Original Research

Inadequate Heart Rate Control Is Associated with Worse Quality of Life in Patients with Coronary Artery Disease and Chronic Obstructive Pulmonary Disease. The RYTHMOS Study

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Background: Significant evidence shows that elevated heart rate (HR) is an independent risk factor in patients with coronary artery disease (CAD) and influences their prognosis. In addition, patients with chronic obstructive pulmonary disease (COPD) have more frequent episodes of angina and their compliance with heart rate agents, such as beta blockers, is poor. The purpose of the multicenter observational RYTHMOS study was to evaluate the role of heart rate management in the prognosis and quality of life in patients with CAD and COPD.

Methods: Baseline data from 280 patients, enrolled in 22 hospitals representing all types of hospital and all geographical areas of the country, were analyzed. All patients had either a prior myocardial infarction or angiographically documented CAD, and COPD verified either after spirometry or from a clinical evaluation by pulmonologists.

Results: The mean age of the enrolled patients was 71.8 ± 9.3 years, 76% were males, mean body mass index was 28.6 ± 7.9 kg/m^2, 76.3% had hypertension, 31% had diabetes mellitus, and 53.5% of them suffered from heart failure. About 31% of the patients had an angina episode the week before the enrollment and the Canadian Cardiovascular Society (CSS) classification was class I, II, III and IV in 55%, 30%, 14% and 1%, respectively. The mean resting HR was 72.5 bpm; 51% of the patients had resting HR>70 bpm and 22% of them had HR≥80 bpm. Only 52.8% of the study patients were receiving beta-blockade (BB) therapy; they were more likely to have resting HR≤70 bpm (57.4% vs. 42.7%, p<0.001). 16.4% of the patients were receiving ivabradine and they had a higher initial HR compared to the others (78.5 vs. 71.3, p<0.001). Multivariate analysis showed that diabetes mellitus was independently associated with HR>70 bpm. Patients with resting HR>70 bpm had significantly more frequent angina episodes (p<0.001), were less satisfied with treatment (p<0.001), and had a lower quality of life (p<0.001).

Conclusion: The baseline data of this study showed that patients with CAD and COPD present inadequate HR control and frequent angina episodes. Apart from the special characteristics of these patients related to COPD management, underuse of BB therapy largely contributes to the inadequate control of HR. Patients with HR>70 bpm had significantly worse quality of life.

Coronary artery disease (CAD) is a leading cause of death in developed countries today.[1] An elevated resting heart rate (HR) is considered as a significant prognostic risk factor, since it results in reduced myocardial perfusion during diastole and increased myocardial oxygen demand.[2,3] Epidemiological studies have shown a strong association between increased HR and all-cause and cardiovascular mortality, especially in patients with stable CAD.[4-9] In patients who have an elevated heart rate the coronary artery endothelium is exposed to the systolic low and oscillatory shear stresss, and the periodically changing geometry of the coronary arteries affects the hemodynamic parameters.[10] The ideal target resting HR is not clear, but data from the recent BEAUTIFUL (morBidity-mortality EvAlUaTion of the I_f inhibitor ivabradine in patients with coronary disease and left ventricULar dysfunction) multicenter clinical trial indicate that an HR above 70 beats per minute (bpm) is associated with greater cardiovascular risk.[11] Beta-blockers (BB) are considered the cornerstone of HR-lowering therapy and are recommended by current guidelines for all patients after myocardial infarction (MI).[12] They have been shown to reduce total mortality and sudden cardiac death, by reducing HR and myocardial oxygen demand and prolonging the diastolic period of the cardiac cycle, thus improving myocardial perfusion.[13,14] Current practice and available evidence favor the use of selective type β1-blockers, such as metoprolol, atenolol, and bisoprolol, in the treatment of CAD.[12] However, these drugs are associated with adverse effects that include worsening of chronic obstructive pulmonary disease (COPD), bradycardia symptoms, and reduced blood flow to the extremities.[15-17] Ivabradine, a novel selective blocker of I_f sinus node channels, has recently been approved as an HR-reducing medication. Results from BEAUTIFUL in patients with CAD and a left ventricular ejection fraction (LVEF) lower than 40% showed that ivabradine reduced hospitalization and revascularization rates in patients with HR over 70 bpm.[11,18]

