Resting heart rate control and prognosis in coronary artery disease patients with hypertension previously treated with bisoprolol: a sub-group analysis of the BISO-CAD study

Yun-Dai Chen[1], Xin-Chun Yang[2], Vinh Nguyen Pham[3], Shi-An Huang[4], Guo-Sheng Fu[5], Xiao-Ping Chen[6], Binh Quang Truong[7], Yu Yang[8], Shao-Wen Liu[9], Tian-Rong Ma[10], Dong-Soo Kim[11], Tae-hoon Kim[12,13]

[1]Department of Cardiology, China PLA General Hospital, Beijing 100853, China;
[2]Department of Cardiology, Beijing Chao-Yang Hospital, Capital Medical University, Beijing 100020, China;
[3]Department of Cardiology, Tam Duc Hospital, Ho Chi Minh City 700000, Vietnam;
[4]Department of Cardiology, Affiliated Hospital of Guangdong Medical College, Guangzhou, Guangdong 524001, China;
[5]Department of Cardiology, Sir Run Shaw Hospital, Affiliated with School of Medicine Zhejiang University, Hangzhou, Zhejiang 310016, China;
[6]Department of Cardiology, West China Hospital, Chengdu, Sichuan 610041, China;
[7]Department of Cardiology, University Medical Centre HCMC, Ho Chi Minh 700000, Vietnam;
[8]Geriatrics Department, The Second Xiangya Hospital of Central South University, Tianxin, Changsha 410011, China;
[9]Department of Cardiology, Shanghai First People's Hospital, Shanghai 200080, China;
[10]Department of Medical Affairs, Merck Serono Co., Ltd., Beijing 100016, China;
[11]Department of Cardiology, Inje University Busan Paik Hospital, Busan 47392, Korea;
[12]Department of Cardiology, Sejong Hospital, Gyeonggi-do 14754, Korea;
[13]Department of Cardiology, New Korea Hospital, Gyeonggi-do 10086, Korea.

Abstract

Background: Resting heart rate (RHR) is considered as a strong predictor of total mortality and hospitalization due to heart failure in hypertension patients. Bisoprolol fumarate, a second-generation beta-adrenoreceptor blockers (β-blocker) is commonly prescribed drug to manage hypertension. The present study was to retrospectively evaluate changes in the average RHR and its association with cardiovascular outcomes in bisoprolol-treated coronary artery disease (CAD) patients from the CAD treated with bisoprolol (BISO-CAD) study who had comorbid hypertension.

Methods: We performed *ad-hoc* analysis for hypertension sub-group of the BISO-CAD study ($n = 866$), which was a phase IV, multination, multi-center, single-arm, observational study carried out from October 2011 to July 2015 across China, South Korea, and Vietnam. Multivariate regression analysis was used to identify factors associated with incidence of composite cardiac clinical outcome (CCCO), the results were presented as adjusted odds ratio (OR) along with 95% confidence interval (CI) and adjusted *P* value.

Results: A total of 681 patients (mean age: 64.77 ± 10.33 years) with hypertension from BISO-CAD study were included in the analysis. Bisoprolol improved CCCOs in CAD patients with comorbid hypertension, with RHR <65 and <70 beats/min compared with RHR ≥65 and ≥75 beats/min, respectively, in the efficacy analysis (EA) set. In addition, it lowered RHR in both intent-to-treat (ITT) and EA groups after 6, 12, and 18 months of treatment. Further, RHR 70 to 74 beats/min resulted in significantly higher risk of CCCOs EA set of patients (adjusted OR: 4.34; 95% CI: 1.19–15.89; $P = 0.03$). Also, events of hospitalization due to acute coronary syndrome were higher when RHR 69 to 74 beats/min compared to RHR <69 beats/min in ITT patients.

Conclusion: Bisoprolol can effectively reduce RHR in Asian CAD patients with comorbid hypertension and hence, improve CCCO without affecting their blood pressure.

Keywords: Bisoprolol; Coronary artery disease; Cardiac outcome; Hypertension; Resting heart rate

Introduction

Hypertension, characterized by abnormal and persistent high blood pressure (BP), that is, systolic BP (SBP) ≥140 mmHg or diastolic BP (DBP) ≥90 mmHg, is among the most common and avoidable risk factor for cardiovascular diseases (CVD). The Global Burden of Disease study reported that abnormal BP majorly contributes to global all-cause mortality.[1] Clinical studies have shown a strong, continuous, and linear relationship between elevated BP

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.1097/CM9.0000000000000802

Correspondence to: Prof. Yun-Dai Chen, Department of Cardiology, China PLA General Hospital, 28 Fuxing Road, Haidian District, Beijing 100853, China
E-Mail: yundaic2019@gmail.com

Chinese Medical Journal 2020;133(10)

Received: 09-12-2019 **Edited by:** Ning-Ning Wang

and CVD.[2] In this context, a meta-analysis revealed that every 10 mmHg reduction in SBP significantly reduced events of CVD, coronary artery disease (CAD), stroke, and heart failure (HF), and all-cause mortality.[3] Another report showed that a reduction of 5 mmHg in SBP lowered stroke and cardiovascular (CV)-related mortality by 14% and 9%, respectively.[4] Due to a linear relationship observed between BP and average resting heart rate (RHR),[5,6] RHR is considered a strong predictor of total mortality and hospitalization due to HF in hypertension patients.[7] Data from the Framingham cohort showed that RHR is an independent risk factor for CV events, particularly for HF and all-cause death.[8] A recent study had shown that higher RHR is associated with poor long-term outcomes in CAD patients who underwent percutaneous coronary intervention.[9] High levels of RHR is concurrent with higher BP in hypertension patients,[5,6] therefore, the control of RHR is imperative for better prognosis of people suffering from hypertension.

Beta-adrenoreceptor blockers (β-blockers) are among the common prescribed drugs to manage hypertension.[10] They are heterogenous in their activity and are categorized accordingly. First generation β-blockers non-selectively bind either β1 or β2 adrenoreceptors, whereas those of second generation are cardio-selective with higher affinity for β1 than β2 adrenoreceptors.[11] Third-generation β-blockers are vasodilators that block α1 adrenoreceptors, stimulate β2 adrenoreceptors, generate NO, and are anti-inflammatory.[11-13] β-blockers act by lowering the RHR, thereby the cardiac output and reducing renin release, and sympathetic nervous system (SNS) activity.[14-16] They are prescribed for myocardial infarction (MI), angina pectoris, and left ventricular dysfunction.[17-19]

However, the *Joint National Committee guidelines* did not recommend β-blockers as first line therapy based on the results of study by Dahlöf *et al*, that reported increase in stroke incidence among atenolol-treated patients with hypertension in comparison to those treated with an angiotensin receptor blocker.[20,21] The recent European Society of Cardiology (ESC) and European Society of Hypertension guideline for hypertension management recommended that all five classes of anti-hypertensive drugs, including β-blockers, should be used for hypertension management.[22] In addition, this task force recommended use of β-blocker in combination for conditions requiring HR control, post-MI and symptomatic angina.[22] Moreover, recent RCTs and meta-analyses have shown that β-blockers are as effective as other classes of anti-hypertensive drugs in preventing major CV events, except for stroke.[3,23,24] Previously, the Cardiac Insufficiency Bisoprolol Study (CIBIS I) showed that bisoprolol can significantly reduce all-cause mortality in patients with HF.[25] This was further confirmed by the CIBIS II results, which showed that bisoprolol improved survival of HF patients, irrespective of their baseline HR.[26] Additionally, in BISO-ART study, bisoprolol lowered central SBP and aortic pulse pressure more significantly than atenolol in hypertension patients.[27]

Bisoprolol fumarate (Merck KGaA, Darmstadt, Germany) is a commonly prescribed second generation β1-blocker for hypertension patients.[28,29] Nevertheless, appropriate dosage and duration of treatment with bisoprolol need to be standardized for a given population to ensure a better prognosis.[25,30] Our previous multinational analysis showed that bisoprolol can adequately control RHR in CAD patients and improve their overall CV health.[31] But still, there is inadequate evidence showing effect of bisoprolol-induced lowering of RHR on CV outcomes in patients with primary or comorbid hypertension. This article reports results of analysis of the sub-group with hypertension from the total population enrolled in the CAD treated with bisoprolol (BISO-CAD) study.[31] In this patient population, we investigated the association of bisoprolol-controlled RHR with composite cardiac clinical outcomes (CCCO). Also, we analyzed bisoprolol dosage and duration of treatments received by CAD patients with hypertension during the trial.

