Journal of Clinical & Experimental Cardiology
ISSN: 2155-9880

Diedrichs et al., J Clin Exp Cardiolog 2015, 6:12
DOI: 10.4172/2155-9880.1000412

Case Report Open Access

# Application of Ranolazine in Stable Angina Pectoris Therapy (ARETHA): Real-World Data from an Observational Study

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**Received date:** Nov 10, 2015; **Accepted date:** Dec 19, 2015; **Published date:** Dec 29, 2015



## Abstract

### Objective

Ranolazine, a late sodium current inhibitor, is indicated in adults as add-on therapy for the symptomatic treatment of patients with stable angina pectoris who are inadequately controlled or intolerant to first-line anti-ischaemic therapies. This study was conducted to assess the use of ranolazine as well as its safety and efficacy in patients with stable angina pectoris from different causes in a real world scenario.

### Methods

Patients with stable angina pectoris (AP) receiving ranolazine were enrolled in this non-interventional study. Data were documented at baseline and after 3 months of ranolazine treatment. Endpoints included changes in the number of AP attacks per week, frequency of using short-acting nitrates, current status of the CCS classification, overall estimate of quality of life assessed by both, the physician and the patient, and safety.

### Results

In total, 1,537 patients were eligible for efficacy evaluation. After 3 months, the mean (±SD) number of AP episodes per week significantly decreased from 4.4 ± 4.0 at baseline to 1.1 ± 1.8 ($p<0.0001$), and the weekly use of short-acting nitrates was significantly reduced from 3.4 ± 3.4 to 0.8 ± 1.5 ($p<0.0001$). Improvement occurred independent of diagnosed coronary heart disease (CHD). The CCS classification improved in 69.0% of patients and remained stable in 27.1%. Quality of life, assessed on a numerical analogue scale by physicians and patients, improved significantly by 43.7% and 44.9%, respectively ($p<0.0001$). Safety analysis was based on 2,726 patients. A total of 63 adverse drug reactions (ADRs) occurred in 37 patients (1.4%) and led to discontinuation in 34 patients (1.2%). By the end of the observation period, all ADRs were resolved or resolving.

### Conclusion

The adjuvant therapy with ranolazine is an effective treatment option with a positive benefit-risk balance for patients with angina pectoris of different causes, e.g. small vessel disease, endothelial dysfunction, including those without prior CHD diagnosis.

**Keywords** Ranolazine, angina pectoris, coronary heart disease, chronic ischaemic heart disease, small vessel disease, ischaemia, short-acting nitrates

## Introduction

Stable angina pectoris is a common manifestation of chronic ischaemic heart disease (CIHD). The pharmacologic management of CIHD aims at relieving ischaemic symptoms and preventing cardiovascular events [1]. First-line treatment of angina pectoris includes a short-acting nitrate for chest pain relief as well as beta-blockers and calcium-channel inhibitors for controlling heart rate and symptoms [1]. However, despite treatment with these agents and/or revascularisation, many patients remain symptomatic [2]. In order to meet the need for a drug with an anti-ischaemic mechanism complementary and therefore potentially additive to those of the existing agents, international guidelines recently included the inhibitor of the late sodium current ranolazine as second-line treatment [1,2,4]. Ranolazine is indicated in adults as add-on therapy for the symptomatic treatment of patients with stable angina pectoris who are inadequately controlled or intolerant to first-line anti-anginal therapies.