Registry and clinical trial data have shown that patients with CAD and coexisting COPD generally fail to receive optimal therapy or appropriate drug dosages for HR reduction.[19] As a result, a higher HR has been reported in these patients compared with those without COPD. This is mainly due to overdiagnosis of COPD, leading to suboptimal therapy or inappropriate dosages, particularly in the case of BBs.[19,20] The most common reason for withholding BB treatment in elderly patients after MI is comorbid conditions such as COPD and asthma.[21] In Greece, COPD is a substantial health problem that affects both men and women. As reported by Tzanakis et al,[22] the overall prevalence of COPD in the Greek population aged >35 years with a smoking history of >100 cigarettes per lifetime was 8.4%. The sex-standardized COPD prevalence was 11.6% in men and 4.8% in women. COPD prevalence between urban and rural areas varied between 9.1% (Athens was an exception with 6%) and 10.1%, respectively. More recent data from the HELIOS observational study showed that about 71% of Greek patients with acute myocardial infarction were current or ex-smokers (84% males and 32% females), proving the strong association between smoking and CAD in the Greek population.[23]

To our knowledge, RYTHMOS is the first prospective, multicenter countrywide study that was specifically designed to address the issue of heart rate management in patients with stable CAD and COPD.

Patients and Methods

Patients

The study population included consecutive ambulatory patients, male or female, with stable CAD and COPD. Patients had to be >55 years old, or >18 years in the case of concomitant diabetes, and have documented CAD (history of coronary revascularization or coronary angiography showing ≥1 stenosis >50%), and/or history of MI or acute coronary syndrome, and/or clinical angina and a positive ischemia test.

Stable CAD was defined by the absence of acute coronary syndrome and coronary revascularization during the last 3 months before inclusion in the study. The characteristic symptoms of COPD are chronic and progressive dyspnea, cough, and sputum production, as defined by the Global Strategy for the Diagnosis, Management, and Prevention of COPD (GOLD).[23] The chronic airflow limitation characteristic of COPD is caused by a mixture of small airways disease (obstructive bronchiolitis) and parenchymal destruction (emphysema), the relative contributions of which vary from one person to another. Airflow limitation is best measured by spirometry, because this is the most widely available reproducible test of lung function. Spirometry is essential for diagnosis and provides a useful description of the severity of pathologic changes in COPD. Specific spirometric cut points (postbronchodilator forced expiratory volume

in 1 second/forced vital capacity [FEV1/FVC] ratio <70% or FEV1<80%, 50%, or 30% of predicted value) are used for purposes of simplicity, although they have not been clinically validated.[24]

Exclusion criteria included recent (≤6 months) MI or coronary revascularization procedure, recent (<3 months) stroke or transient ischemic attack, implanted pacemaker or cardiac defibrillator, and cardiac rhythm disturbances, such as atrial fibrillation/flutter, sick sinus syndrome, sinoatrial or atrioventricular block, congenital long-QT syndrome, and symptoms of severe heart failure (New York Heart Association [NYHA] class III or IV). Additional exclusion criteria were malignancies, life expectancy less than 1 year, and severe hepatic or renal insufficiency.

Study design

RYTHMOS was a prospective, cross-sectional epidemiological observational study conducted in the cardiology departments of 22 Greek hospitals that are representative of all major geographical areas of the country. A total number of 301 patients at baseline who satisfied the inclusion/exclusion criteria referred to above were screened for enrollment. Since this was an observational study, no changes in standard patient management were made by the investigators. Follow-up visits were scheduled 6 and 12 months after the enrollment date.

Patients were fully informed and provided written consent before their enrollment. The study complies with the principles of the Declaration of Helsinki, and the protocol was approved by the ethics committees of all participating hospitals, as well as by the Greek Regulatory Authorities.

Study endpoints

The primary endpoint was the evaluation of the influence of resting HR on prognosis and quality of life (QoL) in patients with CAD and COPD. A patient questionnaire was developed in order to evaluate the QoL in the study population. This questionnaire takes into account the frequency of the angina episodes, the impact of these episodes in patients' daily activities, the patient's treatment satisfaction regarding relief of symptoms, and finally the overall QoL. Thus, using patients' answers, indexes were calculated for the degree of patient activity restriction, for the frequency of angina episodes within the previous month, and for the effectiveness of current therapy additional to the patients' awareness. The Canadian Cardiovascular Society's (CCS) functional classification system was also used to examine the relationship between HR values and classification of angina. Secondary endpoints included: (i) total and cardiovascular death rates; (ii) hospitalization for MI or new-onset or worsening heart failure; and (iii) coronary revascularization.

