Treatment of Stable Angina Pectoris With Ivabradine in Everyday Practice: A Pan-Hellenic, Prospective, Noninterventional Study

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ABSTRACT

Introduction: In coronary artery disease (CAD), medical treatment is the main clinical strategy for controlling ischemia and angina symptoms while restoring a satisfactory level of usual activities and improving quality of life (QOL). This study's purpose was to evaluate in CAD patients the antianginal efficacy of 4-month treatment with ivabradine plus a β-blocker and to record patient compliance and the effect of treatment on QOL.

Methods: In this noninterventional study, 2403 patients with chronic stable angina were prospectively studied from 245 private cardiology offices. Data were recorded at baseline and at 1 and 4 months after inclusion. Patient quality of life was assessed using the EuroQol 5 dimensions (EQ-5D) questionnaire.

Results: From baseline to study completion, mean heart rate decreased from 81.5 ± 9.7 bpm to 63.9 ± 6.0 bpm ($P < -0.001$), mean number of anginal attacks decreased from 2.0 ± 2.0 times/wk to 0.2 ± 0.6 times/wk ($P < 0.001$) and nitroglycerin consumption decreased from 1.4 ± 2.0 times/wk to 0.1 ± 0.4 times/wk ($P < 0.001$). The percentage of patients with Canadian Cardiovascular Society angina class I increased from approximately 38% (baseline) to 84% (study completion; $P < 0.001$). The reduction in anginal attacks, nitroglycerin consumption, and angina score was correlated with reduction in heart rate ($P < 0.001$). The mean EQ-5D visual analogue scale index increased by 16.1 points ($P < 0.001$), and compliance with treatment was high throughout the trial (96%).

Conclusions: Ivabradine administration on top of optimal individualized dose of β-blockers is associated with decreased anginal events and with improvement of QOL in CAD patients.

Introduction

Coronary artery disease (CAD) is one of the main causes of morbidity and mortality worldwide.[1] Stable angina pectoris (AP) is a common clinical expression of myocardial ischemia. Angina significantly limits the ordinary activities of most of these patients and worsens their quality of life (QOL), in terms not only of physical activity/pain but also mental health.[2–4] Medical treatment is the main clinical strategy for controlling ischemia and angina symptoms while restoring a satisfactory level of usual activities and improving QOL.

Ivabradine is a heart rate–lowering agent that inhibits the sinus node I_f pacemaker current but does not directly affect other cardiac or hemodynamic parameters. By reducing heart rate, ivabradine reduces oxygen demand, and by prolonging diastolic time and enabling coronary vasodilation, it maximizes myocardial oxygen supply and facilitates diastolic left ventricular (LV) filling during exercise.[5–7] Ivabradine is currently indicated for patients with chronic stable angina[8] who are intolerant to or inadequately controlled by β-blocker therapy, as well as for patients with chronic heart failure (New York Heart Association classes II–IV) with systolic dysfunction, in combination with standard therapy. The current indication in chronic stable angina is based mainly on the results of several studies that have proven the antianginal and anti-ischemic

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effect of ivabradine in patients with CAD. In the ADDITIONS study[9] and several others,[10–12] the addition of ivabradine not only reduced heart rate, the number of angina attacks, and the time to angina onset, but also decreased nitrate consumption and improved QOL of patients with stable AP.

Objectives

Our aim in this study was to evaluate in CAD patients in Greece the antianginal efficacy of a 4-month individualized treatment with ivabradine plus a β-blocker and the effect of this treatment on the patients' QOL.

The study objectives were the following: to record the reduction in heart rate at 1 and 4 months after the administration of ivabradine; to record anginal attacks and nitroglycerin consumption 1 week before each study visit, as well as to record the angina score using the Canadian Cardiology Society (CCS) classification; to record the effect of ivabradine on the patients' QOL and their compliance with the 4-month treatment; and to record comorbidities and coexisting risk factors at inclusion in the study.

