Clin Hypertens. 2025 Mar 1;31:e8
https://doi.org/10.5646/ch.2025.31.e8
eISSN 2056-5909

Clinical Hypertension

Research Article

Posttreatment pulse rate reduction and not baseline pulse rate as an indicator of blood pressure response to nebivolol: a subanalysis from the real-world BENEFIT-KOREA study

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Received: Dec 12, 2024
Accepted: Jan 30, 2025
Published online: Mar 1, 2025

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Abbreviations

ACE, angiotensin-converting enzyme; ADR, adverse drug reaction; AE, adverse event; ARB, angiotensin receptor blocker; BP, blood pressure; DBP, diastolic blood pressure; GLM, generalized linear model; HF, heart failure; MedDRA, Medical Dictionary for Regulatory Activities; PR, pulse rate; SBP, systolic blood pressure.

Trial Registration

ClinicalTrials.gov Identifier: NCT03847350

Presentation

The data of this article was presented online at the Joint Meeting of the European Society of Hypertension–International Society of Hypertension (ESC-ISH) 2021 on April 11–14, 2021 (Shin J, et al. Pulse rate is the independent factor to predict more effective blood pressure reduction by nebivolol in a real-world clinical study for hypertension patients).

ABSTRACT

Background: This subanalysis of BENEFIT-KOREA cohort assessed the impact of baseline pulse rate (PR) and posttreatment PR reduction on the blood pressure (BP)-lowering efficacy of nebivolol in patients with hypertension.

Methods: South Korean patients with hypertension were enrolled in the BENEFIT-KOREA study; 3,011 patients received nebivolol as monotherapy/add-on therapy. Time-averaged BP, calculated by sum of the product of BPs at weeks 12 and 24 corrected for number of participants at these timepoints, was evaluated with/without adjustment for baseline BP. Change in BP in baseline PR groups of < 70, 70–79, and ≥ 80 beats/min and posttreatment PR reduction groups of < 1, 1–9, and ≥ 10 beats/min at 24 weeks were evaluated.

Results: The unadjusted time-averaged systolic BP (SBP) at 24 weeks was not significantly different within baseline PR groups or posttreatment PR reduction groups, but the unadjusted time-averaged diastolic BP (DBP) was significantly different within both baseline PR ($P < 0.001$) and posttreatment PR reduction groups ($P < 0.001$). Significant differences were observed in adjusted time-averaged SBP (≥ 10 beats/min group: β, −3.4148; $P = 0.006$) and time-averaged DBP (≥ 10 beats/min: β, −4.5781; $P < 0.001$) only within the posttreatment PR reduction groups. The majority of adverse events reported with nebivolol were mild.

Conclusions: The efficacy of nebivolol for BP reduction seems to be indicated not by baseline PR but by posttreatment PR reduction. These findings suggest the presence of other

Funding

The BENEFIT-KOREA study was funded by A. Menarini Korea Ltd.

Competing interest

Shin J has received honorarium from Menarini, Hanmi, Boryong, Viatris, and Organon, and grant from Sanofi. Cha DH, Bae WH, Jung IH, Hong SP, Kim SH, Do JY, Hwang WM, and Koh YY have no competing interests to declare. Mancia G has received compensations as speaker/chairman/consultant from Astra Zeneca, Berlin Chemie, Böhringer Ingelheim, Gedeon Richter, Medtronic Vascular Inc, Menarini, Merck Healthcare KGaA, Medtronic Inc USA, Neopharmed-Gentili, Novartis Pharma, Recordati, Sandoz, Sanofi, and Servier in the past 24 months. Manolis AJ has received lecture fees from Menarini. Lee M is an employee of A. Menarini Korea Ltd.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The study was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki. All enrolled patients provided written informed consent prior to undergoing any study-related procedure. The study protocol and relevant documentation were approved by the institutional review board/independent ethics committee(s) of all 66 study sites.

Consent for publication

Not applicable.

