CLINICAL TRIAL UPDATES

Antianginal Efficacy of Ivabradine/Metoprolol Combination in Patients With Stable Angina

John Zarifis MD | Manolis Kallistratos MD | Apostolos Katsivas MD | on behalf of the investigators of the Prospective, Non-interventional, Observational Study of the Antianginal Efficacy of Ivabradine During a 4-Month Treatment of a Greek Population With Coronary Artery Disease

Cardiology Department (Zarifis), George Papanikolaou General Hospital, Thessaloniki, Greece; Cardiology Department (Kallistratos), Asklepeion General Hospital, Athens, Greece; First Cardiology Department (Katsivas), Korgialeneio-Benakeio E.E.S. General Hospital, Athens, Greece

Corresponding Author: Manolis S. Kallistratos, MD, Cardiology Department, Asklepeion General Hospital, 1 Vas. Pavlou Street, 16673, Voula, Greece (kallistrat1972@gmail.com)

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Medical treatment is the main clinical strategy for controlling patients with chronic stable angina and improving their quality of life (QoL). Ivabradine treatment on top of metoprolol decreases angina symptoms and improves QoL in patients with stable angina and coronary artery disease (CAD). This is a post hoc analysis (636 CAD patients given ivabradine/metoprolol free combination) of a prospective, noninterventional study that included 2403 patients with CAD and stable angina. Data were recorded at baseline at 1 and 4 months after inclusion. Patient QoL was assessed using the EQ-5D questionnaire. From baseline to study completion; ivabradine administration on top of metoprolol decreased heart rate (HR) from 80.8 ± 9.6 to 64.2 ± 6.2 bpm ($P < 0.001$). Mean number of angina attacks decreased from $2.0 \pm 2.0/\text{wk}$ to $0.2 \pm 0.6/\text{wk}$ ($P < 0.001$), whereas nitroglycerin consumption decreased from 1.4 ± 1.9 times/wk to 0.1 ± 0.4 times/wk ($P < 0.001$). The percentage of patients in Canadian Cardiovascular Society angina class III to IV decreased from 15.4% to 1.9% ($P < 0.001$). The improvement of symptoms and angina class led to a significant 14.7-point increase in EQ-5D questionnaire score ($P < 0.001$). Patients with increased HR showed greater improvement ($P = 0.001$). Adherence to treatment during the entire trial was high (98%). Ivabradine combined with metoprolol significantly decreased angina symptoms and use of nitroglycerin in patients with stable angina and CAD, leading to improved QoL. The benefits observed with this combination explain the high rate of adherence to treatment.

KEYWORDS

Stable angina, ivabradine, metoprolol, quality of life, nitroglycerin consumption

1 | INTRODUCTION

Stable angina is a common but highly debilitating symptom in patients with stable coronary artery disease (CAD). Caused by myocardial ischemia, angina limits most patients' everyday activities and impacts negatively on their quality of life (QoL). Ivabradine is an established antianginal drug that decreases angina symptoms and improves QoL in patients with stable CAD and angina.¹⁻⁴ Adding ivabradine to the treatment plan improves all treadmill exercise tolerance test parameters, such as total exercise duration, time to limiting angina, time to angina onset, and time to 1-mm

ST-segment depression.⁵ By restoring a satisfactory level of usual activities, ivabradine administration also improves QoL in these patients.¹⁻⁵

2 | METHODS

2.1 | Objectives

Ivabradine is usually administered on top of a β -blocker. Here, we assessed the effect of ivabradine administration on top of metoprolol

(a common β -blocker used in stable CAD) over 4 months, in patients with CAD and stable angina. The study objectives were to record the effect of ivabradine on resting heart rate (HR), angina attacks, and use of nitroglycerin, as well as on angina classification (on the basis of the Canadian Cardiovascular Society [CCS])⁶ and on QoL, 1 and 4 months after administration.

2.2 | Study Design and Study Population

This study was designed in line with the recommendations of the latest Declaration of Helsinki (2013), ISPE Guidelines for Good Pharmacoeconomics Practice, and rules of Good Clinical Practice (ICH-GCP), and was approved by the appropriate ethics committees (Scientific Councils) of participating hospital departments. Copyright permission to use the EuroQOL 5-dimension (EQ-5D) QoL questionnaire⁷ was received. All patients were informed and gave their consent to participate prior to their inclusion in the study.

Inclusion criteria were male or female ambulatory patients age >18 years, diagnosed with CAD and stable angina, with resting HR >60 bpm despite treatment with β -blockers at the optimal individualized dose and a need for co-administration of ivabradine. Ivabradine treatment was initiated at the dose of 5 mg twice daily. The optimal individualized dose was assessed by the treating physician. The decision to administer ivabradine was taken regardless of the likelihood of the patient being included in the study, and ivabradine treatment was started no more than 5 days before inclusion. The treating physician chose the dosage of ivabradine, taking into consideration the summary of product characteristics and HR.