Patients and Methods

This study was designed in line with the recommendations of the current Helsinki Declaration, the International Society of Pharmacoepidemiology Guidelines for Good Pharmacoepidemiology Practices (ISPE-GPP), and the International Conference on Harmonisation Guideline on Good Clinical Practice (ICH-GCP) and was approved by the appropriate ethics committee (scientific committee) of participating hospital departments. Prior to their inclusion in the study, all patients were informed and gave their consent to participate.

Patients

Patient inclusion criteria were male or female ambulatory patients age >18 years, diagnosed with CAD and stable AP (documented through the patients' history), with heart rate >60 bpm (in sinus rhythm) despite treatment with β-blockers at the optimal individualized dose, and need for ivabradine administration. The decision to administer ivabradine was taken regardless of the likelihood of the patient being included in the study, and the treatment was initiated no more than 5 days before inclusion in the study.

Excluded were patients hospitalized for cardiovascular disease during the last 3 months, including undergoing revascularization or scheduled for revascularization. In addition, patients with other comorbidities such as serious end-stage diseases, severe neuropsychiatric diseases, pregnancy, lactation, or willingness to become pregnant were also excluded.

Study Design

This was a multicenter, prospective, noninterventional study in 2403 patients with CAD followed up from 245 private cardiology offices and coordinated by 2 cardiology departments of Greek hospitals. The participating physicians were from all over Greece, in urban, suburban, and rural areas, mimicking available epidemiological patterns of Greece.[13] The total follow-up period was 4 months, and the evaluations were performed at 3 intervals: at inclusion, and at 1 and 4 months after inclusion. Patient QOL was assessed using the Greek version of the EuroQol 5 dimensions (EQ-5D) questionnaire (EQ-5D index and visual analogue scale [VAS]), recorded at baseline and study completion. The EQ-5D includes 5 dimensions: mobility, autonomy in self-care, usual activities, pain/discomfort, and stress/distress, stratified in 3 levels leading to 243 health conditions in total. Each health condition is stratified according to individual preference among several health conditions.[14–16]

Patient compliance with ivabradine treatment was evaluated using a 5-level scale (recorded at the second and third visits):

1. The patient had taken the treatment daily during the interval from the previous visit.
2. The patient had taken the treatment very often (the patient might have forgotten it once or twice) during the interval from the previous visit.
3. The patient had taken the treatment half of the days during the interval from the previous visit.
4. The patient had not taken the treatment for most of the days during the interval from the previous visit.
5. The patient had never taken the treatment during the interval from the previous visit.

The tolerability and safety of the treatment were evaluated by recording the time of and reason for study treatment discontinuation and the reported adverse events.

β-Blocker Dosage

During the study, β-blockers were prescribed at a dosage considered optimal for each individual patient by the treating physician. The target dose of the most common β-blockers was defined as atenolol 100 mg/d, betaxolol 10 mg/d, bisoprolol 10 mg/d, carvedilol 100 mg/d, celiprolol 200 mg/d, metoprolol 200 mg/d, nebivolol 10 mg/d, propranolol 160 mg/d, and sotalol 160 mg/d.

Statistical Analysis

For the main parameter, a 97.5% confidence interval (CI) was given for the difference in values between baseline and study completion. The Friedman test was used to compare heart rate, number of anginal events, and nitroglycerin consumption between the 3 visits. The same test was used to compare categorized heart rate (1: <70, 2: 70–80, 3: >80 bpm/1: 55–60 bpm, 0: otherwise) and categorized number of anginal events between the 3 visits. The Wilcoxon test was used to compare the angina classes and the values of the 5 dimensions of the EQ-5D, between baseline and study completion. Multiple logistic regression (stepwise selection) tested the relation of β-blocker dosage (0: <50, 1: ≥50 of optimal dose for the total trial duration), calcium antagonists and long-acting nitrate administration for the total trial duration, heart rate difference and the relation of VAS difference between baseline and study completion, as well as the relation of heart rate difference to β-blocker dosage (<50, ≥50 of optimal dose for the total trial duration), with the following parameters (independent

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variables): sex, age, baseline angina score, baseline heart rate, diabetes mellitus (DM), LV systolic dysfunction, angina events difference, nitroglycerin consumption difference, heart rate difference, and calcium antagonists and long-acting nitrate administration for the total trial duration. The same technique tested the relation of VAS difference with β-blocker dosage (<50, ≥50 of optimal dose for the total trial duration). The Spearman correlation coefficient was computed for each pair of differences between baseline and study completion: heart rate, number of anginal events, nitroglycerin consumption. Significance level for all tests (P value) was set at 0.05.

