Effectiveness of Ivabradine Treatment in Different Subpopulations with Stable Angina in Clinical Practice: A Pooled Analysis of Observational Studies

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Key Words

Stable angina pectoris · Subpopulation · Heart rate ·
Ivabradine · Pooled analysis · Clinical practice ·
Observational studies

Abstract

Objectives: The efficacy of ivabradine has been demonstrated in different subpopulations of stable angina patients in randomized clinical trials. This study explored its effectiveness in subpopulations seen in clinical practice as they often differ from those of randomized trials. **Methods:** Data were pooled from three German observational studies with similar inclusion criteria (stable angina and heart rate ≥ 60 bpm). All patients received 2.5, 5, or 7.5 mg b.i.d. of ivabradine for 4 months, with or without concomitant beta-blocker. Anti-anginal effectiveness was analyzed in subpopulations defined by gender, age, heart rate, angina severity, use of concomitant beta-blocker, previous percutaneous coronary intervention procedure, and comorbidities (including previous myocardial infarction and diabetes). **Results:** Treatment data

were available on 8,555 patients, where therapy with ivabradine was associated with a significant reduction in the frequency of angina attacks and consumption of short-acting nitrates of 87%. Effectiveness was maintained in all investigated subpopulations, with a reduction in antianginal parameters of 82–90%. Clinical status (Canadian Cardiovascular Society class) and quality of life were also improved. Ivabradine was well tolerated in all subgroups. **Conclusions:** Ivabradine is effective and safe in all subpopulations of angina patients seen in clinical practice, independent of age, comorbidities, and use of beta-blocker.

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Introduction

Uncontrolled heart rate can induce or worsen myocardial ischemia and angina symptoms by disrupting myocardial oxygen balance [1, 2]. Elevated heart rate increases the demand of myocardial oxygen and at the same time limits oxygen supply to the heart by reducing

the time for diastolic perfusion. Both mechanisms contribute to myocardial ischemia, making heart rate reduction an obvious strategy to prevent oxygen imbalance and improve angina symptoms [3]. Such a strategy can be achieved by using a beta-blocker, which is a well-established treatment to control the heart rate and symptoms in stable angina patients [4]. However, besides their effects on heart rate, beta-blockers have additional properties that can negatively affect cardiac function [3]. Ivabradine, an inhibitor of the I_f pacemaker current, selectively targets the heart rate and, in contrast to beta-blockers, does not reduce myocardial contractility or relaxation [5]. The mechanisms of anti-ischemic and antianginal efficacy of ivabradine were first elucidated in experimental studies [5] and confirmed in recent clinical trials. This includes an increase in myocardial diastolic perfusion time [6], enhancement in coronary flow reserve [7], improvement in endothelial function [8], and enhancement in coronary collateral flow in patients with chronic stable coronary artery disease [9]. This makes ivabradine an important antianginal and anti-ischemic therapeutic strategy.

The anti-ischemic effect of ivabradine had been demonstrated in a range of randomized clinical trials (RCTs) [10–14], supporting its use for the treatment of symptoms in patients with stable angina alone or in combination with a beta-blocker [15]. Moreover, the antianginal efficacy of ivabradine has been established across a variety of subpopulations with diverse comorbidities, as demonstrated by a pooled analysis of five RCTs [16]. However, patients seen in clinical practice often differ from those included in RCTs and may not respond similarly to treatment. The stringent inclusion/exclusion criteria used in RCTs, with the frequent exclusion of elderly patients and patients with comorbidities, usually lead to populations with a lower risk profile compared with real-world settings [17]. Therefore, the question of the effect of ivabradine in patients with stable angina seen in everyday routine practice has been addressed in a range of observational studies, which confirmed both the effectiveness and safety of the drug when assessed in real-life situations [18–20]. The question remains whether this beneficial effect observed in real clinical practice in a broad population still applies to subpopulations with specific characteristics.

The aim of the study described here was to assess the effectiveness and safety of ivabradine in different subpopulations of stable angina patients in clinical practice. This was achieved by pooling the data from three available observational trials: ADDITIONS (Practical Daily Efficacy

and Safety of Procoralan® in Combination with Beta-Blockers) [18], REDUCTION (Reduction of Ischemic Events by Reduction of Heart Rate in the Treatment of Stable Angina with Ivabradine) [19], and RESPONSIfVE (Evaluation of Effectiveness and Therapeutic Response to Ivabradine in Daily Practical Use for Chronic Stable Angina Patients) [20], which led to a population large enough for meaningful subgroup analysis.