Methods

Ethical approval

As the BISO-CAD study was approved by ethics committees (No. EMR200006-52) of all the participating centers and conducted as per the *International Conference on Harmonization guidelines* (ICH-GCP E6, 1996), separate ethical approval and informed consent were not required for the present sub-group study.

Study design

We previously published results from the BISO-CAD study, which was a multi-center, single-arm, phase IV, open-label observational study conducted at 39 centers, from October 25, 2011 to July 17, 2015, across China, South Korea, and Vietnam.[31] The BISO-CAD study aimed to evaluate the association between RHR and CCCO in Chinese patients with CAD who were receiving bisoprolol. The patients were followed-up at 6, 12, and 18 months from the baseline. The inclusion criteria were: age ≥20 years; patients with CAD; presence of stable angina or unstable angina, concurrent type 2 diabetes mellitus or having ≥3 risk factors (males aged ≥55 years or females aged ≥65 years, hypertension, dyslipidemia, smoking, family history of CAD, obesity); office RHR of ≥70 beats/min; signing informed consent; receiving bisoprolol fumarate before enrollment. Patients were excluded if they: were hypersensitivity or with contra-indications to bisoprolol; experienced acute MI in preceding 1 month; had active myocarditis; experienced coronary HF; had impaired renal or hepatic function; had severe or uncontrolled hypertension (SBP >180 mmHg or DBP >110 mmHg); received complete revascularization for a single CAD; had implanted pacemaker; were females of childbearing age who were not taking contraceptive measures, pregnant or lactating and any other incompatible condition as decided by the investigator.

The present study was an *ad hoc* analysis of data from the sub-group of patients with hypertension from the BISO-CAD cohort and was performed to determine the

association between the RHR and CAD prognosis in comorbid hypertension. Only CAD patients with comorbid hypertension (with resting SBP ≥140 mmHg and/or DBP ≥90 mmHg, or using anti-hypertensive treatment) were included.[31] Other inclusion and exclusion criteria were same as for the BISO-CAD study.[31]

Treatments

The patients were treated with bisoprolol at baseline and their clinical parameters were evaluated after 6, 12, and 18 months of treatment. Bisoprolol was given orally, and its administered dose ranged from 1.25 to 10 mg/day orally. Initially, lower dose was given, which was further increased up to a dose of 10 mg/day based on the CV health of the patient.

Study outcomes

The primary and secondary outcomes were similar as evaluated in the BISO-CAD study.[31] In brief, the primary outcome was the occurrence of CCCO (the composite of CV mortality, non-fatal acute MI and hospitalization due to unstable angina or for revascularization) till 18 months. Other primary endpoints included were change in mean dosage of bisoprolol (baseline to 18 months), mean BP (baseline: 6, 12, and 18 months), percentage of population with BP control (baseline: 6 and 18 months).

HR was measured at the baseline and 6, 12, and 18 months during the study. RHR was the average of all the HRs reported during the course of the study weighted by the actual number of days from the previous HR measurement till the present HR measurement. For the primary analysis, RHR was treated as a categorical variable. For RHR measurement, patients were asked to avoid smoking, excitatory food and beverages for 30 min before measurement, and sit for 5 min before measurement. Measurements were recorded for three continuous minutes. Heart beat/min was recorded as used to calculate RHR.

Secondary outcomes were as mentioned for the BISO-CAD study, such as: (i) heart function parameters, that is, HR, ejection fraction (EF), shortening fraction (FS), left ventricular end-systolic dimension (LVESD), interventricular septal thickness (IVST), left ventricular posterior wall thickness (LVPWT), E/A ratio, Tei index; (ii) carotid-artery intima media thickness (CIMT); (iii) all-cause mortality; (iv) CV mortality; (v) hospitalizations due to acute coronary syndrome (ACS) and coronary artery revascularization. In addition, angina events and last BP were included in the current analysis. The procedure used for BP measurement was same as described for the BISO-CAD study.[31] Safety was evaluated in all the patients who were enrolled. All endpoints were evaluated and compared for patients with an RHR of ≥75 *vs.* those with <75 beats/min, patients with an RHR of ≥70 *vs.* those with <70 beats/min, patients with an RHR of ≥65 *vs.* those with <65 beats/min, and patients with an RHR of ≥60 *vs.* those with <60 beats/min.

Statistical analysis

Statistical analysis was carried out as described for the BISO-CAD study using Statistical Analysis System (SAS) Version 9.1 (SAS Institute Inc., Cary, NC, USA).[31] Patients were divided into intent-to-treat (ITT) and efficacy analysis (EA) sets as shown in Figure 1. The ITT set included all patients of BISO-CAD study who had comorbid hypertension and were given at minimum one dose of trial drug treatment. Patients who adhered to inclusion/exclusion criteria and continued with the study till primary end point comprised EA set. Efficacy analysis was performed using both ITT and EA set.

The association of RHR with CCCO was analyzed using Poisson regression model and presented with point

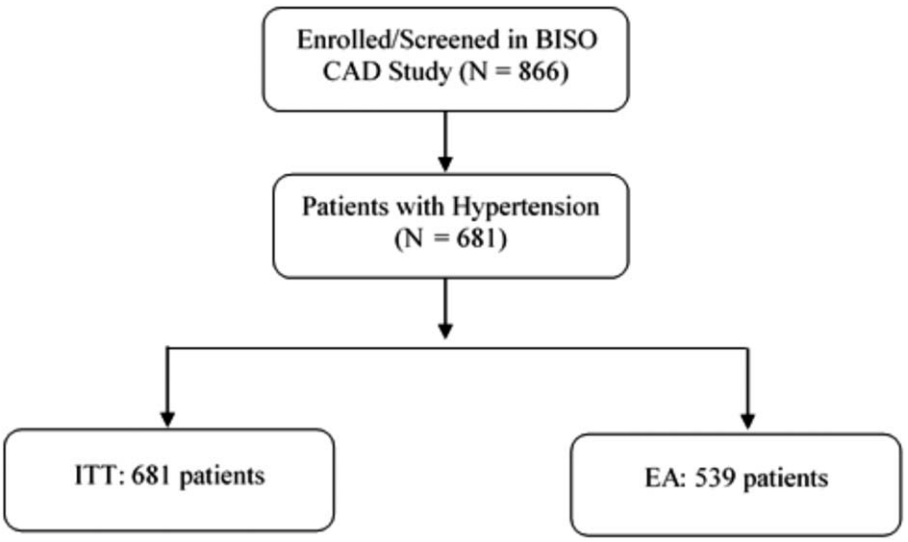

Figure 1: Subject disposition of coronary artery disease patients with hypertension previously treated with bisoprolol. BISO-CAD: Coronary artery disease treated with bisoprolol; EA: Efficacy analysis; ITT: Intent-to-treat set.

estimate and 95% confidence interval (CI). If Poisson regression was found unsuitable, logistic/survival regression was used for analysis. For continuous secondary end points (heart function parameters, CIMT), mixed model repeat measures were used, whereas Cox proportional hazard model was used for safety analysis. Descriptive statistics summarized the recorded mean HR corresponding to their respective maximal doses of bisoprolol (2.5, 5.0, 7.5, and 10.0 mg). We used multiple linear regression for exploratory analysis of effect of last dose, last SBP, and last DBP on last HR. Adverse events (AEs) were defined using the Medical Dictionary for Regulatory Activities. The data were presented with 95% CI, standard error (SE), and *P* value, wherever suitable. Multivariate regression was used to analyze association of various factors with incidence of CCCOs and results were presented as adjusted odds ratio (OR) along with 95% CI and adjusted *P* value. *P* values were used for descriptive purpose only, except for multivariate analysis.

Results

Patient demographics and characteristics

We included a total of 681 hypertensive patients in the ITT set (mean age: 64.77 ± 10.33 years; 69.0% males, 31.0% females; Body mass index [BMI]: 25.53 ± 3.29 kg/m^2). Cardiac disorders at baseline were reported in 95.9% of patients in the ITT set. Baseline mean SBP and DBP were 134.2 ± 15.2 and 78.5 ± 10.5 mmHg, respectively. In the ITT set, baseline RHR was 75.7 ± 6.8 beats/min, whereas in the EA set, it was 75.5 ± 6.6 beats/min. Almost all the patients (99.4%) had >1 ongoing medical history (18.4% with grade 1, 46.1% with grade 2, 34.4% with grade 3, and 0.6% with grade 4 condition). The EA set included 539 patients out of the ITT population. Table 1 presents baseline characteristics and Figure 1 shows subject disposition [Table 1].