Results

Of 2403 CAD patients who participated in the study, 52 (2.2%) prematurely discontinued treatment. Approximately 66% of the patients were male. The patients had a mean age of 67.2 ± 10.7 years and mean body mass index (BMI) of 28.3 ± 4.0 kg/m^2. The patients' baseline characteristics are shown in Table 1.

Table 1. Baseline Characteristics (N = 2403)

Male sex	66.1
Age, y	67.2 ± 10.7
BMI, kg/m^2	28.3 ± 4.0
Heart rate at rest, bpm	81.6 ± 10.0
SBP, mm Hg	135.6 ± 15.2
DBP, mm Hg	80.7 ± 9.1
Smoking	33.1
Hypercholesterolemia	71.0
HTN	69.9
DM	30.8
Previous MI	31.5
Coronary angiogram with >50% stenosis in 1 coronary artery	39.5
CABG or PCI	38.5
Chest pain with concomitant myocardial ischemia, documented in a stress test, an echocardiogram stress test, or scintigraphic myocardial imaging	42.6
PVD	14.9
Depression	12.3
LV systolic dysfunction	12.2
Cerebrovascular disease or carotid disease	8.9
Renal failure (serum Cr >2 mg/dL)	2.1
COPD	10.2

Abbreviations: BMI, body mass index; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; Cr, creatinine; DBP, diastolic blood pressure; DM, diabetes mellitus; HTN, hypertension; LV, left ventricular; MI, myocardial infarction; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; SBP, systolic blood pressure; SD, standard deviation.
Data are presented as % or mean ± SD.

Concomitant Medication

In addition to ivabradine, all patients received β-blockers at their inclusion in the study (Table 2). Approximately 48% (975) of them received ≥50% of the optimal β-blocker dose for the total trial duration. The percentage of patients who received ≥50% of the optimal β-blocker dose for the total trial duration was statistically greater in patients with lower angina scores ($P = 0.049$), and in patients with higher heart rate ($P = 0.036$). A total of 115 patients discontinued β-blockers during the trial due to intolerance (60 patients) or other reasons (55 patients).

In addition to treatment with ivabradine and β-blocker, 1971 patients (82% of the total sample) also received another medication during the trial: 28.6% received angiotensin-converting enzyme inhibitors (ACEIs), 27.6% angiotensin II receptor blockers (ARBs), 21.4% diuretics, 71.2% anticoagulants (mainly antiplatelets), and 63.1% lipid-lowering drugs.

For the total trial duration, 482 patients (20.1% of the sample) received calcium antagonists and 576 patients (24.0%) received long-acting nitrates. Patients with DM ($P < 0.001$), patients with higher heart rate at baseline ($P = 0.001$), and older patients ($P < 0.001$) had a higher percentage of calcium antagonist administration. Male patients ($P = 0.038$), patients with DM ($P = 0.004$), with higher angina scores ($P < 0.001$), with lower heart rate at baseline ($P < 0.001$), and older patients ($P < 0.001$) had a higher percentage of long-acting nitrate administration.