Exclusion criteria included patients hospitalized for cardiovascular disease during the last 3 months (including revascularization) or who had a scheduled revascularization. In addition, patients with other conditions like serious end-stage diseases (cancer, serious liver, respiratory, heart, or renal insufficiency), severe neuropsychiatric diseases, cerebrovascular events with serious residual lesions, cases of pregnancy, lactation, or willingness to become pregnant were excluded.

This is a post hoc analysis describing 636 CAD patients given ivabradine on top of metoprolol. The primary study was a multicenter, prospective, noninterventional study in 2403 patients with CAD and stable angina cared for in 245 private cardiology practices. The study was coordinated by 2 cardiology departments of Greek hospitals.⁴ The total forecasted duration of follow-up for the needs of the study was 4 months, and the evaluations were performed at inclusion and at 1 and 4 months after inclusion. Quality of life was assessed by means of the EQ-5D questionnaire (EQ-5D index and visual analogue scale [VAS]; recorded at baseline and study completion). The EQ-5D questionnaire 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, and each health condition is stratified according to individual preference among several health conditions.⁷⁻⁹

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

1. The patient had taken the treatment daily since the previous visit.

2. The patient had taken the treatment very often (the patient might have forgotten it once or twice) since the previous visit.
3. The patient had taken the treatment on half of the days since the previous visit.
4. The patient had not taken the treatment on most days since the previous visit.
5. The patient had never taken the treatment since the previous visit.

The tolerability of the treatment was evaluated by recording the time and reason for study-treatment discontinuation.

2.3 | Statistical Analysis

Continuous variables are presented using the mean, median, SD, and minimum and maximum values. The categorical variables are presented using tables of frequencies. Repeated measures analysis of variance compared the values of HR, number of angina events, and nitroglycerin use between the 3 visits, and the *t* test was applied to each pair of visits. Friedman's test was used to compare categorized HR (1: <70, 2: 70–80, 3: >80 bpm) and categorized number of angina events between the 3 visits; the Wilcoxon test was applied to each pair of visits. Cochran's Q test was used to compare categorized HR (1: 55–60 bpm, 0: otherwise) between the 3 visits, whereas the McNemar test was applied to each pair of visits. The Wilcoxon test was used to compare angina scale values and the values of the 5 dimensions of the EQ-5D index, between visits 1 and 3. The *t* test was used to compare the values of the EQ-5D index and the VAS values, between visits 1 and 3. The Pearson correlation coefficient was computed for the following pairs of differences between the first and third visits: EQ-5D index and VAS. The same technique was used for each pair of differences between the first and third visits for HR at rest, number of anginal events, and use of nitroglycerin. Pearson correlation coefficients were computed between the reduction of CCS angina class and the reduction of the following parameters between the first and third visits: HR at rest, number of anginal events, and use of nitroglycerin. Multiple logistic regression (stepwise selection) tested the relation of calcium antagonists and administration of long-acting nitrates for the duration of the trial with the following parameters (independent variables): sex, age, CCS angina class, HR at the first visit, diabetes mellitus (DM; yes/no), and left ventricular systolic dysfunction (yes/no). The same technique was used to test the relation of HR difference between the first and third visits, with the following independent parameters: sex, age, CCS angina class, HR at the first visit, DM (yes/no), left ventricular systolic dysfunction (yes/no), calcium antagonists (yes/no), and administration of long-acting nitrates (yes/no) for the total trial duration. Multiple linear regression (stepwise selection) was used to test the relation of VAS difference between the first and third visits, with the following independent parameters: VAS at the first visit, sex, age, CCS angina class at the first visit, DM (yes/no), left ventricular systolic dysfunction (yes/no), angina attacks difference between the first and third visits, nitroglycerin use difference between the first and third visits, HR difference between the first and third visits, calcium antagonists (yes/no), and administration of long-acting nitrates (yes/no) for the

total trial duration. The significance level for all tests (*P* value) was 0.05.

3 | RESULTS

The patients included were 70.1% male and had a mean age of 66.5 ± 10.7 years and mean body mass index of 28.4 ± 3.8 kg/m². Baseline characteristics are shown in Table 1.

Mean doses of ivabradine and metoprolol at the first visit were 10.2 ± 1.6 mg and 85.8 ± 39.8 mg, respectively. Ivabradine and metoprolol dosages at each study visit are shown in Table 2. Of 636 patients who participated in the study, only 7 (1.1%) prematurely discontinued treatment. In addition to ivabradine and metoprolol, 57.4%, 21.4%, 18.7%, and 23.6% of the patients were receiving angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, calcium antagonists, diuretics, and long-acting nitrates, respectively, during the study. In addition, 68.9% of the patients were receiving lipid-lowering agents and 74.1% anticoagulant drugs (mainly antiplatelets).

