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

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Abstract

Background: Resting heart rate (RHR) is considered as a strong predictor of total mortality and hospitalization due to heart failure in hypertensive 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, multinational, 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
Beta-adrenoreceptor blockers (β-blockers) are among the common prescribed drugs to manage hypertension. They are heterogeneous 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. Third-generation β-blockers are vasodilators that block α1 adrenoreceptors, stimulate β2 adrenoreceptors, generate NO, and are anti-inflammatory. β-blockers act by lowering the RHR, thereby the cardiac output and reducing renin release, and sympathetic nervous system (SNS) activity. They are prescribed for myocardial infarction (MI), angina pectoris, and left ventricular dysfunction.

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. 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. In addition, this task force recommended use of β-blocker in combination for conditions requiring HR control, post-MI and symptomatic angina. 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. Previously, the Cardiac Insufficiency Bisoprolol Study (CIBIS I) showed that bisoprolol can significantly reduce all-cause mortality in patients with HF. This was further confirmed by the CIBIS II results, which showed that bisoprolol improved survival of HF patients, irrespective of their baseline HR. Additionally, in BISO-ART study, bisoprolol lowered central SBP and aortic pulse pressure more significantly than atenolol in hypertension patients.

Bisoprolol fumarate (Merck KGaA, Darmstadt, Germany) is a commonly prescribed second generation β1-blocker for hypertension patients. Nevertheless, appropriate dosage and duration of treatment with bisoprolol need to be standardized for a given population to ensure a better prognosis. Our previous multinational analysis showed that bisoprolol can adequately control RHR in CAD patients and improve their overall CV health. 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. 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. 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 $\geq 140$ mmHg and/or DBP $\geq 90$ 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 $\geq 75$ vs. those with $<75$ beats/min, patients with an RHR of $\geq 70$ vs. those with $<70$ beats/min, patients with an RHR of $\geq 65$ vs. those with $<65$ beats/min, and patients with an RHR of $\geq 60$ 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
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/m²). 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].

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 RHR (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-

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 | 78.9 ± 10.5 |
| BMI (kg/m²), 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) |
| Myocardial ischemia | 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.
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
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 = 187) 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 CCOs

Multivariate analysis revealed that age, gender, concomitant diabetes, or BMI did not affect the odds of having CCOs in the study population. However, patients with RHR in range of 70 to 74 beats/min in EA group had
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.\textsuperscript{[25,32-34]} This study analysis of

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.

| Factors                      | ITT group | EA group |
|------------------------------|-----------|----------|
| Average heart rate           | Adjusted odds ratio (95% CI) | β | P     | Adjusted odds ratio (95% CI) | β | P     |
| ≥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          | 1.00          | 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          | 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          | 1.00          | 1.00          |
| BMI (kg/m²)                  | 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.
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 CCCCO 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 CCCCO 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. 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 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 which showed that bisoprolol reduced pulse rate and hence, improved baroreflex sensitivity and vascular stiffness to a greater extent than that caused by celpirolol. SNS plays a pivotal role in initiation and maintenance of hypertension through various mechanisms of affecting BP, HR, and their mutual interactions.

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 systolic and isolated systolic hypertension of elderly patients. Hence, drugs such as β-blockers that can antagonize the effects of high SNS activity are considered to be helpful in managing hypertension. 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 <75 beats/min. Additionally, the BEAUTIFUL study found that in stable CAD patients with left ventricular systolic dysfunction and a RHR of ≥70 beats/min, ivabradine can reduce hospitalization for fatal and non-fatal MI, and also events such as coronary revascularization, compared with the placebo group. 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. As bisoprolol reduced RHR during the course of the study, we speculate that it might have reduced SNS tone that eventually resulted in improved CCCCOs 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 speculations.

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 CCCCOs 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. 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. The CIBIS trial reported improved CV outcomes in HF patients following bisoprolol treatment. Further, the CIBIS-elderly trial (CIBIS-ELD) showed a significant improvement in their cardiac outcomes upon treatment with bisoprolol. 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. 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. Interestingly, a recent clinical study by Kazuo Eguchi et al showed that bisoprolol effectively lowers BP in hypertension patients. Also, in a study by Lauri Suojanen et al, bisoprolol significantly lowered peripheral as well as central BP in hypertension patients. 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-
α-blocking agents have different proven efficacies in various CVD conditions due to heterogeneity in their action and therefore, it is imperative to examine role of a particular α-blocking agent 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, but they were not considered as effective as other classes of anti-hypertensive drugs unless hypertension is present as a comorbid disorder. 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.

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. 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. Nevertheless, most of the studies included in the meta-analysis reported effects of atenolol. 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. 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. 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.

Previously, CIBIS-ELD researchers emphasized that bisoprolol dose for any given patient should be dependent on the measured RHR. Furthermore, Eguchi et al had shown that lower doses of bisoprolol can effectively lower BP in hypertension patients without inducing adverse effects. Consequently, 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, 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. Accordingly, we observed that RHR affected heart function parameters such as LVEF, 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. In addition, these results are in-line with the findings of the BEAUTIFUL study.

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.

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