Objectives of the Study

At baseline, 87% of the patients had heart rate ≥70 bpm, despite treatment with β-blockers. Treatment with ivabradine decreased mean heart rate from 81.5 ± 9.7 bpm at baseline to 68.6 ± 7.4 at the second visit and 63.9 ± 6.0 bpm at the third ($P < 0.001$) Heart rate decrease was statistically greater in patients with higher baseline heart rate values ($P < 0.001$). Patients with heart rate >80 bpm at baseline showed a greater heart rate decrease (average decrease 23.6 bpm) than patients with heart rate 70 to 80 bpm (average decrease 14.2 bpm), and those with heart rate <70 bmp (average decrease 8.3 bpm). The percentage of patients with heart rate >80 bpm decreased from 45% at baseline, to almost 5% at the second visit, while it was further decreased to almost 1% at the third visit. In contrast, the percentage of patients with heart rate <70 bpm increased from 13% at baseline to almost 70% at the second visit and to almost 90% at the third visit ($P < 0.001$). Mean heart rate decrease was greater by 1.1 bpm in patients who received ≥50% of optimal β-blocker dose, compared with the patients who received <50% of optimal β-blocker dose for the total trial duration ($P = 0.039$).

The mean number of anginal events decreased from 2.0 ± 2.0 times/wk at baseline to 0.5 ± 0.9 at the second visit and 0.2 ± 0.6 times/wk at the third ($P < 0.001$; Figure 1). The percentage of patients with no anginal events during the week prior to the study visits increased from 18.5%

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Table 2. Total Daily Dose of β-Blockers Received at Each Study Visit

	First Visit		Second Visit		Third Visit	
	Mean ± SD	N	Mean ± SD	N	Mean ± SD	N
Atenolol, mg	56.65 ± 25.51	233	55.40 ± 25.62	220	55.16 ± 25.8	223
Betaxolol, mg	15.00 ± 6.45	7	13.33 ± 7.53	6	13.33 ± 7.53	6
Bisoprolol, mg	7.31 ± 2.7	131	7.26 ± 2.93	127	7.24 ± 2.64	124
Carvedilol, mg	20.88 ± 12.5	819	20.57 ± 11.01	777	20.46 ± 1.25	764
Celiprolol, mg	185.71 ± 37.8	7	185.71 ± 37.8	7	185.71 ± 37.8	7
Metoprolol, mg	85.31 ± 40.11	682	82.48 ± 38.15	672	80.41 ± 36.71	652
Nebivolol, mg	4.75 ± 0.77	431	4.78 ± 0.72	412	4.75 ± 0.75	407
Propranolol, mg	70.80 ± 46.34	87	72.15 ± 45.9	79	69.87 ± 44.89	75
Sotalol, mg	120.00 ± 43.82	6	120.00 ± 43.82	6	120.00 ± 43.82	6

Abbreviations: SD, standard deviation.

at baseline to almost 70% at the second visit and to approximately 80% at the third ($P < 0.001$; Figure 2).

Nitroglycerin consumption decreased from 1.4 ± 2.0 times/wk at baseline to 0.3 ± 0.7 at the second visit and 0.1 ± 0.4 times/wk at the third ($P < 0.001$; Figure 1).

The reductions in the number of anginal events and nitroglycerin consumption were both positively correlated with heart rate reduction ($P < 0.001$).

The percentage of patients with CCS class III or IV angina decreased from approximately 18% at baseline to 2% at study completion, whereas the percentage of patients with CCS class I angina increased from approximately 38% to 84% at study completion ($P < 0.001$; Figure 3).

For all dimensions of the EQ-5D, the percentage of patients who answered "No problem"/"Not at all" increased substantially at study completion, compared with baseline ($P < 0.001$). Ivabradine administration increased the percentage of patients with "no mobility problem" by 52% (636 more patients), the "autonomous in self-care" by 19.7% (347 patients), those with "no problem in usual activities" by 58.2% (679 patients), the percentage of patients with "no stress/distress" by 63.8% (535 patients), while it increased almost 4-fold the percentage of patients with "no pain/discomfort" (1293 more patients) ($P < 0.001$). The mean EQ-5D index increased at study completion by 0.3 points, compared with baseline (from 0.6 ± 0.3 to 0.9 ± 0.2), while VAS increased by approximately 16 points (from 62.8 ± 16.3 to 78.9 ± 17) ($P < 0.001$). EQ-5D VAS increase was greater in patients with lower VAS at baseline ($P < 0.001$) and with greater heart rate decrease at study completion ($P < 0.001$), and in patients who were older ($P < 0.001$) and did not receive long-acting nitrates ($P < 0.001$) or calcium antagonists ($P = 0.005$). The improvement in QOL was not statistically significantly associated with β-blocker dose (between the 2 groups <50% and ≥50% of the β-blocker target dose).