Table 1: Demographic and baseline data of coronary artery disease patients with hypertension previously treated with bisoprolol.

Demographic characteristics	Value
Total number of patients (ITT), *n* (%)	681 (100.0)
Males, *n* (%)	470 (69.0)
Age (years), mean ± SD	64.77 ± 10.33
Age categories, *n* (%)	
<60 years	227 (33.3)
≥60 years	454 (66.7)
<70 years	456 (67.0)
≥70 years	225 (33.0)
SBP (mmHg), mean ± SD	134.3 ± 15.2
DBP (mmHg), mean ± SD	78.0 ± 10.5
BMI (kg/m^2), mean ± SD	25.54 ± 3.29
Patients with ≥1 ongoing medical history, *n* (%)	677 (99.4)
Grade 1	125 (18.4)
Grade 2	314 (46.1)
Grade 3	234 (34.4)
Grade 4	4 (0.6)
Cardiac disorders, *n* (%)	653 (95.9)
CAD	518 (76.1)
Angina pectoris	69 (10.1)
Angina Unstable	41 (6.0)
Acute myocardial infarction	30 (4.4)
Arteriosclerosis coronary artery	1 (0.1)
Atrial fibrillation	13 (1.9)
Bundle branch block left	1 (0.1)
Bundle branch block right	1 (0.1)
Cardiac failure	10 (1.5)
Cardiac failure chronic	8 (1.2)
Cardiac valve disease	1 (0.1)
Cardiac ventricular thrombosis	1 (0.1)
Congestive cardiomyopathy	3 (0.4)
Coronary artery occlusion	24 (3.5)
Coronary artery stenosis	12 (1.8)
Ischaemic cardiomyopathy	2 (0.3)
Myocardial infarction	40 (5.9)
Myocardial ischaemia	4 (0.6)
Palpitations	1 (0.1)
Sinus bradycardia	1 (0.1)
Ventricular arrhythmia	1 (0.1)
Vascular disorders, *n* (%)	666 (97.8)

ITT: Intent-to-treat; SD: Standard deviation; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; BMI: Body mass index; CAD: Coronary artery disease.

Association of RHR with CCCOs

We recorded CCCOs in patients grouped according to their average RHR. The data indicated that RHR of 69 to 74 beats/min caused higher CCCO than an RHR of <69 beats/min (26 events in 350 patients *vs*. 16 events in 331 patients; estimate: 1.13; SE: 0.51; 95% CI: 0.14, 2.12). The CCCO events recorded in ≥60 beats/min RHR group (*n* = 646) and <60 beats/min RHR group (*n* = 35) were 41 events and one event, respectively (estimate: 0.80; SE: 1.01; 95% CI: −1.19, 2.78), and for patients with ≥65 beats/min (*n* = 523) *vs*. those with <65 beats/min RHR (*n* = 158) were 37 and five events, respectively) (estimate: 0.80; SE: 0.48; 95% CI: −0.13, 1.74) in the ITT set. Similar results were obtained from the EA set. Interestingly, ≥65 beats/min RHR (*n* = 412) caused higher events of CCCO compared with RHR of <65 beats/min (*n* = 127) in the EA set (33 *vs*. 3 events; estimate: 1.22; SE: 0.60: 95% CI: 0.04, 2.40).

Furthermore, data from the ITT set showed that ≥70 beats/min RHR (*n* = 316) caused higher CCCOs than <70 beats/min RHR (*n* = 365) (23 *vs*. 19 events; estimate: 0.34; SE: 0.31; 95% CI: −0.27, 0.94); however, in the EA group, RHR of ≥70 beats/min (*n* = 231) caused higher CCCOs than <70 beats/min RHR (*n* = 308) (22 *vs*. 14 events; estimate: 0.74; SE: 0.34; 95% CI: 0.07, 1.41). The incidence of CCCOs were similar in patients with ≥75 beats/min RHR (*n* = 148) and those with <75 beats/min RHR (*n* = 533) in the ITT set (8 *vs*. 34 events; estimate: −0.17; SE: 0.39; 95% CI: 0.94, 0.60). The EA set results were in-line with the ITT results.

Change in BP from baseline

Mean BP remained unchanged from the baseline throughout the study in both analysis groups [Figure 2A]. However, bisoprolol increased the percentage of popula-

tion with BP control (if SBP was <140 mmHg and DBP was <90 mmHg, then BP was defined as "Controlled," and "Not Controlled" if values were not in the aforementioned range) from the baseline after 6 months (4.5%) and 18 months of treatment (5.7%) in the ITT set.

Change in RHR from baseline

Bisoprolol decreased RHR from 75.7 ± 6.8 beats/min at the baseline to 68.9 ± 8.4, 69.3 ± 8.1, and 68.8 ± 9.7 beats/min after 6, 12, and 18 months of treatment, respectively, in the ITT set. Similarly, in the EA set, it lowered RHR from 75.5 ± 6.6 beats/min baseline level to 69.0 ± 8.3, 69.2 ± 7.9, and 68.8 ± 9.7 beats/min after 6, 12, and 18 months of treatment, respectively [Figure 2B].

Change in dosage of bisoprolol during the study and treatment durations

The overall mean and mean of maximal bisoprolol dose in the ITT population was 3.7 ± 1.9 and 4.0 ± 2.0 mg, respectively. Among 681 patients of the ITT set, 43.9%, 40.1%, 4.4%, and 4.3% received maximal bisoprolol dose of 2.5, 5.0, 7.5, and 10.0 mg, respectively, while 7.3% received other strengths. The ITT group received bisoprolol for 520.9 ± 135.4 days, while the EA group received it for 541.5 ± 96.6 days. Of the patients from the ITT set, 84.1% took bisoprolol for ≥12 months, whereas 95% patients of the EA set received it for ≥12 months.

Changes in heart function parameters by variations in average RHR

The RHR of ≥70 beats/min positively affected LVESD compared with the RHR of <70 beats/min in the ITT group (least square [LS] mean difference: 1.86; 95% CI: 0.94, 2.77). Results from the EA set were consistent with the ITT results (Least squares [LS] mean difference: 1.77; 95% CI: 0.82, 2.71. Moreover, LVESD events were higher in ≥75 beats/min RHR group than <75 beats/min RHR group in the ITT set (LS mean difference: 1.16; 95% CI: 0.05, 2.28), whereas in the EA set both groups had similar