Baseline assessment

At baseline, the inclusion and exclusion criteria were verified and all the details of concomitant cardiovascular and other medications were recorded. A detailed medical history was taken, in particular regarding the number of MI episodes, the natural history of CAD based upon the number of stenosed vessels and percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) procedures, concomitance of hypertension, heart failure (NYHA

Table 1. Patients' medical history.

	Number	Percent (%)
Myocardial infarction (N=277)	180	65.0
Angina episodes during the last 3 months (N=277)	123	44.4
CCS angina classification (N=174):		
• Category 1	96	55.2
• Category 2	53	30.5
• Category 3	24	13.8
• Category 4	1	0.6
Angina episodes during the week before enrollment (N=88):		
• 1 episode	33	37.5
• 2 episodes	24	27.3
• 3 episodes	13	14.8
• 4 episodes	18	20.5
Coronary angiogram (N=267)	227	85.0
PTCA (N=247)	96	38.8
CABG (N=260)	76	29.2
Number of vessels (N=195):		
• 1 vessel	68	34.9
• 2 vessels	62	31.8
• 3 vessels	63	32.3
Heart failure (N=267)	143	53.5
NYHA classification (N=143):		
• Class I	64	46.4
• Class II	74	53.6
Positive treadmill test (N=253)	59	23.3
Myocardial scintigraphy (N=255)	70	27.5
Hypertension (N=275)	210	76.4
Diabetes mellitus (N=280)	88	31.4

CABG – coronary artery bypass grafting; CCS – Canadian Cardiovascular Society; PTCA – percutaneous transluminal coronary angioplasty.

classification), or diabetes mellitus. When data on left ventricular function were available, the left ventricular ejection fraction (LVEF) value was recorded. The plasma lipid profile was also recorded in patients who had undergone recent biochemistry screening.

Statistics

Baseline data analysis was performed using the SAS® V9.1.3 statistical software. Respective percentages for categorical variables were calculated, based on the number of observations per variable, and continuous variables are presented as mean and standard deviation. Logistic regression was performed in order to examine the effect of risk factors and current treatment on heart rate (HR≤70 vs. HR>70).

Results

Recruitment

During 2009 and 2010, 280 consecutive patients with the abovementioned characteristics agreed to participate in the study and were enrolled in one of the 22 hospitals.

Baseline characteristics of the study population

The mean age of the enrolled patients was 71.8 years (range 35 to 89), 76% were male, mean body mass index (BMI) was 28.6 kg/m^2, 31% of them had diabetes mellitus and 76.4% hypertension. Amongst them 143 (53.5%) patients had heart failure and 53.6% of them were in NYHA functional class II. Thirty-one percent of patients had angina episodes 1 week before enrollment. Mean LVEF was 50% and the majority of patients (85%) had undergone coronary angiography. Mean stenosis percentages in the left main coronary artery (LMA), left anterior descending coronary artery (LAD), right coronary artery (RCA) and left circumflex coronary artery (LCx) were 72.8%, 79.9%, 83.3%, and 78.8%, respectively. The mean time since diagnosis of CAD was 6.2 years, and 23.3% and 27.5% of patients had a positive exercise (treadmill) test and myocardial scintigraphy, respectively (Tables 1 & 2).

Cardiovascular medications

At the baseline visit current cardiovascular treatment was recorded (Table 3). Only 52.8% of study patients were receiving BB therapy, although 53.5% of the

Table 2. Descriptive statistics from patients' medical history.