Patients and Methods

Participants and Study Design

Data were pooled from three German observational studies: ADDITIONS [18], REDUCTION [19], and RESPONSIfVE [20] (table 1). These were multicenter, open-label, prospective studies including patients with stable angina pectoris in 818, 1,503, and 338 centers in Germany, respectively. The studies were chosen for analysis as they are the only published and large-scale (each >1,000 patients) German observational cohorts for ivabradine use in its angina indication. These cohorts show very similar inclusion and evaluation criteria with detailed documentation and follow-up of patients. This provides a representative picture of treatment practice with ivabradine in Germany from three studies with relatively low heterogeneity. All investigators (general practitioners, internal medicine physicians, or cardiologists in private practice) filled out a standardized clinical questionnaire during the patient's treatment that included the following information: medical history and concomitant medication, heart rate, Canadian Cardiovascular Society (CCS) classification, number of angina attacks, consumption of short-acting nitrates, and quality of life using the EQ-5D index and EQ VAS (visual analog scale) scores. Patients were only eligible for inclusion if they had given their written informed consent. For 47 patients in the REDUCTION study, questionnaires were filled out at the end of the study rather than on an ongoing basis, and those patients were excluded from the original trial report [19]. However, these data can still be considered as valid, and these 47 patients (including 24 patients with available effectiveness data) were included in the present pooled effectiveness and safety analysis. All patients in the RESPONSIfVE trial were included in the pooled analysis, whereas three patients in the ADDITIONS trial with unclear beta-blocker therapy were excluded. All three studies were conducted in accordance with the Declaration of Helsinki and complied with the ethical guidelines of the European Independent Ethics Committee.

The three studies had similar inclusion criteria: patients with a resting heart rate ≥ 60 bpm and in need of symptomatic treatment for stable angina pectoris. The main difference related to the use of beta-blocker therapy: concomitant treatment with beta-blocker was part of the inclusion criteria for the ADDITIONS trial [18], while it was optional for both the REDUCTION and RESPONSIfVE trials [19, 20] (table 1).

The study design was similar in all studies, with three scheduled visits: the first visit performed at baseline and the following two visits after approximately 1 and 4 months of treatment. After the baseline visit, therapy was started with ivabradine 5 mg b.i.d. and could be increased to 7.5 mg b.i.d. after 2–4 weeks. A lower

Table 1. Study design and main effectiveness results of the ADDITIONS, REDUCTION, and RESPONSiVE trials [18–20]

	ADDITIONS	REDUCTION	RESPONSiVE
Design			
Type of study	Observational, prospective, in addition to beta-blocker	Observational, prospective, with contraindication or intolerance to beta-blocker	Observational, prospective, with or without beta-blocker
Patients, n	2,330	4,954	1,250
Duration of ivabradine treatment	4 months	4 months	4 months
Mean dose after 4 months	12.37 mg/day	10.5 mg/day	11.1 mg/day
Main effectiveness results			
Resting heart rate, bpm	–19.4	–12.4	–15.4
Angina attacks/week, n	–1.4	–2.0	–1.1
Use of short-acting nitrates/week, n	–1.9	–2.8	–1.4
CCS classification, % of patients		n.a.	
Class I	Increased from 29 to 68%		Increased from 24 to 66%
Class II or III	Decreased from 70 to 32%		Decreased from 76 to 34%

Main effectiveness results are shown as mean change from baseline after 4 months of ivabradine treatment except for CCS classification. n.a. = Not available.

dose of 2.5 mg b.i.d. could be considered in patients with severe renal dysfunction (creatinine clearance <15 ml/min) or a low resting heart rate (<50 bpm) during treatment, or in the elderly (≥75 years). Follow-up lasted 4 months. Further details of the study designs can be found in the respective publications of the trials [18–20].