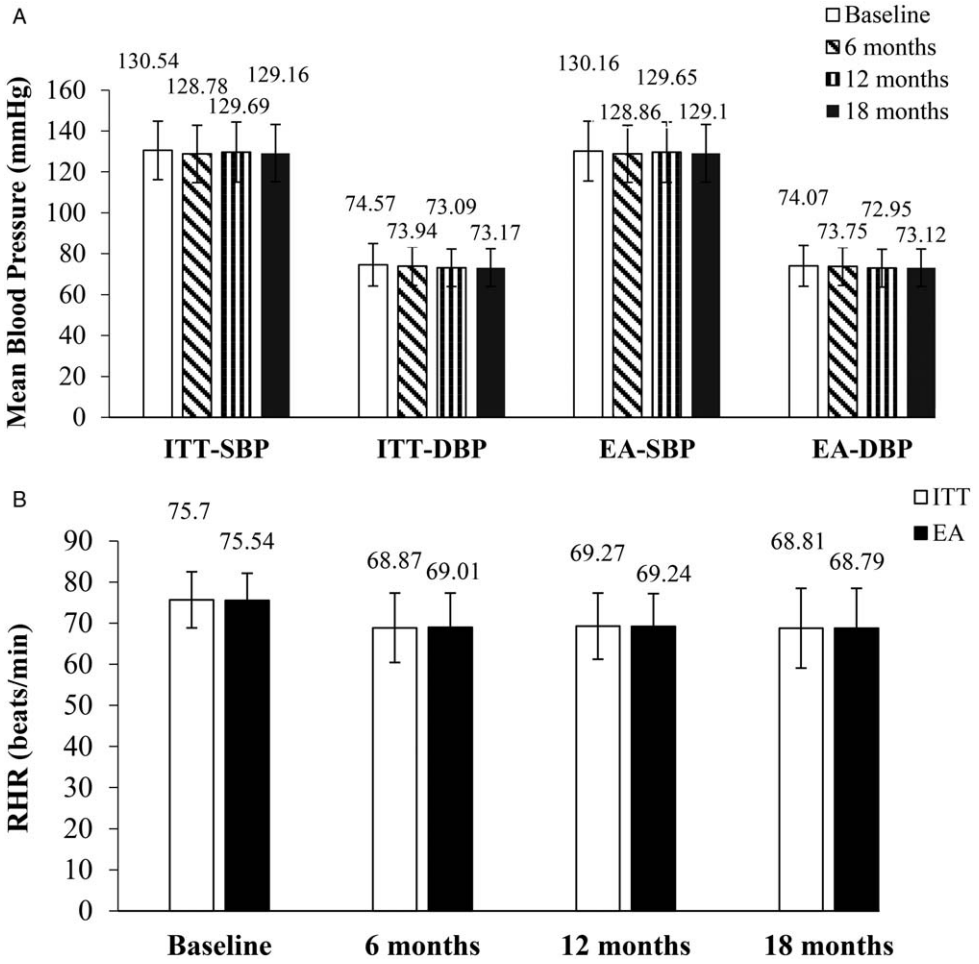

Figure 2: Changes in BP and RHR of coronary artery disease patients with hypertension previously treated with bisoprolol. (A) BP change from baseline to 18 months; (B) RHR change from baseline to 18 months. ITT-SBP and ITT-DBP: Baseline (n = 679); 6 months (n = 530); 12 months (n = 483); 18 months (n = 515); EA-SBP and EA-DBP: baseline (n = 537); 6 months (n = 467) 12 months (n = 443); 18 months (n = 505). EA-SBP: Efficacy analysis-systolic blood pressure; EA-DBP: Efficacy analysis-diastolic blood pressure; ITT-SBP: Intent-to-treat-systolic blood pressure; ITT-DBP: Intent-to-treat-diastolic blood pressure; RHR: Resting heart rate.

Table 2: Association of heart function parameters and carotid intima media thickness (CIMT) with average resting heart rate (RHR) in both ITT and EA set of coronary artery disease patients with hypertension previously treated with bisoprolol.

	≥60 *vs.* <60 beats/min		≥65 *vs.* <65 beats/min		≥70 *vs.* <70 beats/min		≥75 *vs.* <75 beats/min	
Parameter	ITT (<60 45; ≥60,821)	EA (<60 37; ≥60,651)	ITT (<65 203; ≥65,663)	EA (<65,168; ≥65 520)	ITT (≥70,316; <70,365)	EA (≥70,231; <70, 308)	ITT (≥75,194; <75,672)	EA (≥75,133; <75,555)
EF								
LS Mean difference	0.50	0.53	0.78	0.83	−0.25	−0.27	0.88	0.77
95% CI	−1.32, 2.31	−1.37, 2.43	−0.27, 1.83	−0.25, 1.91	−1.19, 0.69	−1.24, 0.70	−0.26, 2.03	−0.40, 1.95
P	0.5901	0.5851	0.1474	0.1316	0.6045	0.5840	0.1288	0.1958
t statistic (df)	0.5388 (864)	0.5462 (686)	1.4501 (864)	1.5096 (686)	0.5182 (679)	0.54788 (537)	1.5203 (864)	1.2949 (686)
FS								
LS Mean difference	−0.21	0.07	0.26	0.34	−0.23	−0.19	0.45	0.35
95% CI	−1.71, 1.29	−1.51, 1.65	−0.61, 1.13	−0.56, 1.24	−1.01, 0.55	−1.00, 0.62	−0.51, 1.40	−0.64, 1.35
P	0.7822	0.9327	0.5593	0.4552	0.5611	0.6483	0.3619	0.4829
t statistic (df)	0.2765 (864)	0.0845 (686)	0.58411 (864)	0.7472 (686)	0.5815 (679)	0.4564 (537)	0.9122 (864)	0.7020 (686)
LVESD								
LS Mean difference	1.06	0.84	0.59	0.52	1.78	1.77	1.16	0.95
95% CI	−0.68, 2.80	−1.00, 2.68	−0.43, 1.62	−0.54, 1.58	0.87, 2.69	0.82, 2.71	0.05, 2.28	−0.20, 2.10
P	0.2328	0.3689	0.2574	0.3374	0.0001	0.0003	0.0408	0.1053
t statistic (df)	1.194 (864)	0.8991 (686)	1.1333 (864)	0.9599 (686)	3.9138 (679)	3.6391 (537)	2.0486 (864)	1.6218 (686)
IVST								
LS Mean difference	0.16	0.10	0.36	0.36	−0.04	−0.05	0.20	0.19
95% CI	−0.49, 0.80	−0.57, 0.77	−0.01, 0.72	−0.02, 0.74	−0.37, 0.29	−0.39, 0.29	−0.21, 0.60	−0.22, 0.61
P	0.6361	0.7635	0.0579	0.0615	0.8022	0.7810	0.3435	0.3634
t statistic (df)	0.4733 (864)	0.3010 (686)	1.8989 (864)	1.87295 (686)	0.2506 (679)	0.2782 (537)	0.9478 (864)	0.9095 (686)
LVPWT								
LS Mean difference	−0.07	−0.13	0.14	0.10	0.17	0.17	0.08	0.10
95% CI	−0.54, 0.40	−0.63, 0.36	−0.14, 0.41	−0.18, 0.39	−0.08, 0.42	−0.09, 0.43	−0.22, 0.38	−0.22, 0.41
P	0.7597	0.5964	0.3302	0.4737	0.1722	0.1897	0.5846	0.5461
t statistic (df)	0.3060 (864)	0.5298 (686)	0.9743 (864)	0.71687 (686)	1.3666 (679)	1.3131 (537)	0.5469 (864)	0.6039 (686)
E/A ratio								
LS Mean difference	3.07	3.70	−2.58	−3.00	−2.87	−2.79	−6.03	−6.20
95% CI	−4.75, 10.88	−4.50, 11.89	−7.15, 2.00	−7.70, 1.70	−6.99, 1.26	−7.04, 1.46	−11.08, −0.97	−11.40, −1.01
P	0.4413	0.3759	0.2688	0.2101	0.1725	0.1975	0.0197	0.0193
t statistic (df)	0.77034 (864)	0.8861 (686)	1.1065 (864)	1.2545 (686)	1.3657 (679)	1.2903 (537)	2.3364 (864)	2.3452 (686)
Tei index								
LS Mean difference	−0.03	−0.03	0.03	0.03	0.03	0.03	0.05	0.04
95% CI	−0.09, 0.03	−0.09, 0.03	0.00, 0.07	−0.00, 0.06	0.00, 0.06	−0.00, 0.06	0.01, 0.08	0.00, 0.07
P	0.2966	0.3996	0.0446	0.0672	0.0395	0.0503	0.0116	0.0479
t statistic (df)	1.0444 (864)	0.8429 (686)	2.0113 (864)	1.8332 (686)	2.0629 (679)	1.9618 (537)	2.5295 (864)	1.9818 (686)
CIMT								
LS Mean difference	0.01	0.01	0.02	0.01	−0.02	−0.02	−0.05	−0.04
95% CI	−0.07, 0.08	−0.07, 0.08	−0.02, 0.05	−0.03, 0.05	−0.05, 0.02	−0.05, 0.02	−0.09, −0.00	−0.08, −0.00
P	0.8787	0.8731	0.4018	0.5332	0.2999	0.3737	0.0279	0.0434
t statistic (df)	0.1527 (864)	0.1598 (686)	0.8388 (864)	0.6234 (686)	1.03744 (679)	0.8903 (537)	2.2024	2.0236 (686)

P values are for descriptive purpose only and do not indicate statistical significance. beats/min: Beats per min; ITT: Intent-to-treat set; EA: Efficacy analysis set; EF: Ejection fraction; CI: Confidence interval; FS: Shortening fraction; LVESD: Left ventricular end-systolic dimension; IVST: Interventricular septal thickness; LVPWT: Left ventricular posterior wall thickness; CIMT: Carotid intima media thickness.

data (LS mean difference: 0.95; 95% CI: −0.20, 2.10). RHR of ≥75 beats/min affected E/A ratio compared with RHR of <75 beats/min in the ITT (LS mean difference: −6.03; 95% CI: −11.08, −0.97) as well as the EA set (LS mean difference: −6.20; 95% CI: −11.40, −1.01) [Table 2].