The approval of ranolazine in the EU (2008) and the US (2006) was based on efficacy and safety data obtained in four randomised controlled trials [5-8]. A cross-over study with 191 chronic angina patients demonstrated that ranolazine monotherapy was well tolerated and significantly increased exercise performance as well as delayed onset of angina compared to placebo [5]. The double-blind phase III study CARISA (combination assessment of ranolazine in stable angina) investigated the use of ranolazine in combination with atenolol, amlodipine, or diltiazem in 823 patients with stable angina. Rates of angina frequency and nitroglycerin use were significantly lower with ranolazine compared to placebo [6]. The ERICA (efficacy of ranolazine in chronic angina) trial confirmed the observed reductions in angina frequency and nitroglycerin use also for patients with persisting symptoms despite maximum recommended doses of amlodipine [7]. The MERLIN-TIMI 36 trial was launched to determine the efficacy and safety of ranolazine during long-term treatment of patients with non-ST-elevation acute coronary syndromes (ACS). While treatment with ranolazine was not inferior to placebo with regards to the incidence of the composite primary endpoint (cardiovascular death, myocardial infarction or recurrent ischaemia), patients receiving ranolazine were significantly less likely to experience recurrent ischaemia compared to those receiving placebo [8]. Furthermore, in a predefined subgroup analysis which had been conducted among 3,565 patients with a medical history of stable angina pectoris, the composite primary endpoint occurred significantly less frequently in patients taking ranolazine than among those taking placebo [9].

In addition to the evidence gained from controlled clinical trials, the EMA and FDA strongly suggest the collection of real life data in order to confirm safety and efficacy of an agent under routine conditions. For this purpose, the non-interventional observational study ARETHA (use of ranolazine in stable angina pectoris therapy) was designed. ARETHA was conducted to assess the use of ranolazine as well as its safety and efficacy in patients with stable angina pectoris from different causes in a real world scenario. In accordance with the risk management plan, educational material regarding the prevention of adverse drug interactions was provided for patients receiving ranolazine.

## Methods

### Study design

The use of ranolazine in daily practice as well as its efficacy and safety under daily routine conditions in patients with stable angina pectoris was evaluated in an open, non-controlled, non-interventional, prospective longitudinal study conducted at 790 centres in Germany between September 2012 and May 2013. Observation time per patient was approximately 3 months. Safety and efficacy data were assessed at baseline and after 3 months, respectively. Patients were free to withdraw from the study at any time and for any reason. The appointment of the follow-up visit was based on the physician's decision with no patient being summoned exclusively for study purposes.

This non-interventional observational study (according to §4 (23) AMG [Medicinal Products Act]) was conducted in accordance with the joint recommendations for the planning, conducting and analysing of observational studies from the Federal Institute for Drugs and Medical Devices (BfArM) and the Paul Ehrlich Institute (PEI) (edition of July 7, 2010). This study was reviewed and approved by the ethics committee of the J. W. Goethe University Hospital Frankfurt. No diagnostic or therapeutic measures, exceeding the already necessary scope were required and treatment routine was not altered by this non-interventional, observational study. All patients provided their written informed consent prior to entering the study.

### Participants

In total, 2,858 patients with stable angina pectoris with or without concomitant diseases being treated with ranolazine were included in the study. The decision to treat the subject with ranolazine had to be taken previously to study enrolment but not more than 4 weeks before. Physicians performed dosing of ranolazine as outlined in the summary of product characteristics [10]. The recommended initial dose of ranolazine is 375 mg twice daily. After 2-4 weeks, the dose should be titrated to 500 mg twice daily and, according to the patient's response, further titrated to a recommended maximum dose of 750 mg twice daily. Selection of patients was subject of the investigator's discretion. Only those patients were monitored who suffered from stable angina pectoris and were treated with ranolazine for the first time ever. This also included those patients who already received a ranolazine prescription from their cardiologist provided that their therapy did not start earlier than 2 to a maximum of 4 weeks previously and the dosage still equalled the recommended starting dose.

### Variables

The primary effectiveness variables were changes from baseline to approximately 3 months after initiation of ranolazine therapy in the frequency of angina pectoris complaints per week and short-acting nitrate use per week. In line with previous clinical trials [6], an observation period of 3 months was chosen in order to allow sufficient time for dose titration under routine practice conditions. Further effectiveness variables were patients' physical impairment according to the Canadian Cardiovascular Society (CCS) classification (I=no AP in normal activity, II=light impairment in normal activity, III=considerable impairment in everyday activity, IV=AP at lightest physical strain), quality of life (rated by patients as well as by physicians on a numerical analogue scale from 1 for no impairment in everyday life to 10 for severest impairment in everyday life) as well as dose and application frequency of ranolazine. Safety variables were occurrence of adverse drug reactions (ADRs) (incidence, severity, causality and outcome) and discontinuation of ranolazine.