Authors' contributions

Data curation: Shin J, Cha DH, Bae WH, Jung IH, Hong SP, Kim SH, Do JY, Hwang WM, Koh YY; Formal analysis: Shin J, Cha DH, Bae WH, Jung IH, Hong SP, Kim SH, Do JY, Hwang WM, Koh YY, Mancia G, Manolis AJ, Lee M; Investigation: Shin J, Cha DH, Bae WH, Jung IH, Hong SP, Kim SH, Do JY, Hwang WM, Koh YY, Mancia G, Manolis AJ, Lee M; Writing - original draft: Shin J, Cha DH, Bae WH, Jung IH, Hong SP, Kim SH, Do JY, Hwang WM, Koh YY, Mancia G, Manolis AJ, Lee M; Writing - review & editing: Shin J, Cha DH, Bae WH, Jung IH, Hong SP, Kim SH, Do JY, Hwang WM, Koh YY, Mancia G, Manolis AJ, Lee M.

mechanisms in addition to sympathetic inhibition which potentially weaken the relationship between baseline PR and BP reduction.

Trial Registration: ClinicalTrials.gov Identifier: NCT03847350

Keywords: Essential hypertension; Nebivolol; Heart rate; Blood pressure

BACKGROUND

Hypertension is an important risk factor for cardiovascular morbidity and mortality worldwide, and antihypertensive drug therapy, in addition to sustained lifestyle modifications, is the mainstay of the treatment strategy for hypertension [1,2]. Antihypertensive drugs may be classified according to their characteristic mechanism of actions, such as angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), calcium channel blockers, diuretics, and adrenoceptor antagonists (β-blockers, α-blockers). Among these classes, β-blockers exert their action by reducing the increased activity of the sympathetic nervous system by adrenergic receptor blockade (particularly through β1, β2, and β3 receptors), resulting in a decrease in blood pressure (BP) and pulse rate (PR) [3]. While guidelines acknowledge that cardiovascular outcomes and mortality are similar with treatment based on initial therapy with all 5 major classes of antihypertensives, β-blockers are recommended as a therapeutic option in hypertensive patients only in specific settings, including symptomatic angina, for control of PR, heart failure (HF), post myocardial infarction and as an alternative to ACE inhibitors and ARBs in younger women [2,4]. The use of β-blockers as monotherapy or in combination with other agents for initial therapy in hypertension is not recommended, attributed to inferior protection against stroke risk and all-cause mortality compared with other antihypertensive agents shown in some studies, as well as their metabolic impact [2,4]. However, a recent meta-analysis reported that lowering BP results in a substantial risk-reduction of all cardiovascular events suggesting the role of β-blocker as an additional agent in hypertensive patients [5].

In patients with hypertension, PR tends to be chronically high, and strong evidence suggests that increase in PR is associated with an increase in cardiac and peripheral sympathetic nerve activity [6,7]. Despite the link between PR and adverse cardiovascular outcomes in hypertension [8-13], PR is not considered when making a choice of antihypertensive medication, although guidelines do recommend β-blockers for PR control in hypertensive patients [2]. Furthermore, it is uncertain whether PR can be used as an indicator or predictor of the BP reducing efficacy of β-blockers.

Nebivolol is a vasodilatory β1-adrenergic receptor antagonist which induces nitric oxide-mediated vasodilatory effects [14,15]. It has been reported to be efficacious and well tolerated for achieving BP control in patients with hypertension [14-18]. In this subanalysis of the BENEFIT-KOREA (Benefits after 24 Weeks of Nebivolol Administration for Essential Hypertension Patients with Various Comorbidities and Treatment Environments in Korea) study [19], we investigated the impact of baseline PR and posttreatment PR reduction on the BP-lowering efficacy of nebivolol in patients with hypertension.

METHODS

Study design

The BENEFIT-KOREA study, an open, noncomparative, noncontrolled, prospective, single-arm, multicenter observational study at 66 sites in the Republic of Korea (**Supplementary Table 1**), demonstrated the efficacy and safety of nebivolol in Asian patients with essential hypertension with and without comorbidities and independent of age, in a real-world setting [19]. It enrolled male and female patients ≥ 19 years of age diagnosed with essential hypertension—newly diagnosed with hypertension and not receiving any antihypertensives, or previously diagnosed and receiving other antihypertensives and making a switch to nebivolol as combination or add-on therapy. The BENEFIT-KOREA study is a retrospectively registered study (ClinicalTrials.gov Identifier: NCT03847350) and details of the study design and methodology are available in the primary manuscript of the study [19].