Furthermore, RHR of ≥65 and ≥75 beats/min increased Tei index compared with RHR of <65 beats/min (LS mean difference: 0.03; 95% CI: 0, 0.07) and RHR of <75 beats/min (LS mean difference 0.05, 95% CI, 0.01, 0.08), respectively, in the ITT set. Result from the EA set for ≥75 *vs.* <75 beats/min was consistent with the ITT set results (LS mean difference: 0.04; 95% CI: 0, 0.07) [Table 2].

CIMT events were affected by ≥75 beats/min RHR compared with <75 beats/min RHR (LS mean difference: −0.05; 95% CI: −0.09, 0). The EA results were consistent with the ITT results (LS mean difference: −0.0; 95% CI: −0.08, −0) [Table 2]. Other parameters (HR, EF, FS, IVST, LVPWT, all-cause deaths, CV deaths, and cerebral and angina events) showed no association with RHR.

Effect of average RHR variation on all-cause mortality, coronary revascularization, and cerebral and angina events

In the EA group, ≥70 beats/min RHR ($n = 231$) increased hospitalization events for ACS compared with <70 beats/min RHR ($n = 308$) (21 *vs.* 13 events; estimate: 0.88; SE: 0.36) [Table 3]. Among the ITT patients, RHR of 69 to 74 beats/min ($n = 184$) resulted in higher events of hospitalization due to ACS compared to <69 beats/min RHR ($n = 331$) (18 *vs.* 15 events; estimate: 1.24; SE: 0.51). RHR did not affect all-cause mortality and events of hospitalization for coronary revascularization in any of the study groups [Table 3].

Factors affecting incidence of CCCOs

Multivariate analysis revealed that age, gender, concomitant diabetes, or BMI did not affect the odds of having CCCOs in the study population. However, patients with RHR in range of 70 to 74 beats/min in EA group had

Table 3: Effect of average resting heart rate on all-cause mortality and hospitalization for acute coronary syndrome and coronary revascularization of coronary artery disease patients with hypertension previously treated with bisoprolol.

Parameter	Study groups	Events, *n*	Estimate hazards ratio	SE	*P*
Hospitalization for ACS					
ITT set	≥60 *vs.* <60 beats/min	39 *vs.* 1	0.73	1.01	0.4707
	≥65 *vs.* <65 beats/min	35 *vs.* 5	0.84	0.048	0.0807
	≥70 *vs.* <70 beats/min	22 *vs.* 18	0.48	0.32	0.1344
	≥75 *vs.* <75 beats/min	7 *vs.* 33	−0.16	0.42	0.7022
EA set	≥60 *vs.* <60 beats/min	34 *vs.* 0	14.08	862.92	0.9870
	≥65 *vs.* <65 beats/min	31 *vs.* 3	1.13	0.61	0.0618
	≥70 *vs.* <70 beats/min	21 *vs.* 13	0.88	0.36	0.0154
	≥75 *vs.* <75 beats/min	7 *vs.* 27	0.14	0.43	0.7416
Hospitalization for coronary revascularization					
ITT set	≥60 *vs.* <60 beats/min	12 *vs.* 0	14.09	1395.36	0.9919
	≥65 *vs.* <65 beats/min	11 *vs.* 1	0.27	1.10	0.8045
	≥70 *vs.* <70 beats/min	8 *vs.* 4	0.93	0.61	0.1306
EA set	≥60 *vs.* <60 beats/min	11 *vs.* 0	14.09	1467.47	0.9923
	≥65 *vs.* <65 beats/min	10 *vs.* 1	0.31	1.10	0.7803
	≥70 *vs.* <70 beats/min	8 *vs.* 3	1.32	0.68	0.0514
All-cause mortality					
ITT set	≥60 *vs.* <60 beats/min	10 *vs.* 0	14.08	1548.76	0.9927
	≥65 *vs.* <65 beats/min	10 *vs.* 0	15.44	1272.82	0.9903
	≥70 *vs.* <70 beats/min	6 *vs.* 4	0.62	0.65	0.3352
	≥75 *vs.* <75 beats/min	6 *vs.* 4	0.95	0.65	0.1424
EA set	≥60 *vs.* <60 beats/min	10 *vs.* 0	14.08	1577.81	0.9929
	≥65 *vs.* <65 beats/min	10 *vs.* 0	16.44	2103.91	0.9938
	≥70 *vs.* <70 beats/min	6 *vs.* 4	0.71	0.65	0.2701
	≥75 *vs.* <75 beats/min	6 *vs.* 4	1.05	0.65	0.1038

**P* values are for descriptive purpose only. SE: Standard error; ITT: Intent-to-treat; EA: Efficacy analysis.

Table 4: Multivariate analysis for association of composite cardiac clinical outcomes with average resting heart rate, age, gender, diabetes, and BMI in ITT and EA groups of coronary artery disease patients with hypertension previously treated with bisoprolol.

	ITT group			EA group		
Factors	Adjusted odds ratio (95% CI)	*β*	*P*	Adjusted odds ratio (95% CI)	*β*	*P*
Average heart rate						
≥75 beats/min	1.80 (0.60, 5.65)	0.59	0.32	3.49 (0.90, 13.59)	1.25	0.07
70–74 beats/min	2.66 (0.92, 5.41)	0.98	0.07	4.34 (1.19, 15.89)	1.47	0.03
65–69 beats/min	1.86 (0.64, 5.40)	0.62	0.26	2.66 (0.73, 9.76)	0.98	0.14
<65 beats/min	1.00			1.00		
Age (years)	1.02 (0.98, 1.05)	0.02	0.40	1.00 (0.97, 1.04)	0	0.95
Gender						
Female	1.02 (0.48, 2.13)	0.02	0.97	1.04 (0.46, 2.33)	0.04	0.93
Male	1.00			1.00		
Concomitant diabetes						
Yes	1.21 (0.62, 2.36)	0.19	0.57	1.34 (0.66, 2.72)	0.29	0.43
No	1.00			1.00		
BMI (kg/m^2)	1.02 (0.92, 1.14)	0.02	0.67	1.01 (0.90, 1.12)	0.01	0.94

ITT: Intent-to-treat; EA: Efficacy analysis; CI: Confidence interval; BMI: Basal metabolic index.

significantly higher risk of CCCOs (adjusted OR: 4.34; 95% CI: 1.19, 15.89; $P = 0.03$) [Table 4].

Safety evaluation

Safety evaluation showed that a total of 163 (23.9%) patients reported AEs, including nine (1.3%) AEs that were related to bisoprolol administration [Table 5]. Serious AEs occurred in 83 (12.2%) patients, while for ten patients (1.5%), AEs proved fatal (two patients died due to CV abnormality).

Discussion

Thus far, limited number of clinical studies have explored the relationship between lowering of the RHR caused by bisoprolol and CV outcomes in patients with primary or comorbid hypertension.[25,32-34] This study analysis of

Table 5: Safety events of coronary artery disease patients with hypertension previously treated with bisoprolol ($n = 681$).

Events	*n* (%)
Any AE	163 (23.9)
Any trial with drug-related AE	9 (1.3)
Any serious AE	83 (12.2)
Any trial with drug-related serious AE	0
Any AE leading to dose increase, reduction, interruption, or discontinuation of the trial drug	39 (5.7)
Any AE leading to discontinuation from the trial	10 (1.5)
Any AE leading to death	10 (1.5)

AE: Adverse event.

change in RHR and its relationship with CCCO in bisoprolol-treated CAD patients with comorbid hypertension. This ad hoc analysis (data from CAD patients enrolled in the BISO-CAD study, who had comorbid hypertension) showed that bisoprolol reduced RHR and hence, improved CCCO in hypertension patients, independent of its BP lowering effect.