### Statistical analyses

All data analyses were carried out according to a pre-established analysis plan. No formal sample size calculation was performed for this study. No centre-related bias was expected since a mean number of four subjects per centre were included in the study. Data source for this non-interventional study were the investigator's patient records. The collected data were analysed with epidemiological methods, using SAS (SAS Institute Inc., Cary, NC, USA). For continuous variables, statistic parameters including arithmetic mean, standard deviation and range were calculated. Frequency distributions for discrete variables were provided as percentage in relation to the total sample. Free text answers were transferred post hoc into adequate coding schemes and analysed as frequency distribution. Evaluation of parameters regarding the clinical course were performed by intraindividual difference analysis (baseline vs. follow-up visit) using the paired sample t-test to achieve a 95% confidence interval for the difference and a descriptive p-value. All tests were two-sided, and significance was declared at the

0.05 level. Patients with missing data for one or both variables were not imputed. Missing data in any demographic and baseline characteristics as well as in effectiveness endpoints was not substituted. Subgroups of patients with and without confirmed CHD were analysed in addition to the total sample.

## Results

### Patient disposition and baseline characteristics

In total, 2,858 patients from 790 centres were enrolled. However, 132 (4.6%) of these patients did not meet the documentation criteria and were excluded from analysis. Therefore, a total of 2,726 patients (95.4%) were included in the safety analysis set (SAS). Of these, 1,537 patients (53.8%) had valid baseline and follow-up data on angina pectoris events and use of nitrates constituting the full analysis set (FAS). The remaining patients were excluded from the efficacy set due to lack of reliable data regarding angina pectoris events and nitrate use, possibly in consequence of poor recollection.

| Parameter | SAS (n=2,726) | FAS (n=1,537) |
|---|---|---|
| Age, years (mean ± SD) | 70.6 ±10.4 | 71.0 ± 10.2 |
| Gender, n (%) | | |
| Male | 1,706 (62.6%) | 974 (63.4%) |
| Female | 1,013 (37.2%) | 558 (36.3) |
| Missing | 7 (0.3%) | 5 (0.3%) |
| Diagnosis of CHD, n (%) | | |
| Yes | 2,206 (80.9%) | 1,266 (82.4%) |
| No | 287 (10.5%) | 152 (9.9%) |
| Missing | 233 (8.6%) | 119 (7.7%) |
| Revascularisation therapy, n (%) | 1,435 (52.6%) | 826 (53.7%) |
| Stent | 1,234 (52.5%) | 721 (51.2%) |
| Balloon dilatation | 662 (28.2%) | 421 (29.9%) |
| Coronary bypass surgery | 455 (19.4%) | 264 (18.8%) |
| Disease duration, n (%) | | |
| ≤6 months | | 404 (26.3%) |
| >6 to ≤12 months | | 161 (10.5%) |
| >1 to ≤2 years | | 194 (12.6%) |
| >2 to ≤3 years | | 163 (10.6%) |
| >3 to ≤4 years | | 124 (8.1%) |
| >4 to ≤5 years | | 92 (6.0%) |
| >5 years | | 399 (26.0%) |

**Table 1:** Baseline demographics, SAS: Safety analysis set, FAS: Full analysis set

Baseline characteristics are summarised in Table 1. Approximately 80% of the patients had confirmed CHD. About half of the patients received revascularisation therapy. The most frequent procedure was stent followed by balloon dilatation and coronary bypass surgery. Approximately a quarter of patients (27.6% of FAS patients) had more than 5 risk factors (Table 2, FAS). The most frequent risk factors were hypertension (87.1%) and hyperlipidaemia (71.8%) with similar proportions for males and females but with higher proportions for patients with confirmed CHD.

