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Ivabradine in Combination with Metoprolol Improves Symptoms and Quality of Life in Patients with Stable Angina Pectoris: A post hoc Analysis from the ADDITIONS Trial

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Key Words
Ivabradine · Metoprolol · Angina pectoris · Quality of life · ADDITIONS trial

Abstract
Objectives: Elevated heart rate can increase myocardial oxygen demand and reduce myocardial perfusion, provoking myocardial ischemia and angina symptoms. We evaluated adding ivabradine to the therapy of patients on metoprolol. ***Methods:*** ADDITIONS (prActical Daily efficacy anD safety of Procoralan® In combinaTION with betablockerS) was a multicenter, 4-month, noninterventional, prospective, open-label trial that involved stable-angina patients. Along with metoprolol, patients received ivabradine (5 or 7.5 mg, b.i.d.). We investigated the effect of ivabradine on heart rate, angina attacks, nitrate consumption, quality of life (QoL) and tolerability as well as the influence of baseline heart rate. ***Results:*** Heart rate fell by 19.7 ± 11.2 bpm, with an 8-fold decrease in weekly angina attacks (1.7 ± 2.2 to 0.2 ± 0.7) and nitrate consumption (2.4 ± 3.4 to 0.3 ± 0.9). Patient numbers in Canadian Cardiovascular Society class I more than doubled (i.e. from 29 to 65%) and QoL improved (the EQ-5D index and visual analog scale scores rose from 0.68 ± 0.27 to 0.84 ± 0.20 and 58.1 ± 18.4 to 72.2 ± 15.5 mm, respectively). The effect of ivabradine was greater in patients with a baseline heart rate ≥70 bpm (mean reduction in heart rate –21.2 ± 10.4 bpm, with a relative reduction in angina attacks and short-acting nitrate consumption of 87.1 and 87.2%, respectively). ***Conclusions:*** Ivabradine combined with metoprolol safely and effectively reduces heart rate, angina attacks and nitrate use, and improves QoL in stable-angina patients.

Introduction

Angina pectoris affects 112 million people globally and is associated with a lower quality of life (QoL) and a poor prognosis [1–6]. An elevated heart rate can affect the myocardial oxygen equilibrium by increasing myocardial oxygen demand as well as reducing myocardial perfusion time due to the shortening of diastole. This imbalance can lead to myocardial ischemia, which in turn can trigger angina symptoms [7]. Symptoms of angina are associated with lower QoL and limiting physical functioning [8]. Reducing a high heart rate is therefore important when treating patients with stable angina and coronary artery disease (CAD) [9, 10].

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Beta-blockers reduce myocardial ischemia by decreasing heart rate, resulting in the prevention of angina symptoms [7, 11]. Ivabradine selectively inhibits the funny current (I_f), which reduces heart rate, leading to a decrease in myocardial oxygen demand while increasing both coronary filling time and blood flow, protecting against ischemia and angina symptoms [7, 12–14]. As a result, ivabradine is effective in the treatment of symptomatic angina [15, 16]. Combining ivabradine with a beta-blocker has been shown to further reduce the heart rate of patients with stable angina along with myocardial ischemia and the symptoms of angina [17, 18].

The ADDITIONS (prActical Daily efficacy anD safety of Procoralan® In combinaTION with betablockerS) trial evaluated the effect of adding ivabradine to the therapy of patients who had stable angina and were already being treated with a beta-blocker [18]. The results showed that a combined ivabradine and beta-blocker therapy effectively reduced heart rate, the frequency of angina attacks and nitrate consumption as well as improving the QoL of patients. We examined the effect of adding ivabradine to the therapy of patients in a subgroup of ADDITIONS who took metoprolol [18], the most commonly used beta-blocker (43%).

Methods

Study Design

ADDITIONS was a multicenter, noninterventional, prospective, open-label trial conducted over a 4-month period. Details of the methods can be found in Werdan et al. [18]. A total of 2,330 patients with stable angina pectoris were included in 818 centers in Germany. At each visit, the investigators, who included general practitioners, physicians specialized in internal medicine or cardiologists in private practice, completed a standardized questionnaire.