	N	Mean ± SD
Age (y)	278	71.8 ± 9.3
BMI (kg/m^2)	276	28.6 ± 7.9
Heart rate (bpm)	273	72.5 ± 10.9
LVEF	203	50 ± 10.0
LAD (%)	139	79.9 ± 17.3
RCA (%)	113	83.3 ± 17.1
LCx (%)	92	78.8 ± 17.4
LMA (%)	16	72.8 ± 17.6
FEV1/FVC (%)	91	67.9 ± 11.4
FEV1	92	64.7 ± 15.0
Serum cholesterol (mg/dL)	234	176.6 ± 38.0
Serum LDL (mg/dL)	240	110.6 ± 35.8
Serum HDL (mg/dL)	234	41.9 ± 9.9
Triglycerides	224	129.5 ± 62.3
	Number	**Percent (%)**
Male (N=280)	214	76.4
Smokers (N=272)	106	39.0
Diabetes mellitus (N=88)	12 (type I)	13.6
	76 (type II)	86.4

BMI – body mass index; FEV1 – forced expiratory volume in 1 second; FVC – forced vital capacity; HDL – high-density lipoprotein cholesterol; LAD – left anterior descending coronary artery; LCx – left circumflex coronary artery; LDL – low-density lipoprotein cholesterol; LMA – left main coronary artery; LVEF – left ventricular ejection fraction; RCA – right coronary artery.

Table 3. Patients' medical treatment at baseline.

	Number of patients	Percentage (%) (of total patients)
β-Blockers:	148	52.86
• Carvedilol	62	22.14
• Metoprolol	57	20.36
• Nebivolol	17	6.07
Calcium channel blockers:	123	43.93
• Diltiazem	57	20.36
• Amlodipine	47	16.79
• Verapamil	4	1.43
Ivabradine	46	16.43
Nitrates	127	45.36
Antiplatelet agents	273	97.50
Renin-angiotensin system: agents:	204	72.80
• ACE inhibitors	124	44.29
• ARBs	80	28.57
Statins	181	64.64
Amiodarone	15	1.71
Diuretics	51	5.80

ACE – angiotensin-converting enzyme; ARB – angiotensin receptor blocker.

whole study population had chronic heart failure. It should be noted that in the majority of the patients who were on carvedilol treatment the daily dosage was very low (6.25 mg bid). Despite the low dosage, patients on BB therapy were more likely to achieve a resting HR≤70 bpm (57.4% vs. 42.7%, p<0.001). Patients receiving ivabradine (16.4% of the whole study population) had a higher initial HR compared with other patients (78.5 vs. 71.3, p<0.001). About 21.7% of the study population received calcium channel blockers (CCBs) with negative chronotropic effects (diltiazem 20.3% and verapamil 1.4%). Agents acting on the renin-angiotensin system were taken by 72.8% of patients (angiotensin-converting enzyme [ACE] inhibitors 44.3% and angiotensin receptor blockers [ARBs] 28.6%), antiplatelet agents by 97.5%, statins by 64.6%, and nitrates by 45.3%.

Resting heart rate

Mean resting HR was 72.5 bpm and 51% of the patients had a resting HR>70 bpm, while 22% had a resting HR≥80 bpm (Table 2). The distribution of HR is shown in Figure 1.

Multivariate analysis

Multivariate regression analysis was performed to identify demographic factors (age, sex), clinical characteristics (diabetes, smoking, obesity, hypertension), and medical treatments that were linked independently to the presence of HR>70 bpm. The results showed that diabetes mellitus tended to be independently associated with HR>70 bpm (odds ratio, OR=1.682, p=0.06) (Table 4). Beta-blockade therapy marginally tended to be inversely associated with HR>70 bpm (OR=0.988, p=0.094) (Table 5).

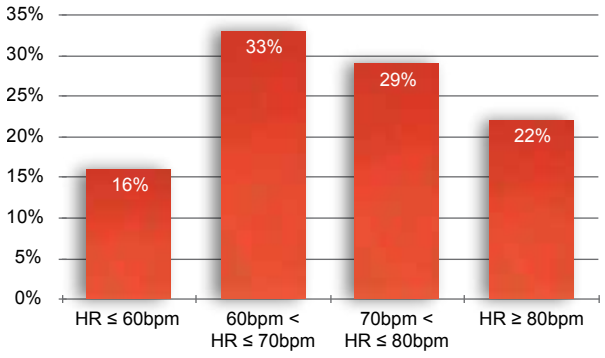

Figure 1. Heart rate distribution at baseline.

Table 4. Multiple regression analysis of prognostic significance of risk factors in relation to heart rate scores.