Definition of Subpopulations

The pooled data were analyzed in different subpopulations of interest defined according to the following baseline criteria: gender, age (≥75 years), heart rate (≥70 bpm), angina severity (CCS classification), concomitant medication (any beta-blockers or metoprolol), previous percutaneous coronary intervention (PCI), or comorbidities: previous myocardial infarction (MI), diabetes, asthma/chronic obstructive pulmonary disease (COPD), and renal dysfunction. The effectiveness of ivabradine was also assessed in patients with concomitant metoprolol and heart rate ≥70 bpm, closely reflecting the practical application of ivabradine in combination with the most commonly used beta-blocker in the analyzed studies.

Measured Parameters and Statistical Methods

The following parameters were evaluated for effectiveness in the pooled data set: resting heart rate (determined after at least 5 min at rest by manual assessment or ECG recording), number of angina attacks, use of short-acting nitrates, and CCS classification. Quality of life data (EQ-5D index and EQ VAS scores) were only available for the ADDITIONS trial. Absolute and relative changes from baseline were analyzed by a one-sample t test. Changes in CCS classification were analyzed by the signed-rank test. Safety was assessed by analyzing the frequency of adverse events, which were coded with MedDRA version 17.1. All analyses were performed in a descriptive manner using SAS software (version 9.3), without any formal testing of predefined statistical hypotheses.

Results

Characteristics of the Pooled Population

The pooled population used for effectiveness analysis comprised a total of 8,555 patients with available data: 2,327 patients from the ADDITIONS trial, 4,978 patients from the REDUCTION trial, and 1,250 patients from the RESPONSiVE trial.

The baseline characteristics of the pooled population are presented in table 2: mean age was 65.4 years, 41% were female, and 19% were ≥75 years. Half of the population had undergone PCI (49%), and about two fifths (41%) had a history of MI. Hypertension and dyslipidemia were present in the vast majority of patients (91 and 80%, respectively). Diabetes (46%) and asthma/COPD (35%) were frequent, while renal dysfunction was less common (6%). Patients had a mean heart rate of 83.3 bpm at baseline and experienced a mean of 2.1 angina attacks per week. The distribution of CCS classification was 27% for class I, 53% for class II, and 20% for class III + IV.

Concerning angina related-treatments, 40% of patients were receiving a beta-blocker at baseline (predominantly metoprolol: 16%), 19% a calcium antagonist, and 18% a long-acting nitrate. Other concomitant medications were typical of those used in cardiovascular patients: aspirin (77%), statins (64%), and angiotensin-converting enzyme inhibitors (49%).

Concerning quality of life parameters, aged patients (≥75 years) had a lower quality of life at baseline com-

Table 2. Baseline characteristics in the pooled data set

Characteristic (number of patients with data)	Pooled population
Demographic characteristics	
Age (n = 8,525), years	65.4 ± 10.58
≥75 years (n = 8,525)	1,644 (19)
Female sex (n = 8,198)	3,347 (41)
Height (n = 8,329), cm	170.8 ± 8.37
Weight (n = 8,320), kg	81.4 ± 14.30
Medical history	
Previous MI (n = 8,363)	3,405 (41)
Previous PCI (n = 8,387)	4,073 (49)
Hypertension (n = 7,763)	7,091 (91)
Dyslipidemia (n = 7,655)	6,124 (80)
Diabetes mellitus (n = 5,757)	2,619 (46)
Asthma/COPD (n = 8,555)	2,975 (35)
Renal dysfunction (n = 8,555)	483 (6)
Clinical findings	
Heart rate (n = 8,511), bpm	83.3 ± 14.13
Number of angina attacks/week (n = 8,207)	2.1 ± 2.79
Use of short-acting nitrates/week (n = 7,593)	2.8 ± 3.95
Quality of life^a	
EQ-5D index (n = 2,257)	0.66 ± 0.27
EQ VAS scores (n = 2,170)	57.4 ± 18.30
CCS classification (n = 8,091)	
Class I	2,163 (27)
Class II	4,264 (53)
Class III	1,600 (20)
Class IV	64 (<1)
Medication	
Beta-blockers (n = 8,539)	3,413 (40)
Metoprolol (n = 8,555)	1,376 (16)
ACE inhibitors (n = 8,555)	4,205 (49)
Calcium antagonists (n = 8,555)	1,597 (19)
Long-acting nitrates (n = 8,555)	1,518 (18)
Molsidomine (n = 8,555)	1,102 (13)
Aspirin (n = 8,555)	6,569 (77)
Statins (n = 8,555)	5,473 (64)

Values are means ± SD or n (%) of patients. ACE = Angiotensin-converting enzyme.