Bisoprolol administration for 18 months effectively reduced RHR from the baseline in CAD patients with comorbid hypertension in both the ITT and the EA analysis sets. Previously, Tendera *et al*[35] reported inadequate control of RHR in patients with CAD receiving β-blockers in the prospective, longitudinal CLARIFY registry. Similar findings were reported by Alcocer-Gamba *et al* and Stepinska *et al*[36,37] who analyzed Mexican and Polish population, respectively, from the CLARIFY registry; a total of 52.1% of Mexican and ~50% of Polish population had >70 beats/min RHR. However, our results showing bisoprolol induced reduction in RHR in CAD patients with comorbid hypertension are in contrast to these reports. Our results are in accordance with results of study by Eguchi *et al*,[34] which showed that bisoprolol reduced pulse rate and hence, improved baroreflex sensitivity and vascular stiffness to a greater extent than that caused by celiprolol. SNS plays a pivotal role in initiation and maintenance of hypertension through various mechanisms of affecting BP, HR, and their mutual interactions.[38]

Higher SNS tone has been reported in conditions such as pre-hypertension, borderline, mild, moderate and severe hypertension, primary hypertension (particularly in younger patients), pregnancy related hypertension, and in systo-diastolic and isolated systolic hypertension of elderly patients.[39-41] Hence, drugs such as β-blockers that can antagonize the effects of high SNS activity are considered to be helpful in managing hypertension.[11] Previously, the EUROPA trial published by ESC in 2008 showed that among 12,205 stable angina patients, the total mortality, CV mortality and total hospitalization rate of patients with a RHR >75 beats/min were increased by 21%, 24%, and 51%, respectively, compared to those with a RHR of <75beats/min.[42] Additionally, the BEAUTIFUL study found that in stable CAD patients with left ventricular systolic dysfunction and a RHR of ≥70beats/min, ivabradine can reduce hospitalization for fatal and non-fatal MI, and also events such as coronary revascularization, compared with the placebo group.[43] The management guidelines for unstable angina and NSTEMI in China also recommend the use of β blockers to achieve the target RHR of 50 to 60 beats/min. While a target RHR of 55 to 60 beats/min is recommended, its lower limit could even be reduced further to 50 beats/min if symptoms of bradycardia are absent in patients with severe angina. Thus, we categorized patients as per the RHR to explore the optimized target RHR for better outcomes by categorizing patients as per the RHR. RHR is considered a marker of the functional status of the adrenergic CV drive, although with limited reliability due to the involvement of parasympathetic nervous system on sinus node activity.[44-46] As bisoprolol reduced RHR during the course of the study, we speculate that it might have reduced SNS tone that eventually resulted in improved CCCOs in the CAD patients with comorbid hypertension. A study in future measuring SNS tone in patients with hypertension receiving bisoprolol will be required to confirm our speculation.

Interestingly, only the EA set in this study showed an association between RHR and CV outcomes after the treatment with bisoprolol. Our results revealed that lower RHR resulted in lesser events, whereas higher RHR led to higher number of events in <65 *vs.* ≥65 beats/min and <70 *vs.* ≥70 beats/min patient groups. Risk of CCCOs was significantly higher in patients with RHR in range of 70 to 74 beats/min in the EA set. Similar observations were made in the BEAUTIFUL study by Kim Fox *et al*, which reported an increased risk of CV outcomes in CAD patients with left ventricular systolic dysfunction who had ≥70 beats/min HR.[46] In addition, Ariel Diaz *et al* demonstrated that RHR acts as a risk factor for all-cause and CV mortalities, through a study carried out on 25,000 CAD patients.[47] The CIBIS trial reported improved CV outcomes in HF patients following bisoprolol treatment.[25] Further, the CIBIS-elderly trial (CIBIS-ELD) showed a significant improvement in their cardiac outcomes upon treatment with bisoprolol.[48,49] Hence, our results were in-line with previous studies, which showed that RHR is associated with CV outcomes and higher RHR increases risk of CV outcomes.[43,47,48,50-52]

β-blockers are effective in treating hypertension patients, particularly those with comorbid hypertension, as they lower BP in these conditions by reducing adrenergic tone, that is, SNS activity.[27] Interestingly, a recent clinical study by Kazuo Eguchi *et al* showed that bisoprolol effectively lowers BP in hypertension patients.[34] Also, in a study by Lauri Suojanen *et al*, bisoprolol significantly lowered peripheral as well as central BP in hypertension patients.[53] Percentage of population of patients with CAD and comorbid hypertension having controlled BP (BP <140/90 mmHg) increased after 6 and 18 months of treatment, which shows that bisoprolol can help in controlling BP. However, there was no substantial change in BP from baseline during entire course of the study. This was due to the fact that baseline BP in these patients itself was not high due to concomitant intake of anti-hyperten-

sive medications. Therefore, in the current study, bisoprolol improved CCCO in these patients by lowering RHR, and this effect is independent of change in BP.

β-blockers have different proven efficacies in various CVD conditions[27,54,55] due to heterogeneity in their action and therefore, it is imperative to examine role of a particular β-blocker in a specific disease condition, so as to determine its suitability against that disease. Bisoprolol has been prescribed as standard medication to hypertension patients, from years,[50] but they were not considered as effective as other classes of anti-hypertensive drugs unless hypertension is present as a comorbid disorder.[15] Decline in the usage of β-blockers in hypertension as first line of therapy is attributed to reports of higher incidences of stroke and CV mortality observed with their use.[56,57]

A systematic analysis showed that β-blocker caused higher CV mortality and stroke events in hypertension patients, aged ≥60 years, compared with other anti-hypertensive drugs.[57] In addition, Lindholm *et al* revealed with a meta-analysis that β-blockers are not as effective as other anti-hypertensive drugs in preventing stroke events in patients with primary hypertension.[56] Nevertheless, most of the studies included in this meta-analysis reported effects of atenolol.[56] Another meta-analysis showed that β-blockers lowered RHR and thereby, reduced, though not significantly, CV events and mortality in patients with MI, HF, and CAD patients; though, they caused higher incidences of CV events and deaths in patients with hypertension.[58] However, results of our study, that used bisoprolol as β-blocker, are in contrast to these previous reports as there was no considerable effect of bisoprolol on CV mortality observed in CAD patients with comorbid hypertension. In addition, recent meta-analyses have demonstrated that β-blockers have same level of efficacy as other class of anti-hypertensive drugs against major CV events excluding stroke.[3,23,24] William *et al* speculated that the difference observed for stroke could be due to the small differences in the attained BP that affected sensitive cerebrovascular system.[22]

Previously, CIBIS-ELD researchers emphasized that bisoprolol dose for any given patient should be dependent on the measured RHR.[49] Furthermore, Eguchi *et al* had shown that lower doses of bisoprolol can effectively lower BP in hypertension patients without inducing adverse effects.[34] So, we aimed to check mean dose of bisoprolol required during the study to control RHR in patients with CAD patients who had comorbid hypertension. Our results showed bisoprolol-controlled RHR and improved CCCO in majority of the population (83.9%: 43.9% patients took bisoprolol at a dose of 2.5 mg/day, while 40.1% received a dose of 5 mg/day) at dosage ≤5 mg/day. The initial dose of bisoprolol given is based on the baseline RHR,[48] therefore, patients with comparatively lower RHR were given lower dose, whereas those with higher RHR were provided with higher dose of bisoprolol. Patients for whom these doses could not control RHR, higher doses, that is, 7.5 or 10 mg was given. We suspect confounding factors (other underlying diseases or concomitant medications, which were not included in the analysis) might have played a role in lower reduction of RHR in these patients observed with 5 mg/day dose.

A study has reported that RHR is negatively associated with health outcomes in CAD patients and those with ACS.[59] Accordingly, we observed that RHR affected heart function parameters such as LVESD, E/A ratio, Tei index, and CIMT. Higher RHR caused higher events of hospitalization for ACS (≥70 *vs.* <70 beats/min) in EA set. These results are supported by study from Kovar and colleagues, which reported a higher mortality rate in patients with ACS who had a higher HR.[60] In addition, these results are in-line with the findings of the BEAUTIFUL study.[46]

Our finding that bisoprolol improves cardiac outcomes and is well tolerated in Chinese patients with CAD and hypertension, may promote beta-blockers usage in clinical practice for patients with comorbid hypertension in real-world practice, especially in China. Also, our results highlight the importance of controlling RHR in patients with hypertension as higher RHR in these patients was associated with poor cardiac outcomes.

Our study had few limitations, which were similar to those with the BISO-CAD study. First, number of patients in the ITT set and the EA set were highly varied as in the BISO-CAD study, which might have negatively affected the analysis of results for various parameters. A study with comparable number of patients in both groups may verify these differences. Second, we did not include medical history, that is, concomitant medication and other medical conditions in the analysis. Third, the study duration was only 18 months. Monitoring CV outcomes for a longer duration could have provided information on long-term effects of bisoprolol treatment in these patients. Fourth, as various parameters were compared across groups categorized as per the RHR of patients in both the analysis sets, the results presented have huge amount of statistical analysis data, which might appear as over-presentation of the results. Fifth, none of the *P* values (except for multivariate analysis) were adjusted for multiple testing. Sixth, there may be some unmeasured confounders affecting the findings of this study. We will continue to collect more information about potential confounders for further study. Lastly, 83.9% of the patients received bisoprolol at a dose of ≤5 mg/day and hence, effect of higher doses of bisoprolol on CV outcomes in CAD patients with hypertension remains unclear.