| Parameter | Total (n=1,537) | CHD diagnosed (n=1,266) |
|---|---|---|
| Number of risk factors, n (%) | | |
| 0 | 39 (2.5%) | 27 (2.1%) |
| 1 | 65 (4.2%) | 47 (3.7%) |
| 2 | 146 (9.5%) | 113 (8.9%) |
| 3 | 246 (16.0%) | 191 (15.1%) |
| 4 | 324 (21.1%) | 264 (20.9%) |
| 5 | 293 (19.1%) | 250 (19.7%) |
| >5 | 424 (27.6%) | 374 (29.5%) |
| Cardiovascular risk factors | | |
| Hypertension | 1,338 (87.1%) | 1,115 (88.1%) |
| Hyperlipidaemia | 1,104 (71.8%) | 953 (75.3%) |
| Obesity | 655 (42.6%) | 548 (43.3%) |
| Diabetes mellitus type 2 | 544 (35.4%) | 463 (36.6%) |
| Family predisposition | 504 (32.8%) | 438 (34.6%) |
| Smoker status | | |
| Former smoker | 664 (43.2%) | 551 (43.5%) |
| Smoker | 460 (29.9%) | 376 (29.7%) |
| Stress/psychological tension | | |
| Low | 226 (14.7%) | |
| Moderate | 514 (33.4%) | |
| High | 423 (27.5%) | |
| Very High | 63 (4.1%) | |
| Missing | 311 (20.2%) | |

**Table 2:** Risk factors -FAS. FAS: Full analysis set. Information on CHD status was missing in 119 patients.

### Treatment with ranolazine

The mean (±SD) initial ranolazine dose of the FAS was 763.1 ± 125.2 mg/day. The initial dose was adjusted throughout the study in 735 patients. After a mean period of 35 days, 698 patients were titrated

to a dose of 1,000 mg/d. 115 patients had a second dose adjustment to the recommended maximum dose of 1,500 mg/d. The mean (±SD) period of exposure to ranolazine was 96.4 ± 23.4 and 97.2 ± 22.1 days in the SAS and the FAS, respectively. In accordance with the summary of product characteristics [10], ranolazine was administered as add-on medication to other cardiovascular drugs (Table 3, FAS). The most frequently administered concomitant medications were RAS blockers and beta blockers (70.7%, respectively). About one third of patients (32.7%) received short-acting nitrates. The proportion of patients receiving concomitant medication was significantly higher for those with confirmed CHD.

| Medication | Total (n=1,537) | CHD diagnosed (n=1,266) | CHD not diagnosed (n=152) |
|---|---|---|---|
| RAS blocker | 1,087 (70.7%) | 923 (72.9%) | 77 (50.7%) |
| Beta blocker | 1,086 (70.7%) | 935 (73.9%) | 75 (49.3%) |
| Aggregation inhibitor | 881 (57.3%) | 769 (60.7%) | 44 (28.9%) |
| Nitrate (short-acting) | 502 (32.7%) | 417 (32.9%) | 48 (31.6%) |
| Calcium antagonist | 348 (22.6%) | 287 (22.7%) | 30 (19.7%) |
| Nitrate (long-acting) | 353 (23.0%) | 308 (24.3%) | 20 (13.2%) |

**Table 3:** Concomitant medication –FAS, FAS: Full analysis set. Information on CHD status was missing in 119 patients.

## Efficacy

Over the course of the study there was a significant and clinically relevant reduction in angina pectoris events (Figure 1). For the overall population, the weekly rate of AP events decreased by 74.5% (p<0.0001). Patients with confirmed CHD at baseline reported higher numbers of AP events per week as compared to patients not suffering from CHD (4.5 [95% CI 4.3-4.7] vs. 3.5 [95% CI 3.0-3.9]).