^a Quality of life was only available for the ADDITIONS trial.

pared with younger patients (EQ-5D: 0.57 ± 0.28 for ≥ 75 years vs. 0.68 ± 0.26 for < 75 years; EQ VAS score: 52.8 ± 17.50 for ≥ 75 years vs. 58.5 ± 18.34 for < 75 years).

Effect of Ivabradine on Heart Rate

Heart rate was reduced from 83.3 ± 14.13 bpm at baseline to 72.7 ± 10.48 bpm after 1 month (12% relative reduction) and to 68.6 ± 9.07 bpm after 4 months of ivabradine treatment (16% relative reduction). Overall, 85% of patients had achieved a heart rate < 70 bpm or a reduc-

tion in heart rate of ≥ 10 bpm after 4 months of treatment (58% with heart rate < 70 bpm and 69% with heart rate reduction of ≥ 10 bpm).

Antianginal Effectiveness of Ivabradine

In the overall population, treatment with ivabradine was associated with a progressive reduction in the mean number of angina attacks per week (from 2.1 ± 2.79 at baseline to 0.7 ± 1.86 and 0.3 ± 1.25 at 1 and 4 months, respectively; fig. 1a). A similar decrease was observed for use of short-acting nitrates per week (from 2.8 ± 3.95 at baseline to 1.0 ± 2.12 and 0.4 ± 1.40 at 1 and 4 months, respectively; fig. 1b). Treatment with ivabradine was also associated with a significant improvement in the clinical status of the overall population assessed by the distribution of CCS class (fig. 1c). The majority of patients shifted to class I at the end of the study treatment (from 27% at baseline to 67% at 4 months), while the proportion of patients in the more severe classes was substantially reduced (class II: from 53% at baseline to 29% at 4 months; class III + IV: from 20% at baseline to 4% at 4 months).

A similar pattern in antianginal effectiveness was observed in patients receiving concomitant metoprolol at baseline (fig. 2). In that subset of patients, the mean number of angina attacks progressively decreased from 1.6 ± 2.20 at baseline to 0.5 ± 1.20 and 0.3 ± 0.91 at 1 and 4 months, respectively. Use of short-acting nitrates was reduced from 2.2 ± 3.26 at baseline to 0.7 ± 1.43 and 0.3 ± 1.08 at 1 and 4 months, respectively. Finally, an improvement in CCS class distribution was noted at the end of the study, with the majority of patients (64%) graded as class I at the last visit (baseline: 26%) and fewer patients as class II (32%) and III + IV (4%; versus 51 and 22%, respectively, at baseline). The effects of ivabradine on angina attacks, nitrate use, and CCS reclassification were comparable for other concomitantly used cardioselective beta-blockers (bisoprolol, carvedilol, and nebivolol).

The antianginal effectiveness of ivabradine in various subpopulations of interest defined by demographic characteristics, heart rate at baseline, angina severity, comorbidities, and concomitant medication, is presented in figure 3. The relative reduction in the number of angina attacks per week at 4 months was consistent among all investigated subgroups, ranging from 82 to 90%, and was comparable to that seen in the overall population (87%). Similar findings were observed for use of short-acting nitrates, with a consistent relative reduction in all subgroups (from 82 to 90%), in line with the overall reduction of 87% in the pooled population.

Fig. 1. Antianginal effectiveness of ivabradine in the overall population. **a** Number of angina attacks/week. **b** Use of short-acting nitrates/week. **c** Distribution of CCS class. Bars are means $\pm$ SD. * $p < 0.0001$ for changes from baseline or CCS class changes.

Fig. 2. Antianginal effectiveness of ivabradine in patients with concomitant metoprolol at baseline. **a** Number of angina attacks/week. **b** Use of short-acting nitrates/week. **c** Distribution of CCS class. Bars are means $\pm$ SD. * $p < 0.0001$ for changes from baseline or CCS class changes.