Treatment dose and time for each patient was determined in compliance with routine medical practice; the decision to switch therapy to nebivolol as well as the equivalent drug and dosage for switching was determined by physician discretion (range, 1.25–10 mg; indicated therapeutic dose of nebivolol is 5 mg once-daily). In consideration of the fact that the pharmacokinetics of nebivolol could be influenced by age or decreased renal function, 2.5 mg was the initial dose in elderly and frail patients and in those with chronic kidney disease.

BP measurement

BP was measured when patients were in a stable sitting state with 5 minutes rest according to the standardized methods in the guidelines [2]. The mean seated cuff BP was measured twice within 1-minute interval (with patients in a stable state after 5 minutes rest) using upper arm sphygmomanometer (manual or automated devices were permitted). BP measurements were recorded and presented as an average of 2 measurements. The PR was generated by an automated device, or the PR measured for 15 seconds (manual measurement) multiplied by 4 was regarded as the PR per minute.

Statistics

The primary efficacy and safety results from the BENEFIT-KOREA study and results from a subanalysis based on age and sex have been published previously [20,21]. In this manuscript, we describe the results of a subanalysis of the participants for time-averaged BP as the primary efficacy parameter of 24 weeks of nebivolol treatment, based on baseline PR groups of < 70, 70–79, and ≥ 80 beats/min as well as posttreatment PR reduction groups of < 1, 1–9, and ≥ 10 beats/min. Time-averaged BP was calculated as follows [22]:

$$\frac{(Mean\ BP\ at\ Week\ 12\ \times\ Number\ of\ patients\ at\ Week\ 12)\ +\ (Mean\ BP\ at\ Week\ 24\ \times\ Number\ of\ patients\ at\ Week\ 24)}{Number\ of\ patients\ at\ Week\ 12\ +\ Number\ of\ patients\ at\ Week\ 24)}$$

Safety was assessed by recording adverse events (AEs) and adverse drug reactions (ADRs) and monitoring vital signs at each visit.

The safety set was defined as all participants who were administered nebivolol and underwent follow-up at least once during the study period. Efficacy parameters were analyzed in the efficacy set defined as all participants from the safety set who also had efficacy assessment data at 12 or 24 weeks. For baseline characteristics, descriptive statistics (mean ± standard deviation for continuous data; number of subjects and percentage for categorical data) is presented by baseline PR groups as well as posttreatment PR reduction groups. Statistical

significance for change from baseline at 12 weeks and 24 weeks in systolic BP (SBP) and diastolic BP (DBP) by the PR groups and posttreatment PR reduction groups was examined using paired t-test. Time-averaged SBP and DBP at 24 weeks were compared among baseline PR groups and posttreatment PR reduction groups using a multiple linear regression approach with age, sex, obesity, diabetes mellitus, cardiovascular disease, mode of prescription (de novo, switching—monotherapy or combination therapy, add-on for combination therapy), mean daily dose of nebivolol and baseline BP as covariates. Using generalized linear model (GLM), the time-averaged BPs adjusted for covariates were calculated and posttreatment comparisons between groups were done by Bonferroni correction. The *P*-value of < 0.05 was considered as significant level in all tests. Data analysis was performed using SAS ver. 9.4 (SAS Institute Inc., Cary, NC, USA). Safety endpoints of treatment emergent AEs were assessed using the MedDRA (Medical Dictionary for Regulatory Activities) standardized terms.

RESULTS

Table 1 outlines the baseline characteristics of the study population according to the baseline PR groups. Majority of the participants had baseline PR ≥ 80 beats/min, and a majority were male. There was significant difference in age between the group with baseline PR < 70 beats/min and the other 2 groups, as well as between the groups with PR 70–79 beats/min and PR ≥ 80 beats/min (all $P < 0.001$). Participants' preexisting antihypertensive drug use pattern is outlined in **Supplementary Table 2**. The dose of nebivolol at the final visit was 1.25 mg in 14 patients, 2.5 mg in 516 patients, 5 mg in 2,049 patients, 7.5 mg in 3 patients, and 10 mg in 3 patients.