Conclusions

In conclusion, bisoprolol improved CCCOs in CAD patients with comorbid hypertension from the baseline by the end of the study. There was no considerable reduction in BP from the baseline in these patients due to concomitant medication with anti-hypertensive drugs. Therefore, the improvement of CV outcomes observed was independent of the BP lowering effect of bisoprolol.

Acknowledgement

The authors acknowledge Dr. Amit Bhat (Indegene, Bangalore, India) for providing medical writing support and technical assistance in the development of this manuscript.

Funding

This study was funded by Merck Serono Co., Ltd, an affiliate of Merck KGaA, Darmstadt, Germany.

Conflicts of interest

Tian-Rong Ma is an employee of Merck Serono Co., Ltd. China, an affiliateion of Merck KGaA Darmstadt, Germany. Rest all authors declare no competing financial interest.

References

1. GBD 2015 Risk Factors Collaborators. Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet Lond Engl 2016;388:1659–1724. doi: 10.1016/S0140-6736(16)31679-8.
2. Wu C-Y, Hu H-Y, Chou Y-J, Huang N, Chou Y-C, Li C-P. High blood pressure and all-cause and cardiovascular disease mortalities in community-dwelling older adults. Medicine (Baltimore) 2015;94:e2160. doi: 10.1097/MD.0000000000002160.
3. Ettehad D, Emdin CA, Kiran A, Anderson SG, Callender T, Emberson J, *et al*. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. Lancet 2016;387:957–967. doi: 10.1016/S0140-6736(15)01225-8.
4. Oparil S, Acelajado MC, Bakris GL, Berlowitz DR, Cífková R, Dominiczak AF, *et al*. Hypertension. Nat Rev Dis Primer 2018;4:18014. doi: 10.1038/nrdp.2018.14.
5. Fernandes RA, Freitas Júnior IF, Codogno JS, Christofaro DGD, Monteiro HL, Roberto Lopes DM. Resting heart rate is associated with blood pressure in male children and adolescents. J Pediatr 2011;158:634–637. doi: 10.1016/j.jpeds.2010.10.007.
6. Christofaro DGD, Casonatto J, Vanderlei LCM, Cucato GG, Dias RMR. Relationship between resting heart rate, blood pressure and pulse pressure in adolescents. Arq Bras Cardiol 2017;108:405–410. doi: 10.5935/abc.20170050.
7. Wang A, Liu X, Guo X, Dong Y, Wu Y, Huang Z, *et al*. Resting heart rate and risk of hypertension: results of the Kailuan cohort study. J Hypertens 2014;32:1600–1605. doi: 10.1097/HJH.0000000000000230.
8. Ho JE, Larson MG, Ghorbani A, Cheng S, Coglianese EE, Vasan RS, *et al*. Long-term cardiovascular risks associated with an elevated heart rate: the Framingham Heart Study. J Am Heart Assoc 2014;3:e000668. doi: 10.1161/JAHA.113.000668.
9. Zheng Y-Y, Wu T-T, Chen Y, Hou X-G, Yang Y, Ma X, *et al*. Resting heart rate and long-term outcomes in patients with percutaneous coronary intervention: results from a 10-year follow-up of the CORFCHD-PCI study. Cardiol Res Pract 2019;2019:5432076. doi: 10.1155/2019/5432076.
10. Ram CVS. Beta-blockers in hypertension. Am J Cardiol 2010;106:1819–1825. doi: 10.1016/j.amjcard.2010.08.023.
11. Gorré F, Vandekerckhove H. Beta-blockers: focus on mechanism of action. Acta Cardiol 2010;65:565–570. doi: 10.2143/AC.65.5.2056244.
12. Triposkiadis F, Karayannis G, Giamouzis G, Skoularigis J, Louridas G, Butler J. The sympathetic nervous system in heart failure physiology, pathophysiology, and clinical implications. J Am Coll Cardiol 2009;54:1747–1762. doi: 10.1016/j.jacc.2009.05.015.
13. Bakris G. An in-depth analysis of vasodilation in the management of hypertension: focus on adrenergic blockade. J Cardiovasc Pharmacol 2009;53:379–387. doi: 10.1097/FJC.0b013e31819fd501.
14. Antman EM. Cardiovascular Therapeutics: a Companion to Braunwald's Heart Disease. 4th ed.London: Elsevier Health Sciences; 2012.
15. Wiysonge CS, Bradley HA, Volmink J, Mayosi BM, Opie LH. Beta-blockers for hypertension. Cochrane Database Syst Rev 2017. CD002003. doi: 10.1002/14651858.CD002003.pub5.
16. Dézsi CA, Szentes V. The real role of β-blockers in daily cardiovascular therapy. Am J Cardiovasc Drugs 2017;17:361–373. doi: 10.1007/s40256-017-0221-8.
17. Steg PG, De Silva R. Beta-blockers in asymptomatic coronary artery disease. J Am Coll Cardiol 2014;64:253–255. doi: 10.1016/j.jacc.2014.04.043.
18. Custodis F, Reil J-C, Laufs U, Böhm M. Heart rate: a global target for cardiovascular disease and therapy along the cardiovascular disease continuum. J Cardiol 2013;62:183–187. doi: 10.1016/j.jjcc.2013.02.018.
19. Wiysonge CS, Bradley HA, Volmink J, Mayosi BM, Mbewu A, Opie LH. The Cochrane Collaboration . Beta-blockers for hypertension. Cochrane Database of Systematic Reviews Chichester, UK: John Wiley & Sons, Ltd; 2012. doi: 10.1002/14651858.CD002003.pub3.
20. James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, *et al*. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA 2014;311:507–520. doi: 10.1001/jama.2013.284427.
21. Dahlöf B, Devereux RB, Kjeldsen SE, Julius S, Beevers G, de Faire U, *et al*. Cardiovascular morbidity and mortality in the Losartan intervention for endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. Lancet Lond Engl 2002;359:995–1003. doi: 10.1016/S0140-6736(02)08089-3.
22. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, *et al*. 2018 ESC/ESH guidelines for the management of arterial hypertension. Eur Heart J 2018;39:3021–3104. doi: 10.1093/eurheartj/ehy339.
23. Thomopoulos C, Parati G, Zanchetti A. Effects of blood-pressure-lowering treatment on outcome incidence. 12. Effects in individuals with high-normal and normal blood pressure: overview and meta-analyses of randomized trials. J Hypertens 2017;35:2150–2160. doi: 10.1097/HJH.0000000000001547.
24. Emdin CA, Rahimi K, Neal B, Callender T, Perkovic V, Patel A. Blood pressure lowering in type 2 diabetes: a systematic review and meta-analysis. JAMA 2015;313:603. doi: 10.1001/jama.2014.18574.
25. CIBIS-II Investigators and Committees. The cardiac insufficiency bisoprolol study II (CIBIS-II): a randomised trial. Lancet 1999;353:9–13. doi: 10.1016/S0140-6736(98)11181-9.
26. Lechat P, Hulot J-S, Escolano S, Mallet A, Leizorovicz A, Werhlen-Grandjean M, *et al*. Heart rate and cardiac rhythm relationships with bisoprolol benefit in chronic heart failure in CIBIS II trial. Circulation 2001;103:1428–1433. doi: 10.1161/01.CIR.103.10.1428.
27. Mann SJ. Redefining beta-blocker use in hypertension: selecting the right beta-blocker and the right patient. J Am Soc Hypertens 2017;11:54–65. doi: 10.1016/j.jash.2016.11.007.
28. Channaraya V, Marya RK, Somasundaram M, Mitra D, Tibrewala KD. Efficacy and tolerability of a β-1 selective β blocker, bisoprolol, as a first-line antihypertensive in Indian patients diagnosed with essential hypertension (BRIGHT): an open-label, multicentric observational study. BMJ Open 2012;2:e000683. doi: 10.1136/bmjopen-2011-000683.
29. Minushkina LO. Bisoprolol: opportunities in the treatment of hypertension (in Russian). Kardiologiia 2012;52:80–85.
30. Whelton PK, Carey RM, Aronow WS, Casey DE, Collins KJ, Dennison Himmelfarb C, *et al*. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines. Hypertension 2018;71:1269–1324. doi: 10.1161/HYP.0000000000000066.
31. Chen Y, Yang X, Nguyen Pham V, Huang S, Fu G, Chen X, *et al*. Heart rate control is associated with reduced cardiovascular events in Asian patients with coronary artery disease treated with bisoprolol (BISO-CAD): results from a multi-national, real-world experience. Curr Med Res Opin 2018;34:217–225. doi: 10.1080/03007995.2017.1363729.
32. Pousset F, Copie X, Lechat P, Jaillon P, Boissel JP, Hetzel M, *et al*. Effects of bisoprolol on heart rate variability in heart failure. Am J Cardiol 1996;77:612–617. Doi: 10.1016/S0002-9149(97)89316-2.
33. Copie X, Pousset F, Lechat P, Jaillon P, Guize L, Le Heuzey JY. Effects of beta-blockade with bisoprolol on heart rate variability in advanced heart failure: analysis of scatterplots of R-R intervals at selected heart rates. Am Heart J 1996;132:369–375. Doi: 10.1016/S0002-8703(96)90435-4.
34. Eguchi K, Hoshide S, Kario K. Effects of celiprolol and bisoprolol on blood pressure, vascular stiffness, and baroreflex sensitivity. Am J Hypertens 2015;28:858–867. doi: 10.1093/ajh/hpu245.
35. Tendera M, Fox K, Ferrari R, Ford I, Greenlaw N, Abergel H, *et al*. Inadequate heart rate control despite widespread use of beta-blockers in outpatients with stable CAD: findings from the international prospective CLARIFY registry. Int J Cardiol 2014;176:119–124. doi: 10.1016/j.ijcard.2014.06.052.