Quality of life data at 4 months, assessed by the EQ-5D index and VAS scores, are presented in table 3 for the overall ADDITIONS population and subgroups of interest. As previously shown, ivabradine significantly improved quality of life parameters in the whole population

as well as in patients with previous PCI and with concomitant metoprolol medication [18, 21, 22]. Here, we extend the findings to a larger range of patient subgroups, where ivabradine showed consistent improvement in quality of life, using both measurement systems, in all

Fig. 3. Antianginal effectiveness after 4 months of treatment with ivabradine in different subpopulations. Bars are relative changes from baseline (means ± SD). Values shown in bars are absolute changes from baseline (means ± SD). $p < 0.0001$ for all changes.

considered subgroups (absolute changes from baseline ranging from 0.11 ± 0.18 to 0.26 ± 0.28 for EQ-5D index and from 6.3 ± 9.60 to 16.2 ± 16.94 for EQ VAS score; $p < 0.0001$ for all changes).

Beta-blocker treatment was stopped in 1% ($n = 79$) and initiated in 0.4% ($n = 36$) of patients in the total cohort during the study period. Ivabradine was discontinued in 4% ($n = 361$) of patients.

Safety and Tolerability

The pooled population considered for analysis of safety included a total of 8,578 patients: 2,327 patients for the ADDITIONS trial, 5,001 patients for the REDUCTION trial, and 1,250 patients for the RESPONSIVE trial.

Overall, adverse drug reactions were rare (1.2% of patients, $n = 99$) and mainly not serious. Nausea (0.2%, $n =$

15), dizziness (0.2%, $n = 14$), photopsia (0.2%, $n = 13$), and bradycardia (0.1%, $n = 9$) were the most reported reactions. The frequency and type of adverse drug reactions were similar in the overall population and in all analyzed subgroups, including in older (≥ 75 years) versus younger (< 75 years) patients (1.5 vs. 1.1%, respectively).

Discussion

This pooled analysis shows that the antianginal effectiveness of ivabradine is similar across a large range of subpopulations of stable angina patients seen in real-world clinical practice. Our results indicate that ivabradine is associated with a sustained and significant reduction in angina attacks and consumption of short-act-

Table 3. Quality of life after 4 months of treatment with ivabradine in different subpopulations

	EQ-5D index			EQ VAS score		
	n	baseline	change from baseline*	n	baseline	change from baseline*
Overall	2,171	0.66±0.27	0.17±0.23	2,037	57.4±18.30	15.4±15.55
Demographic characteristics and heart rate						
Women	872	0.62±0.28	0.18±0.24	824	55.2±18.21	15.9±15.65
≥75 years	442	0.57±0.28	0.17±0.26	419	52.8±17.50	14.7±15.24
≥70 bpm	1,995	0.66±0.26	0.17±0.23	1,870	57.2±18.23	15.7±15.54
CCS classification						
Class I	578	0.77±0.22	0.11±0.18	565	65.3±17.37	6.3±9.60
Class II	989	0.66±0.23	0.17±0.21	972	57.1±16.81	8.6±10.87
Class III	379	0.49±0.29	0.26±0.28	375	46.1±15.63	11.5±11.60
Medical history						
Previous PCI	1,044	0.67±0.26	0.15±0.22	981	58.7±18.50	14.2±14.97
Previous MI	1,371	0.67±0.26	0.16±0.22	1,284	58.5±18.30	15.1±15.54
Diabetes	726	0.60±0.29	0.19±0.25	687	54.4±18.12	15.9±16.15
Asthma/COPD	419	0.58±0.31	0.18±0.27	392	53.6±18.07	15.8±16.15
Renal dysfunction	162	0.51±0.31	0.21±0.30	150	48.4±16.93	16.2±16.94
Medication						
Any beta-blockers	2,145	0.66±0.27	0.17±0.23	2,012	57.4±18.27	15.3±15.55
Metoprolol	905	0.67±0.27	0.16±0.23	859	57.7±18.25	14.7±15.49
Metoprolol and ≥70 bpm	828	0.68±0.26	0.16±0.22	784	57.5±18.24	15.2±15.43

Values are means ± SD. * $p < 0.0001$ for all changes from baseline.

ing nitrates, and an improvement in CCS class (reflecting exercise tolerance) and quality of life. These results were consistent in all analyzed subgroups, including women, the elderly, patients with a history of PCI or MI, and patients on beta-blockers. In addition, the drug had a good safety and tolerability profile in all considered subgroups.