At baseline, 86.5% of the patients had a resting HR >70 bpm, despite treatment with metoprolol. The combination of ivabradine with metoprolol decreased mean HR from 80.8 ± 9.6 bpm at the first visit to 68.4 ± 7.2 bpm at the second visit and 64.2 ± 6.2 bpm at the third (*P* < 0.001). The percentage of patients with HR >80 bpm decreased from 41.5% at the first visit to almost 4% at the second and almost 1.5% at the third. In contrast, the percentage of patients with HR <70 bpm increased from 13.5% at the first visit to almost 70% at the second visit and 90% at the third (*P* < 0.001). Patients

with higher baseline HR showed greater HR reduction. Specifically, patients with a baseline HR >80 bpm, 70 to 80 bpm, and <70 bpm presented an average HR decrease of 22.8 bpm, 13.7 bpm, and 7.7 bpm, respectively (*P* < 0.001; Figure 1).

The combination of ivabradine with metoprolol significantly reduced angina events and use of nitroglycerin. The mean number of angina attacks decreased from 2.0 ± 2.0 /week at the first visit to 0.5 ± 0.9 /week at the second and 0.2 ± 0.6 /week at the third (average decrease at the third visit compared with the first = 1.8 attacks/week; *P* < 0.001; Figure 2). The reduction of angina events led to a significant reduction in the number of times nitroglycerin was used from 1.4 ± 1.9 /week at the first visit to 0.3 ± 0.6 /week at the second and 0.1 ± 0.4 /week at the third (average decrease at the third visit compared with the first = 1.3/week; *P* < 0.001; Figure 2).

The percentage of patients with angina CCS classes III or IV decreased from 15.4% at the first visit to 1.9% at the third, whereas the percentage of patients with angina CCS class I increased from 41.7% at the first visit to 84.6% at the third (*P* < 0.001; Figure 3).

The ivabradine and metoprolol combination improved all dimensions of the EQ-5D questionnaire, as the percentage of patients who answered "No problem"/"Not at all" increased substantially at study completion compared with baseline, whereas the VAS score increased by 14.7 points (*P* < 0.001). Specifically, this combination increased the percentage of patients with "no mobility problem" by 24.4% (155 more patients), who were "autonomous in self-care" by 9.9% (63 patients), with "no problem in usual activities" by 24.1% (153 patients), with no pain/discomfort by 54.3% (345 more patients), and with no stress/distress by 18.7% (119 patients; *P* < 0.001).

Adherence to treatment was high; 623 patients (98% of the patients who attended visits 2 and 3) were taking their treatment "every day" or "quite often" throughout the trial.

TABLE 1 Baseline Characteristics and Frequency of Deviations Determining Cardiovascular Risk

Male sex	70.1
Age, y	66.5 ± 10.7
BMI, kg/m ²	28.4 ± 3.8
Resting HR, bpm	80.8 ± 9.6
Systolic BP, mm Hg	136.0 ± 14.0
Diastolic BP, mm Hg	81.0 ± 8.8
Smoking	32.5
Hypercholesterolemia	74.2
HTN	71.2
DM	28.1
Previous MI	35.1
PVD	13.7
Depression	12.9
LV systolic dysfunction	9.4
Cerebrovascular disease or carotid disease	6.4
Renal failure (sCr >2 mg/dL)	1.3
COPD	6.4

Abbreviations: BP, blood pressure; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; HR, heart rate; HTN, hypertension; LV, left ventricular; MI, myocardial infarction; PVD, peripheral vascular disease; sCr, serum creatinine; SD, standard deviation.

Data are presented as % or mean $\pm$ SD.

4 | DISCUSSION

Several studies have shown that combination of different antianginal drugs is more effective than monotherapy in controlling symptoms.^{10,11} Metoprolol is a β -blocker widely used in everyday clinical practice and especially in patients with stable angina.