Compliance with ivabradine treatment was high. Throughout the study, 2312 patients (96.2%) were taking their treatment "every day" or "quite often." A constant ivabradine dosage (5 mg bid) was administered throughout the study to 833 patients (36%). At the second visit, 1042 patients (45% of the total sample) were receiving ivabradine 7.5 mg bid, which was maintained during the rest of the study.

Safety Parameters

Thirty-one patients presented 45 adverse reactions and/or adverse events during the study. Twenty-eight patients discontinued the study drug and were withdrawn from the study, whereas 3 patients continued the study following the appearance of the event. Of the 45 adverse reactions and/or adverse events, 20 were adverse events (ie, not related to the study drug) and 25 were adverse reactions, related or possibly related to the study drug (including 8 cases of bradycardia, 2 cases of atrial fibrillation, and 3 cases of phosphenes).

Discussion

This is an important study because provides not only information regarding epidemiology, clinical characteristics, and management of patients with stable AP and CAD in Greece, but also because provides support for the clinical benefits associated with ivabradine co-administration with a β-blocker, particularly with respect to angina relief, reduced nitroglycerine consumption, and improved QOL and CCS angina class after 4 months of therapy.

Coronary artery disease is one of the leading causes of disease burden worldwide,[1] whereas heart rate is a significant modifiable risk factor in terms of morbidity and mortality.[17,18] Heart rate reduction is considered a strategic target in patients with stable angina.[8] However, in several studies and registries,[9,19] as well as in this study, heart rate remains at high levels despite the high usage of β-blockers. In this study approximately 48% of the patients received >50% of the target β-blocker dosage, while similar suboptimal therapy has been observed in terms of uptitration in several studies and surveys with post-MI or stable angina patients.[9,20,21] Usually, β-blocker target dose is not reached because of poor tolerance and

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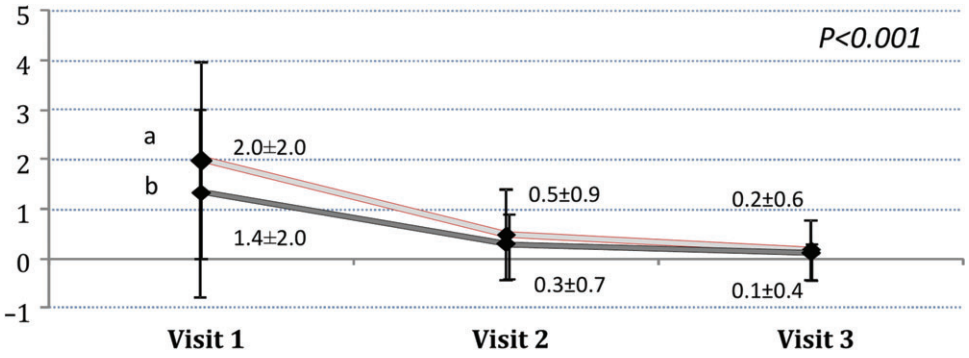

Figure 1. Number of angina attacks (a) and use of short-acting nitrates (b)/mean ± SD at the 3 study visits (N = 2312). Abbreviations: SD, standard deviation.