Patients were only eligible for inclusion if they had symptomatic chronic stable angina pectoris, were on beta-blocker therapy and had a resting heart rate >60 bpm. Two further reasons for eligibility were: if their angina pectoris was insufficiently controlled by beta-blocker alone or if they were treated with a different but insufficiently effective antianginal medication or one to which they were intolerant, leading to a change in treatment. Patients were only eligible for inclusion if they had given their written informed consent and met the inclusion criteria. Ivabradine treatment was initiated at 5 mg b.i.d. However, after a 4-week period, the dose could be increased to a dose of 7.5 mg b.i.d., at the discretion of the investigator. For patients with a resting heart rate <50 bpm at follow-up visits or for those aged ≥75 years, the investigator had the option of prescribing a lower dose of 2.5 mg b.i.d. The physician was at liberty to change the ivabradine dose, if deemed necessary, at any point during the trial.

This noninterventional trial was carried out in agreement with the ethical guidelines of the European Independent Ethics Committee and in accordance with the Declaration of Helsinki. The ethical commission of Martin-Luther-University Halle-Wittenberg granted ethical approval for this trial. The ADDITIONS study is registered at www.controlled-trials.com (No. ISRCTN53233058).

Clinical Examinations

In this trial, there were 3 programmed visits: the first at baseline, and the second and third at around 1 and 4 months after baseline, respectively. The general medical and cardiovascular history of the patients, including previous myocardial infarction (MI) and revascularization using percutaneous coronary intervention, was recorded at baseline along with cardiac risk factors, concomitant diseases and medication. At baseline and after 1 and 4 months, the patient's heart rate, the incidence of angina attacks and the frequency of use of short-acting nitrates (within the previous week for both parameters) were recorded. At each visit, the QoL of patients was also evaluated by means of an EQ-5D questionnaire (single scores summarized using the EQ-5D index score) [19]. Safety data such as reasons for discontinuing ivabradine, changes in concomitant medication and suspected adverse drug reactions were recorded at 1 and 4 months. Treating physicians also evaluated patients' tolerance to ivabradine which could be categorized as 'very good', 'good', 'moderate' or 'poor'. As the trial was noninterventional, the participating physicians were permitted to instigate any intervention they considered appropriate for the individual patient.

Analysis

In our post hoc study, we analyzed a subgroup of patients taking ivabradine in combination with metoprolol with documented doses of ivabradine and metoprolol at baseline and the 4-month visits. The effect of ivabradine on heart rate and its impact upon the incidence of angina attacks, the frequency of use of short-acting nitrates, angina classification according to Canadian Cardiovascular Society (CCS) class and QoL using the EQ-5D index and visual analog scale (VAS) score were evaluated. The population was further divided into 2 subgroups according to baseline heart rate – those with a heart rate of <70 versus ≥70 bpm for the analysis of the effect of ivabradine. The mean daily dose of ivabradine was also reported.

Safety

All suspected adverse drug reactions were spontaneously reported by both patient and physician, recorded during the visit and coded using MedDRA (Medical Dictionary for Regulatory Activities). Any reasons for discontinuing ivabradine were also recorded.

Statistics

Data were analyzed using SAS® software v9.1 (SAS Institute Inc., Cary, N.C., USA). Absolute and relative changes between baseline and at each visit were calculated for the heart rate, number of angina attacks, consumption of short-acting nitrates and EQ-5D score. All changes were described using the arithmetic mean and the standard deviation was calculated. Wilcoxon's signed rank test and the χ^2 test were used to assess absolute changes between baseline and follow-up visits. p values should be interpreted descriptively.

Table 1. Baseline characteristics of 877 patients treated with metoprolol

Characteristics	
Demographics	
Age, years	65.5±10.9
Male sex	538 (62)
Body mass index	28.5±4.6
Medical history	
Previous MI	346 (40)
Previous revascularization	523 (60)
Hypertension	780 (89)
Dyslipidemia	602 (69)
Diabetes mellitus	296 (34)
Chronic obstructive pulmonary disease	99 (11)
Peripheral artery disease	64 (7)
Clinical findings	
Heart rate, bpm	84.9±12.0
Number of angina attacks per week	1.7±2.2
Use of short-acting nitrates per week	2.4±3.4
CCS[a]	
Class I	233 (29)
Class II	406 (51)
Class III	148 (19)
Class IV	11 (1)
Medication	
Metoprolol	877 (100)
Calcium-channel blockers	150 (17)
Long-acting nitrates	131 (15)
Molsidomine	84 (10)
Angiotensin-converting enzyme inhibitors	494 (56)
Angiotensin II receptor antagonists	221 (25)
Statins	668 (76)
Aspirin	707 (81)
Clopidogrel	159 (18)
Diuretics	319 (36)
Aldosterone antagonists	38 (4)
QoL	
EQ-5D index score	0.68±0.27
EQ-5D VAS score	58.1±18.4

Values are means ± SD or n (%).
[a] Data available for 798 patients.