Criteria	p	Odds ratio (95% CI)
Age	0.276	1.016 (0.98-1.04)
Sex	0.291	1.384 (0.75-2.53)
BMI	0.110	0.955 (0.90-1.01)
Smoking	0.704	1.109 (0.65-1.89)
Hypertension	0.612	0.859 (0.47-1.54)
Diabetes mellitus	0.060	1.682 (0.97-2.89)

BMI – body mass index.

Table 5. Multiple regression analysis of prognostic significance of current treatment in relation to heart rate scores.

Criteria	p	Odds ratio (95% CI)
Antiplatelet agents	0.120	0.637 (0.37-1.08)
β-blockers	0.094	0.988 (0.59-1.65)
Calcium channel blockers	0.964	1.407 (0.86-2.29)
Nitrates	0.173	0.752 (0.41-1.39)
Statins	0.362	0.704 (0.39-1.24)
ACE inhibitors	0.230	0.806 (0.42-1.53)
ARBs	0.510	0.173 (0.02-1.58)
Ivabradine	0.643	1.218 (0.53-2.79)

ACE – angiotensin-converting enzyme; ARB – angiotensin receptor blocker.

Correlation between quality of life and heart rate

As mentioned above, the study patients completed a questionnaire designed to assess to what extent angina affected their overall QoL. Table 6 shows that patients with resting HR>70 had in general worse values of indexes compared to those with HR≤70 regarding activity restriction (p<0.007), number of angina episodes (p<0.001), therapy effectiveness and tolerability (p<0.001), and quality of life (p<0.001).

Discussion

In daily clinical practice the management of patients with stable coronary disease is relatively difficult, as the therapeutic approach to these patients is an issue of controversy.[25,26] Specifically, the coexistence of CAD and COPD is not rare and the management of those patients may be more demanding, due to the patients' inability to comply with long-term use of BB therapy. In addition, these patients often present a higher HR due to the increased use of adrenergic agonists.

In older patients the incidence of both COPD and CAD is greater, with CAD reported in 10% to

21% of COPD patients; this may reflect a high prevalence of smoking as the main cause for COPD.[19,27] The majority of patients (76.4%) in RYTHMOS were male, which is in line with other recent trials such as the BEAUTIFUL[11] study, where 83% of patients were male. Analysis of baseline data in the RYTHMOS study shows that half the patients (52.8%) were receiving BB therapy, in the majority of cases at inadequate dosages. Mean resting heart rate was 72.5 bpm, which is consistent with other observational studies. In the European Heart Survey, 52% of patients had a mean baseline HR>70 bpm; specifically, patients with respiratory disease had a very high HR (≥83 bpm) at examination.[28] Similarly, in the CARDIf study mean HR was 74.1 and 77.1 in men and women, respectively.[29] Also, in BEAUTIFUL at baseline, mean resting HR was 71.6 bpm and HR was approximately 3 bpm lower in patients on BB therapy (71.1 bpm) compared with those not receiving BBs.[30] A subanalysis of BEAUTIFUL showed that for HR≥70 bpm, there was a 34% increase in risk of cardiovascular death, a 53% increase in admissions to hospital for heart failure, a 46% increase in admissions to hospital for MI, and a 38% increase in coronary revascularization.[11] The 2002 American College of Cardiologists/American Heart Association (ACC/AHA) guidelines for stable angina recommend a target HR of 55-60 bpm for patients with angina receiving BB therapy.[31] Meta-analyses of postinfarction trials suggested that resting HR reduction was the major determinant of the clinical benefit of BB and CCB treatment.[32,33]

In our study, the inadequate usage of BB and their sub-therapeutic dosages may have been related to contraindications and the coexistence of COPD. Moreover, despite the fact that about 54% of our study population suffered from heart failure, only 53% were receiving BBs. Taking into consideration that data on HR and usage of BBs in patients with COPD and CAD in the literature are scarce, our study aimed to examine the therapeutic trends and the potential gaps in the management of those patients. However, other surveys in the general population have shown that the lack of BB therapy is the main independent determinant of the magnitude of HR. In the CARDIf survey, it was found that about 50% of patients with CAD were not receiving BBs, despite the absence of clear contraindications, and also that the difference in HR between treated and untreated patients was only 4 bpm.[29] Ivabradine is a novel, well-tolerated HR-lowering drug, which, beyond its beneficial HR-lowering effects in CAD, has recently been shown to have additional mortality and morbidity-reducing effects in heart failure patients.[34] In the RYTHMOS study, 16.4% of all patients were taking ivabradine and had a higher resting HR compared to others (78.5 vs. 71.3 bpm, p<0.001), reflecting the fact that the physicians used ivabradine in patients with previously insufficient heart rate control.