Compared with pooled randomized trials with ivabradine [16], the patients in our study were older (≥75 years: 19 vs. 4%) and more often women (41 vs. 18%). They also presented with a higher heart rate at baseline (83.3 vs. 73.0 bpm) and more hypertension (91 vs. 59%), dyslipidemia (80 vs. 53%), diabetes (46 vs. 19%), and asthma/COPD (35 vs. 6%). Thus, this pooled analysis complements and extends the demonstration of efficacy and safety of ivabradine in a broader population from that seen in randomized trials [10–14].

Among the subpopulations analyzed, the elderly deserve attention as they represent a growing population of stable angina patients with specific characteristics. Elderly patients are often underrepresented in RCTs [23], and diagnosis of coronary artery disease can be difficult as they can present with atypical symptoms [4]. Aged patients remain challenging to treat because of a higher

prevalence of comorbidities and more frequent side effects or intolerance to drugs [24]. Reduction in angina attacks and consumption of short-acting nitrates has been previously shown in a subgroup of 91 elderly patients with stable angina in a pooled analysis of RCTs [16]. Here, we demonstrated the antianginal effectiveness of ivabradine in a sizeable population of more than 1,600 patients ≥75 years seen in real clinical practice. In addition to the reduction in angina attacks (by 84%) and use of short-acting nitrates (by 82%), ivabradine significantly improved the quality of life in this aged population with impaired health status scores at baseline. Importantly, all these beneficial effects were accompanied by a good safety profile, as ivabradine displayed a similar rate of adverse events compared with younger patients.

Nearly half (46%) of our population had diabetes. Regular physical activity is an important part of the management of diabetes, and this may be impaired by angina [25]. Recent trial data indicate that 82% of patients with coronary artery disease and type 2 diabetes may have angina-related symptoms despite the use of recommended therapies [26]. The need for therapies that effectively reduce symptoms is thus essential. Here, we demonstrated

a significant decrease in the number of angina attacks (by 86%) and use of short-acting nitrates (by 85%) with ivabradine in angina patients with diabetes. Our data are consistent with the improvement in exercise tolerance and the reduction in angina symptoms observed in RCTs with ivabradine in subgroups of patients with angina and diabetes [16, 27]. Diabetic patients often develop cardiac autonomic neuropathy, leading to elevated sympathetic tone and resting tachycardia [28]. Accordingly, in a recent survey, the resting heart rate of stable coronary artery disease patients with diabetes was 5 bpm higher than those without diabetes [29]. As a result, a large proportion of angina patients who have diabetes may be eligible for ivabradine treatment. Another important point to consider is the potential detrimental effects of antianginal therapies, such as beta-blockers and calcium channel blockers, on the glycemic control of diabetic patients [25]. Importantly, ivabradine does not alter glycosylated hemoglobin HbA_{1c} and fasting glucose, whereas atenolol and amlodipine increase levels of both parameters [27]. Our results suggest that ivabradine is a safe and efficient treatment for angina patients with diabetes.

One fifth of patients report symptoms of angina 1 year after an event of acute MI [30]. Moreover, two fifths of patients with stable angina remain symptomatic despite revascularization [31]. In this study, patients with previous MI and PCI accounted for 41% (n = 3,405) and 49% (n = 4,073) of the pooled population, respectively. Ivabradine decreased angina symptoms to the same extent in both subpopulations (angina attacks reduced by 86% and use of short-acting nitrates by 87%), consistent with the results of RCTs [16]. Of note, a recent report indicates that ivabradine can limit episodes of stunning in patients with coronary artery disease [32]. This cardioprotective effect, together with the anti-ischemic properties of ivabradine, could play a significant role in limiting the progression to myocardial hibernation and left ventricular dysfunction commonly observed in patients with a history of MI [33]. In addition, ivabradine was recently shown to improve endothelial function in coronary artery disease patients after PCI [8]. In many patients with ischemic heart disease, microvascular dysfunction is increasingly becoming recognized as an important mechanism of angina, in addition to the more classic obstructive atherosclerosis mechanism [34]. Microvascular dysfunction is particularly prominent in patients with recurrent angina after PCI [35]. By improving endothelial function, ivabradine may contribute to maintaining coronary dilation, hence preventing microvascular dysfunction and the recurrence of angina attacks after coronary intervention.