Table 2. Daily dosage of metoprolol to 877 patients at baseline and at 4 months

Metoprolol daily dosage	At baseline	At 4 months
47.5 mg	83 (10)	107 (12)
50 mg	91 (10)	110 (13)
95 mg	216 (25)	199 (23)
100 mg	230 (26)	227 (26)
190 mg	65 (7)	61 (7)
200 mg	105 (12)	87 (10)
Others	87 (10)	86 (10)

Values are expressed as n (%).

Results

Baseline

Of the 2,330 patients who took part in the ADDITIONS trial, 877 were taking metoprolol at baseline and at the 4-month visit and were included in this post hoc analysis. The average age of this predominantly male group of patients (62%) was 65.5 ± 10.9 years (table 1). The mean length of time for which patients were diagnosed with angina was 47.0 ± 51.9 months. Patients had a mean resting heart rate of 84.9 ± 12.0 bpm. A high proportion of them had hypertension (89%) and dyslipidemia (69%). Many had been revascularized (60%) and had experienced MI (40%). Left-ventricular ejection fraction was well preserved in this study cohort with a mean value of 56%. Chronic obstructive pulmonary disease and peripheral artery disease were also reported in 11 and 7% of patients, respectively. On average, patients experienced 1.7 ± 2.2 angina attacks per week and used short-acting nitrates 2.4 ± 3.4 times per week. Half of the patients (51%) were CCS class II, 29% class I and 20% class III/IV. Over four fifths of the patients (81%) were taking aspirin while two thirds (76%) were taking statins. Angiotensin-converting enzyme inhibitors and diuretics were being taken by 56 and 36% of the patients, respectively. The mean EQ-5D index and VAS scores were 0.68 ± 0.27 and 58.1 ± 18.4, respectively.

Metoprolol and Ivabradine Dose

All of the patients included in this post hoc analysis were taking documented doses of metoprolol at baseline and at 4 months (table 2). The mean daily metoprolol dose taken by patients remained fairly stable over the 4-month trial, dropping slightly from 107.9 ± 50.3 mg/day at baseline to 102.5 ± 49.9 mg/day by month 4. The mean daily dose of ivabradine taken by patients rose from 9.6 mg/day at baseline to 12.6 mg/day at month 1 after which there was no change in dose. One patient (0.1%) was treated with the maximum dose of ivabradine (15 mg/day) at baseline, and this number increased to 482 patients (55.3%) at study end. At baseline, just over half