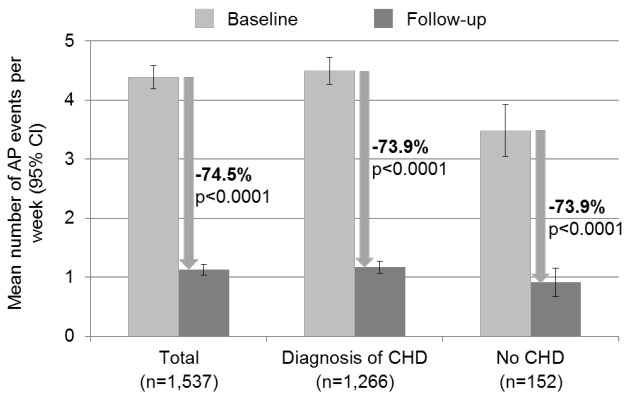


**Figure 1:** Number of AP events at baseline and follow-up visit (FAS). Information on CHD status was missing in 119 patients.

In consistence with the reduction of AP events, the use of short-acting nitrates was significantly less at the 3-months follow-up visit compared to baseline (Figure 2). The number of applications of short-acting nitrates per week correlated with the number of AP events per week. In general, patients with confirmed CHD had a higher frequency of nitrate use per week than patients without CHD diagnosis (3.6 [95% CI 3.4-3.8] vs. 2.2 [95% CI 1.8-2.5]). However, the percentage reduction of nitrate use per week was similar for all patients.

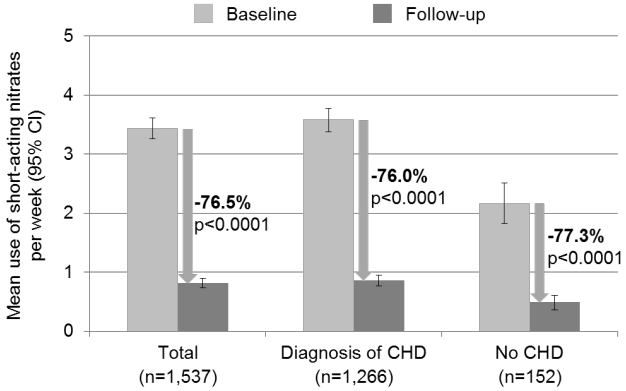


**Figure 2:** Use of short-acting nitrates per week at baseline and follow up visit (FAS). Information on CHD status was missing in 119 patients.

Patient physical impairment as assessed according to the CCS functional classification of angina improved in 69.0% of patients from baseline to the follow-up visit. 57.6% of patients experienced improvement by 1 CCS class, 10.6% by 2 CCS classes, and 0.8% by 3 CCS classes. No change was observed in 27.1%, and 0.7% of patients experienced deterioration. The higher the CCS at baseline, the higher the percentage of patients experiencing improvement (Figure 3).

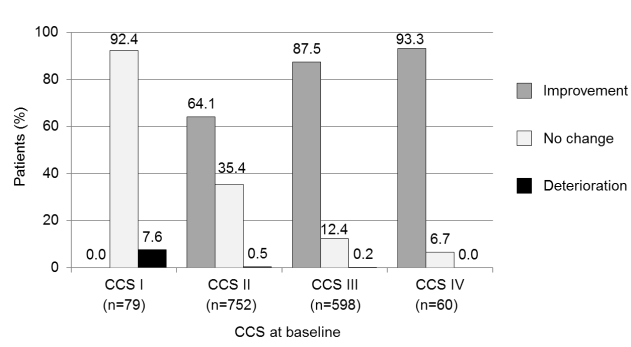


**Figure 3:** Change in CCS classification between baseline and follow-up visit (FAS)

Both, the managing physician and the patient rated the overall quality of life (Figure 4) significantly better at the follow-up visit compared to baseline (p<0.0001). The physician-rated and patient-rated quality of life score improved by 43.7% and 44.9%, respectively. No significant differences were observed for quality of life scores of patients with confirmed CHD compared to patients without confirmed CHD.