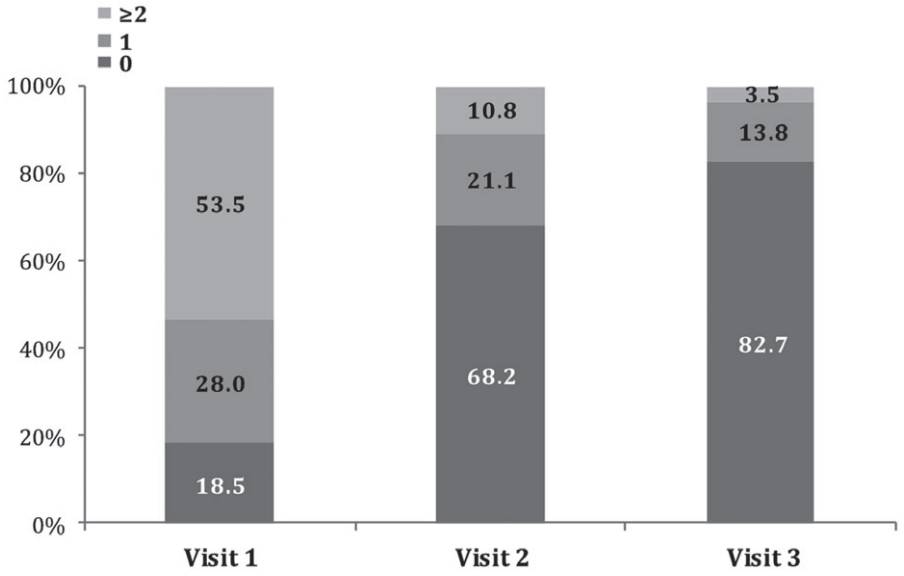

Figure 2. Number of anginal events (% of patients) at the 3 study visits (N = 2312).

adverse effects such as dizziness, fatigue, bradycardia, and hypotension,[22] or as a result of physicians' reservations in the case of existing comorbidities.[20] In this study, at inclusion, 87.4% of the patients had heart rate >70 bpm, despite treatment with β-blockers. Adding ivabradine to the treatment plan led to 17.7 bpm decrease in resting heart rate, without any critical bradycardia. Interestingly, the difference in heart rate between patients who received <50% and >50% of the target β-blocker dosage was only 1.1 bpm. However, similar results were also obtained in several other studies. In an analysis of Metoprolol CR/XL Randomized Intervention Trial in Chronic Heart Failure (MERIT-HF),[23] comparing patients who tolerated <100 mg (mean, 76 mg) of metoprolol succinate vs those who tolerated >100 mg (mean, 192 mg), the achieved heart rate was 67 bpm in both groups. Likewise, in a subgroup analysis of the Cardiac Insufficiency Bisoprolol Study (CIBIS II), heart rate reduction with bisoprolol was similar regardless of the tolerated dose (low, medium, high).[24]

As expected, the addition of ivabradine to the treatment plan decreased the number of angina attacks and nitroglycerin consumption, while was associated with an improvement in CCS angina class. This was mainly related to heart rate reduction, but not to β-blocker dosage. These data are consistent with previous studies showing the antianginal and anti-ischemic effect of ivabradine in patients with CAD.[9–12] Beyond heart rate reduction, ivabradine also seems to have other properties. Several experimental and clinical studies suggest that ivabradine administration also improves endothelial function[25] (yet "If channels" are not known to be present in endothelium) and attenuates the progression of atherosclerosis.[26] In addition, ivabradine seems to improve the coronary collateral circulation in patients with chronic stable CAD, an effect that influences ischemia to at least the same degree as heart rate reduction.[27] Finally, there are studies suggesting that ivabradine administration improves also hyperemic coronary flow velocity and coronary flow reserve in patients with stable CAD while these effects remained even after heart rate was restored by pacing correction indicating improvement of microvascular function,[28] which is frequently altered in patients with angina.[29]