The QoL level was strongly correlated with HR status in patients with CAD. Based on the data from the baseline questionnaire completed by the patients, a significant inverse statistical correlation was found between high HR (>70 bpm) and QoL status. This is consistent with findings from several clinical trials. Diaz et al[35] showed that HR measurement remained a strong predictor of future events. The association between HR and mortality was particularly strong for an HR of 83 bpm, which corresponded to the lower limit of the top HR quintile. Palatini et al examined data from the CArdiovascular STudy in the ELderly (CASTEL study) on the association between high HR and cardiovascular death in elderly men. They found a strong relationship between them and, conversely, better outcomes with lower HR; values between 80 and 85 bpm have been considered as a reasonable cutoff level between normal and high HR.[36] More recently, data from BEAUTIFUL showed that

Table 6. Patient questionnaire results in relation to heart rate (HR).

	Heart rate	Mean score ± SD	p
Patient Activity Restriction Index	HR ≤ 70 bpm	60.28 ± 20.27	0.07
	HR >70 bpm	55.94 ± 20.27	
Angina Frequency Index	HR ≤ 70 bpm	87.94 ± 18.49	<0.001
	HR >70 bpm	74.82 ± 24.69	
Treatment Satisfaction Index	HR ≤ 70 bpm	108.63 ± 26.59	<0.001
	HR >70 bpm	89.09 ± 33.38	
Quality of Life Index	HR ≤ 70 bpm	89.60 ± 28.56	<0.001
	HR >70 bpm	74.7 ± 32.50	

a baseline resting HR of ≥70 bpm or greater versus <70 bpm was associated with an elevated risk for all outcomes assessed, such as cardiovascular death, hospitalization due to heart failure, or MI.[11]

It is known that the autonomic nervous system plays a crucial role in the genesis of sudden cardiac death, and that sympathetic activation can induce life-threatening ventricular arrhythmias. CAD patients with a faster HR are thus conceivably at greater risk of ventricular fibrillation and sudden death.[37] Conversely, a low HR due to parasympathetic activation could have a protective role in maintaining the electrical stability of the heart.[8] Indeed, data derived from the Framingham Study have shown a decreased rate of sudden death in men with bradycardia and an increased rate in those with tachycardia, a relationship that was not present in women.[38] Moreover, a fast HR promotes diastolic dysfunction, which causes discomfort and dyspnea on exertion in patients, especially in the presence of concomitant diseases like COPD.

Diabetes mellitus has been associated with high cardiovascular mortality rates, and coronary artery disease is the leading cause of death in diabetic patients. Especially in Greece, data from the ATTICA study, which was conducted from 2001 to 2006, showed an increased incidence of diabetes, with 5.8 and 5.3 new diagnosed cases in males and females, respectively, per 100 individuals, in proportion to the increased incidence of CAD (11.0% in men and 6.1% in women, $p<0.001$).[39] About 31% of the patients enrolled in RYTHMOS had diabetes mellitus, mainly type 2. Multivariate analysis in our study supports the notion that diabetes mellitus may be an independent predictor of higher heart rate. Diabetes mellitus is considered a "coronary heart disease equivalent"[40] and the mortality rate of diabetic patients after a first MI is high.[41] The significant relationship between elevated HR and diabetes mellitus was established by Facchini et al,[42] a finding consistent with the possibility that increased HR is secondary to insulin-induced sympathetic activity. It is known that long-term sympathetic overactivity can promote insulin resistance.[43] Data from the Bremen Diabetes Study clearly showed that elevated HR was a powerful predictor of cardiovascular death in type 2 diabetic patients, possibly even superior to the traditional cardiovascular risk factors.[44] More recently, Stettler et al, based on a 23-year follow up of the Swiss cohort of the World Health Organization Multinational Study of Vascular Disease in Diabetes, reported, in agreement with previous results, that resting HR was consistently related to all-cause, cardiovascular, cardiac, and ischemic heart disease mortality.[45] The baseline data from the RYTHMOS study showed that diabetic patients with COPD and CAD present a higher HR, and this is in accordance with their worse prognosis. However, whether this is attributed to the autonomic dysfunction of the disease itself or to other characteristics of the diabetic patients cannot be elucidated in our study.

