SBP (mm Hg), mean ± SD	128.5 (14.4)	126.1 (13.5)	0.090
Treated hypertension, n (%)	308 (74.2)	91 (63.2)	0.012
Hyperlipidemia, n (%)	380 (91.6)	119 (82.6)	0.003
Asthma/COPD, n (%)	18 (4.3)	18 (12.5)	0.001
Fasting glucose, mmol/L, median [Q1, Q3]	5.8 [5.3, 6.6]	5.6 [5.0, 6.2]	0.041
No significant coronary artery stenosis, n (%)	19 (4.6)	13 (9.0)	0.048
Symptoms of b-blocker intolerance, n (%)	51 (12.3)	78 (54.2)	<0.001
Ivabradine, n (%)	152 (36.6)	78 (54.2)	0.0002
Verapamil or diltiazem, n (%)	10 (2.4)	23 (16.0)	<0.001
Lipid-lowering drugs, n (%)	388 (93.5)	126 (87.5)	0.023
Diuretics, n (%)	151 (36.4)	35 (24.3)	0.008

LVEF – left ventricular ejection fraction; SBP – systolic blood pressure; COPD – chronic obstructive pulmonary disease.

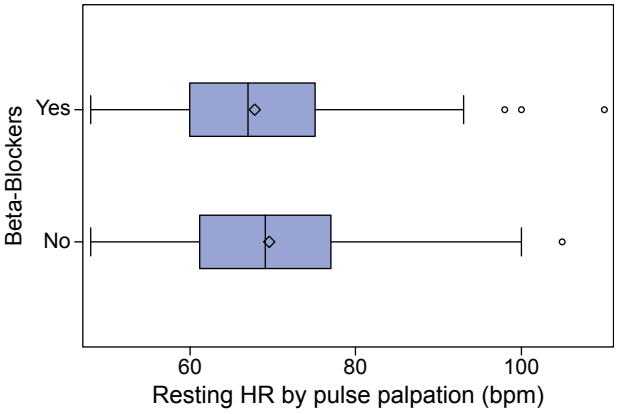

Figure 3. Distribution of heart rate (HR) for Greek patients with and without b-blocker use.

channel blockers (verapamil or diltiazem). Interestingly, there was no statistically significant difference between patients on and off b-blockers in terms of angina and symptoms of chronic heart failure (p=0.4, p=1.0 respectively).

A multivariable analysis was performed to identify variables associated with elevated HR≥70 bpm; these were lack of physical activity and noninvasive testing for myocardial ischemia, higher systolic blood pressure and the presence of asthma/COPD or carotid artery disease (Table 3).

Discussion

Despite the fact that reduction of HR represents an important strategy for the treatment of patients with coronary heart disease and stable angina, in 42% of our entire sample HR was ≥70 bpm.

Although three quarters of patients with stable CAD were treated with b-blockers (74.2%), almost 43% had resting HR≥70 bpm and the percentage of patients on b-blockers did not differ across the three groups HR≤60 bpm, HR 61-69 bpm and HR≥70 bpm. These findings imply that patients on b-blockers are not blocked adequately to achieve a target HR between 55-60 bpm.[12] It appears that there is either inadequate attention to HR as a modifiable treatment target, a lack of prioritization of HR control, or reluctance to up-titrate HR lowering agents, despite the overwhelming evidence of the proven benefit of HR reduction as a means of reducing ischemia and symptoms, and the potential reduction in adverse outcomes in patients with higher HR. This is in accordance with other studies or registries. In the European heart survey,[13] an observational cohort study of 3779 patients with stable angina, 52% of patients had a baseline HR>70 bpm while almost 40% of patients on b-blockers exhibited increased HR (>70 bpm).

Interestingly, in our study, there was no statistical difference in HR between patients on or off b-blockers (due to intolerance or contraindication). The mean HR was 68 bpm on b-blocker and 70 bpm off-blocker. However, patients off b-blockers were receiving other HR lowering agents, such as ivabradine and non-dihydropyridine calcium channel blockers. The fact that those two groups presented similar anginal and chronic heart failure symptoms underlines

Table 3. Multivariable analysis with all significant variables associated with an elevated heart rate (≥70 bpm).

Variable	Level	OR (95%CI)	Pr>Chi-square
Physical activity	Light physical activity most weeks	0.44 (0.24–0.81)	0.002
Physical activity	Vigorous physical activity once or twice a week	0.42 (0.21–0.83)	
Physical activity	Vigorous physical activity three or more times a week	0.19 (0.08–0.44)	
Asthma/COPD	Yes	2.39 (1.06–5.38)	0.035
Carotid disease	Yes	2.16 (1.20–3.92)	0.011
Noninvasive test for myocardial ischemia ever performed?	Yes	0.40 (0.22–0.72)	0.002
Taking any heart rate lowering drugs?	Yes	1.31 (0.67–2.57)	0.431
SBP	(per 10 mmHg)	1.40 (1.21–1.61)	<0.001

OR – odds ratio; CI – confidence interval; COPD – chronic obstructive pulmonary disease; SBP – systolic blood pressure

the importance of the HR lowering strategy in these patients.[14]

Patients with increased HR presented worst clinical conditions, including more anginal symptoms and more comorbidities such as asthma/COPD, carotid artery disease and peripheral arterial disease. The risk factors for CAD were also more common among patients with higher HR. Although there was no difference in the use of b-blockers between the three HR groups, a symptom of b-blocker intolerance was found more often in the higher HR group. Practically, the sample of patients with an increased risk for a worse outcome was composed of those with an increased HR. Several studies have shown that resting HR is a predictor of cardiovascular mortality and that effective HR reduction yields improved clinical outcomes.[4,12]

In addition, the incidence of previous MI or heart failure symptoms did not differ between the on b-blocker and the off b-blocker groups, although these are the patients who benefit the most from b-blockade.[6,15] B-blockade is effective in both women and the elderly, and in this respect we found that age and sex did not differ in relation to b-blocker use. This finding was consistent with the analysis of the international data, which showed that, despite substantial differences in baseline clinical characteristics and management, the rates of one-year cardiovascular clinical outcomes were similar between men and women.[16]

It must be pointed out that a history of COPD or peripheral vascular disease is not *per se* an absolute contraindication for b-blockade. Patients with higher HR had higher blood pressure and plasma lipids and were less often evaluated with noninvasive and invasive procedures, implying an overall less intense diagnosis and treatment, including HR reduction.

Multivariable analysis revealed important factors in determining HR in Greek patients with CAD. The presence of asthma/COPD was one of the strong predictive factors for an elevated HR, associated with less frequent use of b-blockers. Increased physical activity is a well-recognized factor for lowering HR, and was also associated with a lower risk of elevated HR.[17] Higher blood pressure and fewer noninvasive tests were both independent predictors of HR≥70 bpm. Of interest to the practicing physician is that HR assessment can be safely performed by pulse palpation and the ECG is not mandatory, as the correlation between the two was excellent in this cohort.

In conclusion, despite the use of HR lowering agents, the percentage of patients with HR≥70 bpm was high. It is likely that we can further improve HR control in Greek patients with stable CAD by both increasing b-blockade prescription and up-titrating their dose, as well as by using and up-titrating other available HR lowering agents as indicated.

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Appendix. The Greek CLARIFY investigators

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