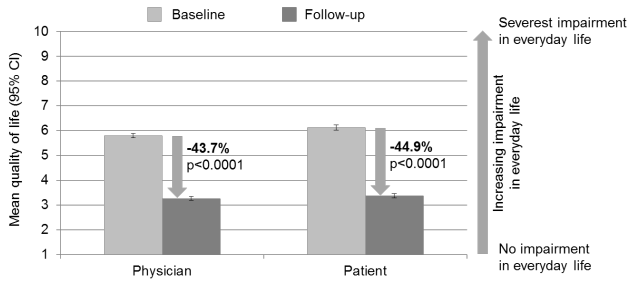


**Figure 4:** Quality of life rated by physician and patient on a numerical analogue scale from 1 for no impairment in everyday life to 10 for severest impairment in everyday life (FAS)

## Safety

In total, 63 adverse drug reactions were reported in 37 patients (1.4% of SAS patients). Of those, one was assessed as serious and the remaining 62 as non-serious. The causality of the serious ADR, neuropathic ulcer, was rated as unlikely and ranolazine was continued. Gastrointestinal disorders (n=25) and nervous system disorders (n=14) were reported most frequently. Severity was either mild (n=43) or moderate (n=16) (n=4 not assessed). At the end of the observation period 61 ADRs were resolved or resolving. For 2 ADRs (abdominal pain and nausea), the outcome was unknown. Ranolazine was discontinued due to ADRs in 34 patients (1.2%).

| System organ class | Frequency |
|---|---|
| Gastrointestinal disorders | 25 |
| Nervous system disorders | 14 |
| General disorders and administration site conditions | 7 |
| Renal and urinary disorders | 4 |
| Eye disorders | 3 |
| Skin and subcutaneous tissue disorders | 3 |
| Ear and labyrinth disorders | 2 |
| Vascular disorders | 2 |
| Cardiac disorders | 1 |
| Investigations | 1 |
| Respiratory, thoracic and mediastinal disorders | 1 |
| Total | 63 |

**Table 4:** Adverse drug reactions-SAS. SAS: Safety analysis set

## Discussion

The present non-interventional study explored the efficacy and safety of ranolazine as well as quality of life in patients with stable angina pectoris using this agent in combination with other drugs in a real world setting. The effectiveness of ranolazine in the reduction of AP events and nitroglycerin use has been demonstrated in various well designed randomized controlled trials [6,7], including the challenging group of patients with diabetes mellitus type 2 [10] which comprise about one third of patients in our study. This was the first study designed to create real-world data on the application of ranolazine under routine practice conditions in Germany.

Significant improvement was achieved in the primary efficacy endpoints AP events per week and use of short-acting nitrates per week. In consistence with previous results from the double-blind phase III study CARISA [6], a reduction of weekly AP episodes as well as consumption of short-acting nitrates per week by approximately 75% was observed over the course of 3 months. Furthermore, patients' physical impairment according to the CCS classification improved for the majority of patients (69%). By analogy to our observation of greater improvement in patients with higher physical impairment at baseline, the authors of the ERICA study reported greater efficacy of ranolazine in patients experiencing more frequent episodes of AP [7]. Quality of life is known to be considerably impaired in AP patients [12]. Consecutively, our study showed a marked increase in quality of life as rated by patients and physicians, in consistence with results from a post-hoc analysis of quality of life data from the MERLIN-TIMI 36 trial [13].

Ranolazine is effective independent of any changes in the heart rate, blood pressure, or vasodilatation. This peculiarity differentiates ranolazine from conventional agents with an anti-ischaemic effect and may be explained by its mechanism of action: The anti-ischaemic effect of ranolazine is based on the inhibition of the late sodium current in the cardiac cells, which reduces the intracellular sodium overload and, subsequently, also the calcium overload in the cardiomyocytes [14]. Thus, ranolazine is capable of counteracting the intracellular ion imbalance of ischaemia by improving the myocardial relaxation, and consequently minimising diastolic left ventricular stiffness [15]. This results in improved micro-circulation and myocard perfusion as well as subsequent reduction in ischaemic complaints.