Mean plasma low-density lipoprotein (LDL) levels in RYTHMOS were 110 mg/dL, with 64.6% of patients taking statins. According to guidelines, the optimal LDL levels should be lower than 100 mg/dL and, especially in high-risk patients, as low as 70 mg/dL. Although underuse of statins is a consistent finding in observational studies, our findings underlie the need for a more aggressive therapeutic hypolipidemic strategy, especially taking into consideration the increased risk of patients with chronic CAD and COPD.

Conclusion

The RYTHMOS study documented on a countrywide basis the main characteristics of patients with CAD and COPD, focusing on HR management and the QoL of these patients. From the clinicians' point of view, our findings confirm that these patients have a poor QoL, especially those with a higher HR. In addition they are often undertreated, in particular with respect to beta-blockade therapy, and thus exhibit inadequate heart rate control. Statins are also underused and the lipid profile is not in accordance with current guidelines. Finally, the use of ivabradine was withheld for a small proportion of the studied patients and diabetes tended to be independently associated with increased HR.

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Appendix: RYTHMOS Study Centers and Investigators

1. University Hospital of Heraklion: Principal Investigator: P. Vardas. Co-investigators: E. Simantirakis, C. Goudis
2. Volos General Hospital: Principal Investigator: T. Tsaknakis. Co-investigators: A. Galapis, K. Tziolas
3. Chios General Hospital: Principal Investigator: A. Kartalis. Co-investigators: G. Georgiopoulos, N. Smirnioudis, P. Moschouris
4. Tripoli General Hospital: Principal Investigator: D. Chrysos. Co-investigators: V. Chronopoulos, N. Laschos, N. Raikos
5. Thiva General Hospital: Principal Investigator: E. Skoumbourdis
6. Halkida General Hospital: Principal Investigator: I. Mantas. Co-investigators: K. Toli, S. Vichos
7. University Hospital of Ioannina: Principal Investigator: I. Goudevenos. Co-investigator: N. Servetas
8. 2nd IKA Hospital Thessaloniki: Principal Investigator: C. Kyrpizidis.
9. Edessa General Hospital: Principal Investigator: K. Oikonomou.
10. Thriassio General Hospital: Principal Investigator: C. Olympios. Co-investigators: M. Stamatelatou, A. Vlachantonis
11. Western Attica General Hospital: Principal Investigator: A. Kranidis. Co-investigator: D. Kontogianni
12. 7th IKA Hospital Athens: Principal Investigator: P. Kalogeropoulos.
13. Komotini General Hospital: Principal Investigator: A. Gotsis.
14. Tzaneio General Hospital Piraeus: Principal Investigator: S. Foussas. Co-investigator: C. Kontos
15. Elpis General Hospital: Principal Investigator: A. Trikas. Co-investigators: A. Kakkavas, P. Spanos, V. Tsoukaki
16. Chania General Hospital: Principal Investigator: A. Pras. Co-investigator: G. Diakakis
17. University Hospital of Patras: Principal Investigator: D. Alexopoulos. Co-investigators: V. Karantalis, E. Mavronasiou
18. Laiko General Hospital: Principal Investigator: V. Votteas. Co-investigator: A. Delaportas
19. Hygeia Hospital Athens: Principal Investigator: A. Pipilis. Co-investigators: N. Sourlas, S. Kaliambakos
20. Euroclinic Hospital of Athens: Principal Investigator: D. Richter. Co-investigators: G. Goumas, C. Fourlas, D. Sakellariou
21. Asklipeion General Hospital Voula: Principal Investigator: A. Manolis. Co-investigators: A. Giannakopoulos, L. Poulimenos, N. Kouremenos
22. University Hospital of Alexandroupolis: Principal Investigator: S. Konstantinides. Co-investigators: K. Mitrousi, P. Kikas