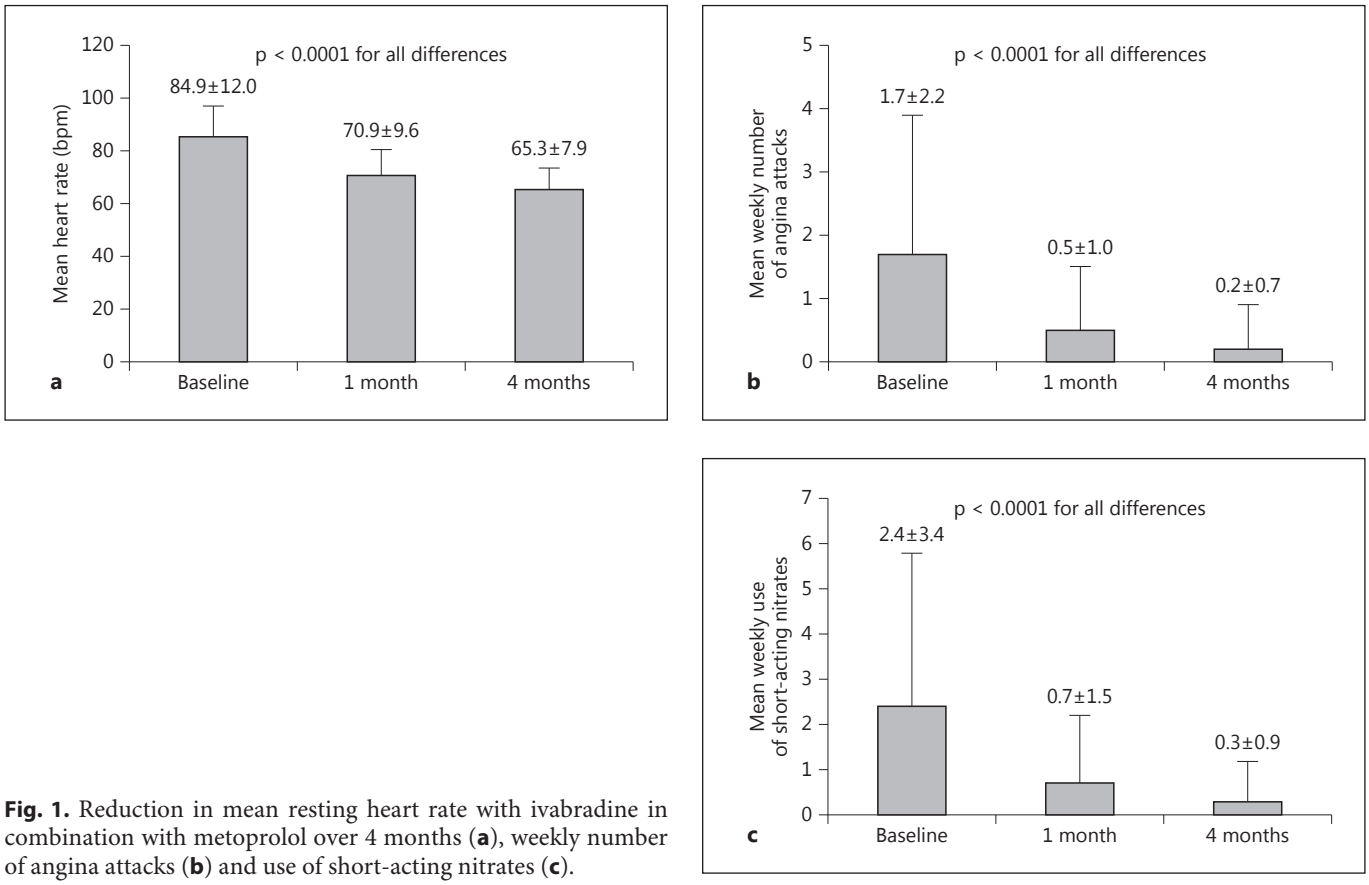

Fig. 1. Reduction in mean resting heart rate with ivabradine in combination with metoprolol over 4 months (**a**), weekly number of angina attacks (**b**) and use of short-acting nitrates (**c**).