36. Alcocer-Gamba MA, Martínez-Sánchez C, Verdejo-Paris J, Ferrari R, Fox K, Greenlaw N, *et al*. Heart rate and use of β-blockers in Mexican stable outpatients with coronary artery disease. Arch Cardiol Mex 2015;85:270–277. doi: 10.1016/j.acmx.2015.01.004.
37. Stępińska J, Marona M, Greenlaw N, Steg G. Polish Clarify Investigators. Heart rate and the use of beta-blockers in stable outpatients with coronary artery disease: polish baseline results of the CLARIFY registry. Kardiol Pol 2014;72:1156–1164. doi: 10.5603/KP.a2014.0134.
38. Parati G, Esler M. The human sympathetic nervous system: its relevance in hypertension and heart failure. Eur Heart J 2012;33:1058–1066. doi: 10.1093/eurheartj/ehs041.
39. Esler M, Lambert G, Jennings G. Increased regional sympathetic nervous activity in human hypertension: causes and consequences. J Hypertens Suppl Off J Int Soc Hypertens 1990;8:S53–S57.
40. Grassi G, Colombo M, Seravalle G, Spaziani D, Mancia G. Dissociation between muscle and skin sympathetic nerve activity in essential hypertension, obesity, and congestive heart failure. Hypertens Dallas Tex 1998;1979:64–67. Doi: 10.1161/01.HYP.31.1.64.
41. Grassi G. Sympathetic neural activity in hypertension and related diseases. Am J Hypertens 2010;23:1052–1060. doi: 10.1038/ajh.2010.154.
42. Fox KM. EURopean Trial On Reduction of Cardiac Events With Perindopril in Stable Coronary Artery Disease Investigators. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study). Lancet Lond Engl 2003;362:782–788. doi: 10.1016/s0140-6736(03)14286-9.
43. Fox K, Ford I, Steg PG, Tendera M, Robertson M, Ferrari R. Heart rate as a prognostic risk factor in patients with coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): a subgroup analysis of a randomised controlled trial. Lancet 2008;372:817–821. doi: 10.1016/S0140-6736(08)61171-X.
44. Levy M, Martin P. Autonomic control of cardiac conduction and automaticity. Alec D. Shepherd, editor. Nervous Control of the Heart Amsterdam: Harwood Academic Publishers; 1996;201–226.
45. Quarti Trevano F, Seravalle G, Macchiarulo M, Villa P, Valena C, Dell'Oro R, *et al*. Reliability of heart rate as neuroadrenergic marker in the metabolic syndrome. J Hypertens 2017;35:1685–1690. doi: 10.1097/HJH.0000000000001370.
46. Grassi G. Sympathomodulatory effects of antihypertensive drug treatment. Am J Hypertens 2016;29:665–675. doi: 10.1093/ajh/hpw012.
47. Diaz A, Bourassa MG, Guertin M-C, Tardif J-C. Long-term prognostic value of resting heart rate in patients with suspected or proven coronary artery disease. Eur Heart J 2005;26:967–974. doi: 10.1093/eurheartj/ehi190.
48. Düngen H-D, Musial-Bright L, Inkrot S, Apostolović S, Edelmann F, Lainščak M, *et al*. Heart rate following short-term beta-blocker titration predicts all-cause mortality in elderly chronic heart failure patients: insights from the CIBIS-ELD trial. Eur J Heart Fail 2014;16:907–914. doi: 10.1002/ejhf.121.
49. Düngen H-D, Apostolovic S, Inkrot S, Tahirovic E, Töpper A, Mehrhof F, *et al*. Titration to target dose of bisoprolol vs. carvedilol in elderly patients with heart failure: the CIBIS-ELD trial. Eur J Heart Fail 2011;13:670–680. doi: 10.1093/eurjhf/hfr020.
50. Andersson C, Shilane D, Go AS, Chang TI, Kazi D, Solomon MD, *et al*. Beta-blocker therapy and cardiac events among patients with newly diagnosed coronary heart disease. J Am Coll Cardiol 2014;64:247–252. doi: 10.1016/j.jacc.2014.04.042.
51. Gillman MW, Kannel WB, Belanger A, D'Agostino RB. Influence of heart rate on mortality among persons with hypertension: the Framingham Study. Am Heart J 1993;125:1148–1154. Doi: 10.1016/0002-8703(93)90128-V.
52. Lithell H, Weiner L, Vessby B, Nordström ML. Effects of small doses of bisoprolol on blood pressure and lipoprotein concentrations in hypertensive patients. Eur J Clin Pharmacol 1993;44:19–22. Doi: 10.1007/bf00315274.
53. Suojanen L, Haring A, Tikkakoski A, Koskela JK, Tahvanainen AM, Huhtala H, *et al*. Haemodynamic influences of bisoprolol in hypertensive middle-aged men: a double-blind, randomized, placebo-controlled cross-over study. Basic Clin Pharmacol Toxicol 2017;121:130–137. doi: 10.1111/bcpt.12771.
54. van der Wall EE. Beta-blocking agents in cardiovascular disease; are they here to stay? Neth Heart J 2014;22:481–483. doi: 10.1007/s12471-014-05*88-y.
55. Cullington D, Yassin A, Cleland J. Beta-blockers in the treatment of cardiovascular disease. Prescriber 2008;19:31–39. doi: 10.1002/psb.253.
56. Lindholm LH, Carlberg B, Samuelsson O. Should β blockers remain first choice in the treatment of primary hypertension? A meta-analysis. Lancet 2005;366:1545–1553. doi: 10.1016/S0140-6736(05)67573-3.
57. Messerli FH, Grossman E, Goldbourt U. Are beta-blockers efficacious as first-line therapy for hypertension in the elderly?: a systematic review. JAMA 1998;279:1903–1907. doi: 10.1001/jama.279.23.1903.
58. Bangalore S, Sawhney S, Messerli FH. Relation of beta-blocker–induced heart rate lowering and cardioprotection in hypertension. J Am Coll Cardiol 2008;52:1482–1489. doi: 10.1016/j.jacc.2008.06.048.
59. Orso F, Baldasseroni S, Maggioni AP. Heart rate in coronary syndromes and heart failure. Prog Cardiovasc Dis 2009;52:38–45. doi: 10.1016/j.pcad.2009.05.006.
60. Kovar D, Cannon CP, Bentley JH, Charlesworth A, Rogers WJ. Does initial and delayed heart rate predict mortality in patients with acute coronary syndromes? Clin Cardiol 2004;27:80–86. Doi: 10.1002/clc.4960270207.

How to cite this article: Chen YD, Yang XC, Pham VN, Huang SA, Fu GS, Chen XP, Truong BQ, Yang Y, Liu SW, Ma TR, Kim DS, Kim Th. Resting heart rate control and prognosis in coronary artery disease patients with hypertension previously treated with bisoprolol: a sub-group analysis of the BISO-CAD study. Chin Med J 2020;133:1155–1165. doi: 10.1097/CM9.0000000000000802