In addition to the pain and discomfort, angina symptoms impair the quality of life of patients by limiting their ordinary physical activities and altering their psychological well-being. Patients with angina may further reduce their daily activities to prevent the occurrence of angina attacks, thereby contributing to the degradation of their quality of life. Restoration of physical activity and functional capacity are thus a major goal of antianginal therapy. Here, we show that ivabradine significantly improved the distribution of CCS class, with a majority of patients (67%) rated as class I at 4 months. The proportion of patients with activity-limiting angina ($\geq$ class II) decreased from 73 to 33%. Accordingly, this reduction in angina severity was accompanied by an improvement in scores of quality of life, which include assessment of mobility, usual activities, and self-care. This improvement was noted in all analyzed subpopulations, including patients with previous MI or PCI, diabetes, and the elderly. These results indicate that ivabradine effectively improves health status and physical activities in a broad range of angina patients seen in clinical practice.

The incidence of adverse drug reactions, especially bradycardia, was considerably lower in our pooled analysis than in large, randomized outcome trials with ivabradine [36–38]. This might be explained by several factors. The baseline (up to 11 bpm) and achieved heart rate (up to 9 bpm) was higher, and mean daily doses of ivabradine were lower (up to 5 mg/day) in our cohort, which may have contributed to prevent bradycardia and other dose-dependent adverse reactions in general. Furthermore, the use of concomitant cardiovascular medication like beta blockers, ACE inhibitors, statins, and aspirin was considerably less pronounced in our study population, which might have also reduced susceptibility to adverse drug reactions, e.g. by avoidance of potential drug interactions.

In line with its indication, our results confirm the antianginal effectiveness of ivabradine in patients with an elevated heart rate (≥ 70 bpm), with a reduction in angina attacks and use of short-acting nitrates by 87%. Moreover, the drug retained a similar effectiveness when used in combination with a beta-blocker. When focusing on patients with an elevated heart rate despite the use of the most commonly prescribed beta-blocker, metoprolol [4], the number of angina attacks and use of short-acting nitrates were significantly reduced with the addition of ivabradine treatment (by 88 and 87%, respectively). Despite the widespread use of beta-blockers, elevated heart rate persists in many patients and is associated with more frequent angina and ischemia [39]. Thus, the addition of

ivabradine may be considered in all eligible patients with a heart rate ≥ 70 bpm, including those already treated by a beta-blocker, to further reduce the heart rate and improve symptoms of angina.

The main limitation of the present analysis is the lack of control group, which might have biased the results by overestimating the treatment effect. Definitions of comorbidities were not prespecified and were left to the judgment of the physicians. Another limitation may be the short treatment duration of 4 months, which on the other hand was sufficient to evaluate symptomatic effects of ivabradine in several controlled trials [10, 12–14]. Antianginal efficacy and safety have also been shown for a longer period of 12 months in a randomized study [11]. Finally, observational trials can lead to an underestimation of adverse events, as they were spontaneously reported and not specifically sought.

Conclusion

We have shown, based on this short-term data, that ivabradine is an effective and well-tolerated antianginal treatment in a broad range of patients seen in real clinical

practice, including diabetic patients as well as patients with previous MI and/or PCI. Antianginal effectiveness was also maintained in the elderly and in patients with concomitant beta-blockers. In addition, ivabradine improved the quality of life in all analyzed subpopulations.

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Conflict of Interest

K. Werdan has been engaged in ivabradine clinical trials fully or partly supported by Servier, has received honoraria for lectures from Servier, was a member of the German ivabradine advisory board of Servier, and received research grants for experimental and clinical ivabradine research from Servier. T. Meinertz was a member of the German ivabradine advisory board of Servier. S. Perings, R. Köster, M. Kelm, and U. Müller-Werdan report no conflicts of interest. G. Stöckl is an employee of Servier (Medical Affairs). This pooled analysis was funded by Servier.

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