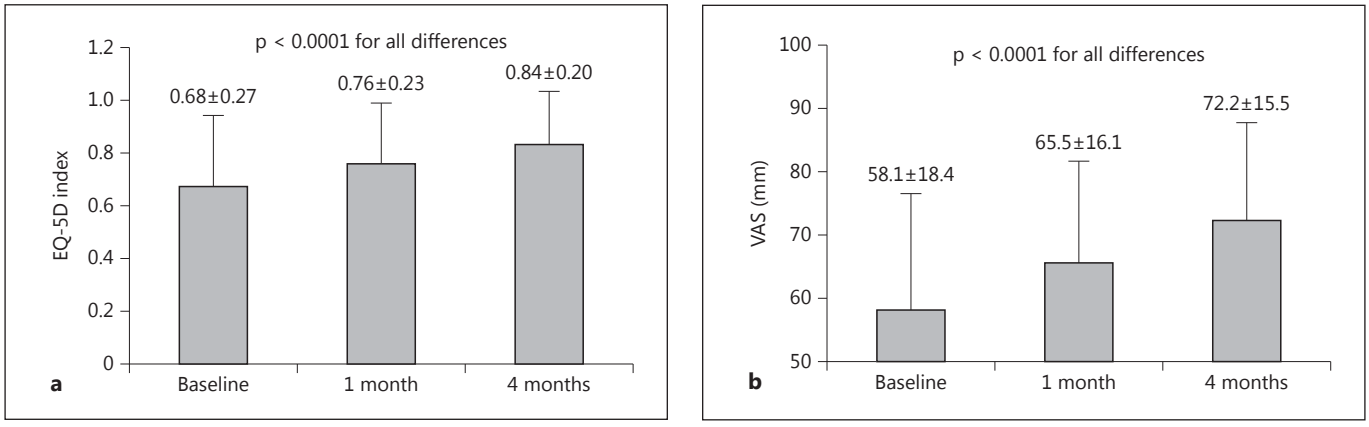

Fig. 2. Quality of life EQ-5D index (**a**) and VAS (**b**) scores.

(51%) of the patients were taking a daily dose of metoprolol of either 95 or 100 mg/day, and this dropped slightly to 49% by month 4. At baseline and at month 4, the majority of patients (71 and 74%, respectively) were taking a daily dose of metoprolol of ≤100 mg/day (table 2).

Effect of Ivabradine

Mean heart rate fell by 19.7 ± 11.2 bpm between baseline and month 4, i.e. from 84.9 ± 12.0 to 65.3 ± 7.9 bpm. After 4 months of treatment with metoprolol and ivabradine, 30.3% of patients reached a heart rate of 55–60

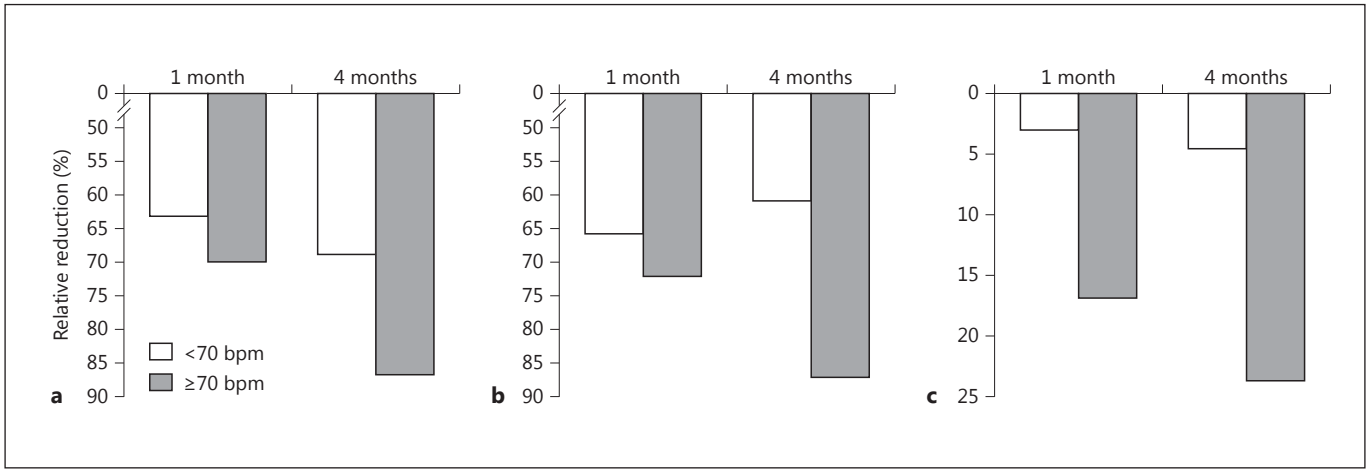

Fig. 3. Relative reduction in the number of angina attacks (**a**) and use of short-acting nitrates per week (**b**) and the heart rate (**c**) in stable-angina patients on metoprolol and ivabradine, compared to baseline values and stratified by baseline heart rate <70 and ≥70 bpm.

bpm. The mean number of weekly angina attacks decreased 8-fold from 1.7 ± 2.2 at baseline to 0.2 ± 0.7 by month 4 (fig. 1). This decrease was accompanied by a decrease in the weekly consumption of short-acting nitrates by patients, which fell during the 4-month period from 2.4 ± 3.4 to 0.3 ± 0.9 per week. At baseline, just under a third of patients (29%) were classified as CCS class I. The number of CCS class I patients more than doubled by month 4, leaving the majority (65%) of patients in this class. The proportion of patients in CCS class II fell from 51% at baseline to 32% by month 4. There was a notable decrease, between baseline and month 4, in the proportion of patients who were graded as CCS class III, dropping from 19 to 3%. Patients' QoL, measured using the EQ-5D index and VAS score, improved during this trial. The EQ-5D index score rose from 0.68 ± 0.27 to 0.84 ± 0.20 while the VAS score increased notably from 58.1 ± 18.4 to 72.2 ± 15.5 mm (fig. 2).