Hence, ranolazine is suitable for patients with symptomatic CIHD of various origins. For instance, in patients with microvascular angina pectoris ranolazine treatment over 4 weeks was shown to improve angina symptoms and quality of life significantly [16]. In this context, the current ESC guidelines highlight the efficacy of ranolazine in some patients with microvascular angina [1]. Furthermore, ranolazine treatment over 4 weeks improved angina in women with evidence of myocardial ischaemia but no obstructive CHD [17]. This observation supports the paradigm shift that has recently been recognised in the ESC guidelines [1]: Obstructive CHD is not the only underlying aetiology for AP, suggesting that other aetiologies for AP, such as endothelial dysfunction and microvascular abnormalities, may be more frequent than previously thought [18,19]. This observation is clinically relevant because many clinicians may attribute AP in these patients to non-cardiac reasons only after CHD is excluded invasively. Furthermore, this patient group with AP and documented myocardial ischaemia without obstructive CHD has been associated with a poor outcome in a large-scale clinical register [20]. With the confirmation of the CHD-independent clinical response under routine practice conditions, ranolazine provides a viable novel treatment option for these patients suffering from myocardial ischaemia without prevalent CHD.

Overall, treatment with ranolazine can be considered safe with a low risk of experiencing any ADR. The ADRs reported in this study were consistent with previous findings [5-8, 21] and, therefore, as expected and described in the summary of product characteristics. All

confirmed, probably or possibly treatment-related adverse events were non-serious. The vast majority was categorised as mild or moderate and resolved or improved during the study independently from ranolazine withdrawal.

The study is limited by its non-interventional design. The lack of a control group and allowance of maintaining concomitant anti-anginal medication might be potential confounders in the interpretation of outcome data. Therefore, causality cannot be concluded. However, each subgroup showed significant improvement per se, and the large number of patients receiving ranolazine ensures statistically conclusive data to provide a comprehensive profile of the clinical situation of AP patients in a real-world setting. The concordance of clinical study outcomes with our results underlines the validity of our data assessment.

In conclusion, consistent with results from randomised controlled trials [5-8], our findings support the safe and beneficial effect of ranolazine as adjuvant treatment in patients with angina pectoris with or without prevalent CHD under routine practice conditions. A significant decrease in the frequency of AP episodes and use of short-term nitrates was achieved over 3 months of treatment, whereby the ADRs reported were within the expected range. Improvement in patient physical impairment and in the patient-reported outcome quality of life underlines the positive benefit-risk balance for the patients. Our data demonstrate the importance of treating patients receiving inadequate therapy. In this context, ranolazine is causal treatment acting at the point of ischaemia, independent of the underlying cause.

## Conflict of interest

The study was funded and conducted by BERLIN-CHEMIE AG. Diedrichs H reports personal fees from BERLIN-CHEMIE AG. Wollenberg U, Limberg R and Schmerbach K are employees of BERLIN-CHEMIE AG. The authors report no other conflict of interest in this work.