In the present study, the combination of ivabradine with metoprolol resulted in a significant decrease in HR. Heart rate reduction in patients with stable angina is mandatory, because increased HR is associated with increased myocardial O₂ consumption and ischemia. Mean HR at baseline was approximately 81 bpm despite the use of metoprolol. This phenomenon has also been observed in several studies and registries where HR remains high despite the widespread use of β -blockers.^{1,12} In the European Heart Survey,¹² a prospective observational study that enrolled 3779 patients with stable angina, mean baseline resting HR was 73 bpm and 52.3% of patients had a baseline HR >70 bpm despite the use of β -blockers. Also in this study, mean HR was increased despite the fact that at the first visit 48.8% and 5.2% of the patients were receiving >50% or 100% of the metoprolol target dose, respectively. The suboptimal dose of β -blockers observed in all these studies may be explained because of

TABLE 2 Ivabradine and Metoprolol Dosage at Each Study Visit

Ivabradine Dosage, mg	Visit 1		Visit 2		Visit 3	
	N	%	N	%	N	%
5	16	2.5	5	0.8	5	0.8
7.5	4	0.6	4	0.6	1	0.2
10	567	89.2	296	47.4	262	42.3
15	49	7.7	320	51.2	352	56.8
Total	636	100.0	625	100.0	620	100.0
Ivabradine Dosage, mg	Mean	SD	Mean	SD	Mean	SD
	10.2	1.6	12.5	2.6	12.8	2.6
Metoprolol Dosage, mg	N	%	N	%	N	%
	50	263	279	43.9	303	47.6
75	30	4.7	27	4.2	28	4.4
100	281	44.2	280	44.0	257	40.4
125	3	0.5	1	0.2	2	0.3
150	26	4.1	23	3.6	22	3.5
200	31	4.9	23	3.6	23	3.6
250	0	0.0	1	0.2	0	0.0
300	2	0.3	2	0.3	1	0.2
Total	636	100.0	636	100.0	636	100.0
Metoprolol Dosage, mg	Mean	SD	Mean	SD	Mean	SD
	85.8	39.8	83.3	38.2	80.8	37.0

Abbreviations: SD, standard deviation.

the poor safety and adverse effects frequently encountered with β -blockers, such as dizziness, fatigue, sexual dysfunction, and hypotension,¹³ or as a result of physicians' reservations in the case of existing comorbidities.¹⁴ Thus, in everyday clinical practice lower doses of β -blockers are used.^{12,14} Adding ivabradine to a β -blocker, such as metoprolol in this case, can overcome all the above-mentioned restrictions and decrease HR adequately.

The combination of ivabradine with metoprolol resulted in significant decreases in angina attacks and in use of nitroglycerin, and it significantly improved the CCS angina class. These findings are in line with several other studies assessing the effect of ivabradine on angina in patients with stable CAD.¹⁻⁵ This was mainly related to HR reduction, however the ivabradine-metoprolol combination seems also to have other properties beyond HR decrease. In experimental models, the administration of ivabradine or metoprolol increases capillary density and improves cardiac angiogenesis in the myocardium

after an infarction.¹⁵ 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 HR reduction.¹⁶

Ivabradine on top of metoprolol led to a significant improvement in QoL, improving the VAS scale score by 14.7 points. Similar results

FIGURE 1 Heart rate at rest; difference between the first and third study visits (N = 636). Abbreviations: bpm, beats per minute. **FIGURE 2** Number of (A) anginal attacks and (B) consumption of short-acting nitrates/mean $\pm$ SD at the third visit of the study (N = 636). Abbreviations: SD, standard deviation.

FIGURE 3 Angina classification according to the Canadian Cardiovascular Society (% of patients) at first and third visits (N = 636).

were obtained in another study assessing the combination of ivabradine with metoprolol where VAS scale score was improved by 14.1 points.¹⁷ Adding ivabradine to the treatment plan improved all treadmill exercise tolerance test criteria and by restoring a satisfactory level of usual activities also improved QoL in those patients.^{1–5} However, not all antianginal drugs improve QoL in such patients. β -Blockers failed to improve QoL when compared with placebo in patients with stable angina,^{18,19} whereas in the Angina Prognosis Study in Stockholm (APSYS)¹⁸ 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.

Compliance with ivabradine treatment was high. This can be explained by its antianginal efficacy and QoL improvement. Finally, prospective, noninterventional studies provide additional information in conjunction with blinded, placebo-controlled clinical studies, because they add data from routine clinical practice and enroll patients with comorbidities who are usually excluded from clinical trials.²⁰

This analysis suggests that combination of ivabradine with metoprolol may be a very useful strategy of antianginal therapy to reduce angina and improve QoL. In addition, high adherence of this combination could further reinforce its clinical efficacy.

4.1 | Study Limitations

This was a post hoc analysis, and therefore the results should be considered as hypothesis-generating. However, the sample size was relevant and the results are plausible and in line with previous data for ivabradine in a pure anginal population.^{1–5} In addition, this was an observational study. The practices and patients enrolled are therefore representative of daily clinical management in private cardiology practice.

5 | CONCLUSION

Ivabradine combined with metoprolol significantly decreased angina symptoms and use of nitroglycerin in patients with stable angina and

CAD, leading to improved QoL. The benefits observed with this combination explain the high rate of adherence to treatment.

Conflicts of Interest

The authors have no other funding, financial relationships, or conflicts of interest to disclose.

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