The absolute and relative changes in heart rate, along with the frequency of angina attacks and nitrate consumption were evaluated in patients with a baseline heart rate of <70 bpm (n = 86) versus ≥70 bpm (fig. 3). A larger absolute decrease in heart rate was observed in patients with a baseline heart rate of ≥70 bpm (from 87.1 ± 11.1 to 66.0 ± 8.2 bpm in 4 months) than in patients with a baseline heart rate of <70 bpm (from 64.6 ± 4.5 to 61.4 ± 7.2 bpm). These heart rate reductions were associated with larger relative reductions in angina attacks and short-acting nitrate consumption (fig. 3) in patients with a baseline heart rate of ≥70 bpm.

Safety

Of the 989 patients in the safety set, <1% (7 patients) reported 14 adverse drug reactions. The most frequently reported were those relating to eye disorders, affecting 4 patients (e.g. phosphenes and visual impairment), and nervous system disorders, affecting 3 patients (dizziness and headache). Bradycardia was reported in only 1 patient. No serious adverse drug reactions occurred. The tolerability of the metoprolol and ivabradine association was rated as 'very good' or 'good' by >99% of physicians. No deaths or MIs were reported.

Discussion

The combination treatment of ivabradine and metoprolol reduced heart rate, the frequency of angina attacks and nitrate consumption, leading to improved QoL in clinical practice. The above-mentioned effects were particularly pronounced in patients who had a baseline heart rate of ≥70 versus <70 bpm. The combination of ivabradine and metoprolol was also safe and well tolerated by patients.

The baseline characteristics of the population in the ivabradine and metoprolol subgroup were similar to those of the overall ADDITIONS population. Heart rate, frequency of angina attacks and short-acting nitrate use fell slightly more in the metoprolol subgroup when compared with the overall population [18]. The reduction in heart rate observed in these patients with stable angina

who were treated with ivabradine and concomitant beta-blocker was in line with results previously observed in ASSOCIATE (evaluation of the Antianginal efficacy and Safety of the aSsociation Of the funny Current Inhibitor ivAbradine with a beTa-blockEr) [17] and REDUCTION (Reduction of ischemic Events by reDUCtion of hearT rate In the treatment Of stable aNgina with ivabradine) [20] as well as in the stable CAD population of BEAUTIFUL (morBidity-mortality EvAlUaTion of the If inhibitor ivabradine in patients with coronary disease and left-ventricULar dysfunction) [21, 22].

Ivabradine use was in line with that approved by the European Commission concerning combination therapy for the treatment of angina, which assumes the insufficient efficacy of beta-blockers at maximally tolerated doses [14]. All registries and surveys confirm that beta-blockers are the most frequently prescribed therapy for the treatment of angina. The latest large international prospective CLARIFY registry demonstrated that three quarters of patients with stable CAD receive beta-blockers, but despite this, heart rate is insufficiently controlled in many patients. While beta-blockers are the most frequent drug class prescribed to patients with stable CAD, they are used at low doses [23, 24]. This low dosing might be partly explained by the absence of a recommended target dose of beta-blocker in treating stable CAD patients in contrast with heart failure patients. This could also be due in part to the reluctance of physicians to prescribe high-dose beta-blockers due to tolerability problems [25]. As such, the addition of ivabradine could be an important therapeutic strategy to control heart rate and improve further symptoms and, in particular, QoL [18]. Moreover, combining ivabradine with a medium-dose beta-blocker reduces heart rate and improves the exercise capacity of patients more effectively than increasing the beta-blocker dosage [26, 27].