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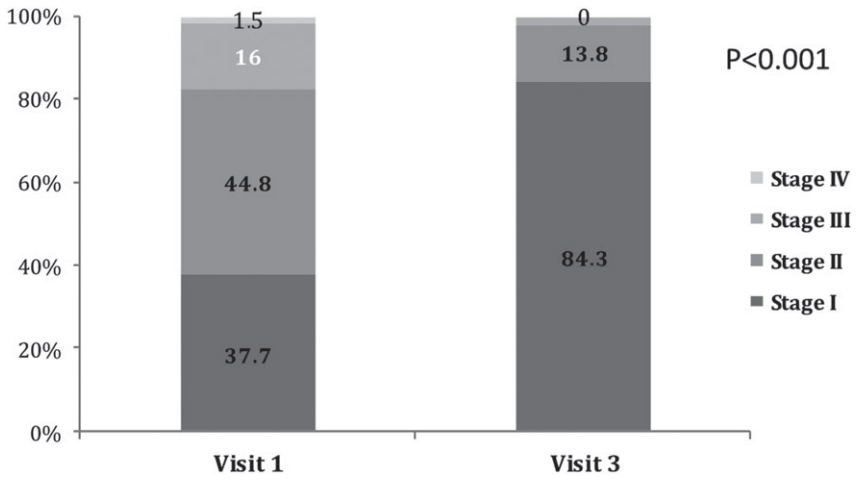

Figure 3. CCS classification (% of patients) at visits 1 and 3 (N = 2312). Abbreviations: CCS, Canadian Cardiovascular Society.

Ivabradine on top of β-blocker therapy was associated with an improvement in QOL. This effect was mainly driven by heart rate lowering and reduction in disease severity (angina events, nitroglycerin consumption, and CCS angina score). In particular, the number of patients with CCS class I angina at study completion was more than doubled in comparison with baseline (from 38% to 84%); this was not related to β-blocker dosage. This is an important finding since there are inconsistent data regarding QOL and treatment in this population. In the Angina Prognosis Study in Stockholm (APSIS) study,[30] metoprolol and verapamil uptitration to target dosage in 800 patients with stable angina was not related to a significant improvement in QOL after 3.4 years of follow-up. Also in this study, the improvement of QOL was mainly related to ivabradine administration, which led to a substantial heart rate reduction, and not to β-blocker dosage since the difference in heart rate was only 1.1 bpm in patients receiving <50% and >50% of the target β-blocker dosage for the total trial duration. In the present study, the EQ-5D VAS score was improved by 16.1 points over 4 months of treatment with ivabradine on top of β-blockers, which is in line with a previous report that ivabradine improved EQ-5D VAS score by 15.3 points.[9]

Despite the decreased number of angina attacks and nitroglycerin consumption observed with ivabradine administration, the question may arise whether the uptitration of β-blockers to target dose would have yielded the same results. However, several registries mentioned above showed that, in everyday clinical practice, the uptitration of a β-blocker to optimum dose is difficult and rarely achieved.[12,22] It seems that the dosage of a β-blocker is not always related to heart rate reduction[23,24] and, in addition, there are clear data from a double-blind randomized study proving that addition of ivabradine to a β-blocker is more effective (in terms of antianginal and anti-ischemic effect) than β-blocker uptitration in patients with stable angina.[11]

Compliance with ivabradine treatment was high. Throughout the trial, 2309 patients (96%) were taking their treatment "every day" or "quite often." Of 1023 patients (50.8%) who received a constant dosage of ivabradine throughout the study, (833 (81.4%) received 5 mg bid and 160 (15.6%) 7.5 mg bid. This high compliance with ivabradine treatment can be explained by its antianginal efficacy and the rarity of adverse reactions.

Ours is an important study because it is one of the few studies to assess coexisting risk factors and comorbidities in a large sample of Greek patients with stable AP and CAD, in urban, suburban, and rural areas, mimicking available epidemiological patterns of Greece.

Study Limitations

This was an observational study and hence treatment or selection bias could also potentially explain the results. Moreover, knowledge of the identity of treatment and the absence of a matching placebo arm to ivabradine are notable limitations. However, prospective, non-interventional studies provide additional information in conjunction with blinded, placebo-controlled clinical studies, since they add data from routine clinical practice and enroll patients with comorbidities that are usually excluded from clinical trials.[31] Finally, one might also argue that a 4-month treatment period is a relatively short duration.

Conclusion

Ivabradine administration on top of optimal individualized dose of β-blockers is associated with decreased anginal events and nitroglycerin consumption, and with improvement of angina classes and QOL in patients with CAD and stable AP.

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