## References

1. Task Force Members, Montalescot G, Sechtem U, Achenbach S, Andreotti F, et al. (2013) 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. Eur Heart J 34: 2949-3003.
2. Boden WE, O'Rourke RA, Teo KK, Hartigan PM, Maron DJ, et al. (2007) Optimal medical therapy with or without PCI for stable coronary disease. N Engl J Med 356: 1503-1516.
3. O' Flynn N, Timmis A, Henderson R, Rajesh S, Fenu E; Guideline Development Group (2011) Management of stable angina: summary of NICE guidance. BMJ 343: d4147.
4. Bundesärztekammer (BÄK), Kassenärztliche Bundesvereinigung (KBV), Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF). Nationale Versorgungsleitlinie Chronische KHK – Langfassung, 2. Auflage. Version 2. 2013, zuletzt verändert: September 2014.
5. Chaitman BR, Skettino SL, Parker JO, Hanley P, Meluzin J, et al. (2004) Anti-ischemic effects and long-term survival during ranolazine monotherapy in patients with chronic severe angina. J Am Coll Cardiol 43: 1375-1382.
6. Chaitman BR, Pepine CJ, Parker JO, Skopal J, Chumakova G, et al. (2004) Effects of ranolazine with atenolol, amlodipine, or diltiazem on exercise tolerance and angina frequency in patients with severe chronic angina: a randomized controlled trial. JAMA 291: 309-316.
7. Stone PH, Gratsiansky NA, Blokhin A, Huang IZ, Meng L; ERICA Investigators (2006) Antianginal efficacy of ranolazine when added to treatment with amlodipine: the ERICA (Efficacy of Ranolazine in Chronic Angina) trial. J Am Coll Cardiol 48: 566-575.
8. Morrow DA, Scirica BM, Karwatowska-Prokopczuk E, Murphy SA, Budaj A, et al. (2007) Effects of ranolazine on recurrent cardiovascular events in patients with non-ST-elevation acute coronary syndromes: the MERLIN-TIMI 36 randomized trial. JAMA 297: 1775-1783.
9. Wilson SR, Scirica BM, Braunwald E, Murphy SA, Karwatowska-Prokopczuk E, et al. (2009) Efficacy of ranolazine in patients with chronic angina observations from the randomized, double-blind, placebo-controlled MERLIN-TIMI (Metabolic Efficiency With Ranolazine for Less Ischemia in Non-ST-Segment Elevation Acute Coronary Syndromes) 36 Trial. J Am Coll Cardiol 53: 1510-1516.
10. Ranexa® Summary of Product Characteristics. July 2014.
11. Kosiborod M, Arnold SV, Spertus JA, McGuire DK, Li Y, et al. (2013) Evaluation of ranolazine in patients with type 2 diabetes mellitus and chronic stable angina: results from the TERISA randomized clinical trial (Type 2 Diabetes Evaluation of Ranolazine in Subjects With Chronic Stable Angina). J Am Coll Cardiol 61: 2038-2045.
12. Jespersen L, Abildstrøm SZ, Hvelplund A, Prescott E (2013) Persistent angina: highly prevalent and associated with long-term anxiety, depression, low physical functioning, and quality of life in stable angina pectoris. Clin Res Cardiol 102: 571-581.
13. Arnold SV, Morrow DA, Wang K, Lei Y, Mahoney EM, et al. (2008) Effects of ranolazine on disease-specific health status and quality of life among patients with acute coronary syndromes: results from the MERLIN-TIMI 36 randomized trial. Circ Cardiovasc Qual Outcomes 1: 107-115.
14. Hasenfuss G, Maier LS (2008) Mechanism of action of the new anti-ischemia drug ranolazine. Clin Res Cardiol 97: 222-226.
15. Belardinelli L, Shryock JC, Fraser H (2006) Inhibition of the late sodium current as a potential cardioprotective principle: effects of the late sodium current inhibitor ranolazine. Heart 92 Suppl 4: iv6-6iv14.
16. Villano A, Di Franco A, Nerla R, Sestito A, Tarzia P, et al. (2013) Effects of ivabradine and ranolazine in patients with microvascular angina pectoris. Am J Cardiol 112: 8-13.
17. Mehta PK, Goykhman P, Thomson LE, Shufelt C, Wei J, et al. (2011) Ranolazine improves angina in women with evidence of myocardial ischemia but no obstructive coronary artery disease. JACC Cardiovasc Imaging 4: 514-522.
18. Ong P, Athanasiadis A, Mahrholdt H, Borgulya G, Sechtem U, et al (2012) Increased coronary vasoconstrictor response to acetylcholine in women with chest pain and normal coronary arteriograms (cardiac syndrome X). Clin Res Cardiol 101: 673-681.
19. Jespersen L, Abildstrøm SZ, Peña A, Hansen PR, Prescott E (2014) Predictive value of the corrected TIMI frame count in patients with suspected angina pectoris but no obstructive coronary artery disease at angiography. Clin Res Cardiol 103: 381-387.
20. Jespersen L, Hvelplund A, Abildstrom SZ, Pedersen F, Galatius S, et al. (2012) Stable angina pectoris with no obstructive coronary artery disease is associated with increased risks of major adverse cardiovascular events. Eur Heart J 33: 734-744.
21. Koren MJ, Crager MR, Sweeney M (2007) Long-term safety of a novel antianginal agent in patients with severe chronic stable angina: the Ranolazine Open Label Experience (ROLE). J Am Coll Cardiol 49: 1027-1034.