The ivabradine and metoprolol combination therapy was evaluated by physicians as being well tolerated. In terms of safety, there was a low rate of reported adverse events, with only 1 patient experiencing the presence of phosphenes and only 1 experiencing symptomatic bradycardia with palpitations, although 30.3% of previously uncontrolled patients reached a heart rate of 55–60 bpm. Heart rates within this range are considered desirable in the treatment of stable angina by current European [9] and US guidelines [10]. All adverse events were spontaneously reported by the treating physicians, as is required and reflecting the reporting behavior of adverse events in routine daily practice.

As the combination of ivabradine and metoprolol was effective and well-tolerated, a fixed-dose combination of these 2 drugs could prove beneficial in terms of adherence to treatment, which could further improve the antianginal effects of this combination therapy. In a meta-analysis conducted by Bangalore et al. [28], the use of fixed-dose combination treatments significantly reduced the risk of nonadherence when compared with nonfixed combination regimens, with a decrease in relative risk of between 24 and 26%. Patients taking only 1 drug were also significantly more likely to adhere to treatment than those on multidrug regimens, and treatment was more likely to be effective [29]. Patel et al. [30] similarly demonstrated that, after a year of taking a fixed combination of treatments, adherence was significantly higher when compared with patients taking each treatment separately. Although better adherence can lead to higher treatment costs in the short term, the accompanied increase in effectiveness results in fewer adverse medical events which, in the long term, results in decreased medical costs [31].

Concerning QoL, the improvement observed in this study was in line with results from other studies pertaining to the QoL of angina patients [32, 33]. However, not all studies report an improvement in the QoL of patients treated with antianginal therapy [34, 35] which may suggest it is therapy dependent. This is particularly important, as beta-blockers failed to improve quality of life when compared with placebo, which could be explained by the impact of well-known side effects related to beta-blocker use [35, 36]. Therefore, the combination treatment of metoprolol and ivabradine could be distinctly useful for improving symptoms and QoL in patients who require intensified antianginal therapy but without the negative cardiodepressant effects of higher doses of beta-blockers, e.g. patients who are more active after MI and/or coronary intervention. A significant increase in exercise capacity has already been demonstrated in angina patients with a moderate left-ventricular systolic dysfunction treated with this combination therapy in comparison with high-dose beta-blockers [26]. This is most likely due to the preservation of the exercise-induced increase in coronary blood flow by ivabradine [37] but not higher doses of beta-blockers, due to unmasked alpha-adrenergic vasoconstriction [37, 38].

One of the limitations of this study was its short duration of 4 months. It was also open-label and there was no placebo group with which the observed treatment effect could be compared. Additionally, adherence to treatment was not assessed, even though the observed significant reduction in heart rate implied good adherence. Another

limitation of the study regarding the subcohorts of patients with combination treatment according to baseline heart rate (<70 or ≥70 bpm) is the small number of patients with baseline heart rate <70 bpm (n = 86). However, it is important to note that ivabradine administration should not be commenced in angina patients with a baseline heart rate <70 bpm according to the recent European Medicines Agency recommendations and current European Union indications [14]. This analysis has an inherent focus on the patient cohort with a heart rate ≥70 bpm. Another limitation is related to the pooled analysis of both metoprolol formulations; often, physicians do not seem to discriminate between the succinate and tartrate formulations of metoprolol for angina treatment in daily practice.

The main strength of this study was that it was carried out on a large population of stable-angina patients in over 800 centers in Germany. Furthermore, due to the noninterventional design of the study, it was possible to assess the treatment in routine clinical practice in terms of effectiveness and safety. Patient groups usually excluded from controlled clinical trials (elderly patients with multiple comorbidities) can be covered and evaluated in open-label, noninterventional studies.

Conclusion

Combining ivabradine with metoprolol is a useful option for improving angina symptoms and QoL in patients with stable angina pectoris. A fixed-dose combination of ivabradine and metoprolol could prove beneficial in the treatment of angina.

Acknowledgments

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Conflict of Interest

U. Müller-Werdan and F. Höpfner report no conflicts of interest. K. Werdan, H. Ebelt and S. Nuding are and have been engaged in randomized controlled trials with ivabradine fully or partly supported by Servier (BEAUTIFUL, SHIFT, SIGNIFY, MODIFY and others). Prof. Werdan received honoraria for lectures from Servier, is a member of their German Procoralan Advisory Board and receives research grants from them. Dr. Stöckl is an employee of Servier (Medical Affairs).

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