Table 1. Baseline demographics in baseline PR groups

Demographics	PR (beats/min)			*P*-value
	< 70 (*n* = 192)	70–79 (*n* = 319)	≥ 80 (*n* = 569)	
Age (yr)	67.66 ± 10.30	62.83 ± 12.41	61.42 ± 14.44	< 0.001[a]
Sex				0.057[b]
Male	97 (50.52)	174 (54.55)	340 (59.75)	
Female	95 (49.48)	145 (45.45)	229 (40.25)	
Comorbidity				
Obesity[c]	68 (35.42)	139 (43.57)	223 (39.19)	0.460[b]
Unknown	57 (29.69)	74 (23.2)	169 (29.7)	
Diabetes mellitus	51 (26.56)	67 (21)	132 (23.2)	0.420[b]
Unknown	6 (3.13)	17 (5.33)	18 (3.16)	
Cardiovascular disease[d]	134 (69.79)	179 (56.11)	333 (58.52)	0.006[b]
Coronary artery disease	109 (56.77)	131 (41.07)	229 (40.25)	-
Heart failure	11 (5.73)	19 (5.96)	36 (6.33)	-
Peripheral vascular disease	4 (2.08)	5 (1.57)	16 (2.81)	-
Other (atrial fibrillation, cerebral infarction, cardiac hypertrophy, etc.)	38 (19.79)	56 (17.55)	115 (20.21)	-
Preexisting antihypertensive drug				-
Monotherapy	16 (8.33)	21 (6.58)	44 (7.73)	
De novo	47 (24.48)	86 (26.96)	149 (26.19)	
Combination therapy[d]				-
CCB including regimen	6 (3.13)	8 (2.51)	19 (3.34)	
ARB or ACE inhibitor including regimen	6 (3.13)	8 (2.51)	19 (3.34)	
Daily dose of nebivolol (mg)	4.22 ± 1.14	4.39 ± 1.11	4.42 ± 1.06	-

Data are presented as mean ± standard deviation or number (%).
PR, pulse rate; CCB, calcium channel blocker; ARB, angiotensin receptor blocker; ACE, angiotensin-converting enzyme.
[a]Kruskal-Wallis test showing the difference in continuous variable between baseline PR group.
[b]Chi-square test showing the difference between baseline PR group and categorical variable except for "unknown."
[c]Defined as body mass index ≥ 25 kg/m^2 or waist circumference > 90 cm for men and > 80 cm for women.
[d]Duplicate counts.

Table 2. Change from baseline in SBP, DBP, and PR with nebivolol at 12 and 24 weeks according to baseline PR groups

Parameters	PR (beats/min)					
	< 70		70–79		≥ 80	
	No. of patients	Data	No. of patients	Data	No. of patients	Data
SBP (mmHg)						
Baseline	192	139.81 ± 18.00	319	142.90 ± 15.41	569	145.50 ± 17.28
Week 12 (± 2 wk)	184	130.84 ± 15.23	306	131.84 ± 14.36	545	130.86 ± 15.06
Week 24 (± 2 wk)	170	129.05 ± 14.17	281	130.33 ± 15.76	477	131.22 ± 15.04
P-value[a]		< 0.001		< 0.001		< 0.001
DBP (mmHg)						
Baseline	192	78.39 ± 12.64	319	84.82 ± 11.98	569	85.95 ± 12.68
Week 12 (± 2 wk)	184	74.62 ± 11.48	305	77.98 ± 10.36	545	77.39 ± 11.30
Week 24 (± 2 wk)	170	73.57 ± 10.67	281	76.09 ± 10.52	476	76.91 ± 10.97
P-value[a]		< 0.001		< 0.001		< 0.001
PR (beats/min)						
Baseline	192	64.56 ± 3.16	319	74.11 ± 2.91	569	92.98 ± 11.64
Week 12 (± 2 wk)	177	64.96 ± 8.80	292	69.78 ± 8.49	527	75.97 ± 12.52
Week 24 (± 2 wk)	165	63.82 ± 9.65	268	68.56 ± 9.08	463	75.59 ± 11.68
P-value[a]		0.372		< 0.001		< 0.001

Data are presented as number only or mean ± standard deviation.
SBP, systolic blood pressure; DBP, diastolic blood pressure; PR, pulse rate.
[a]*P*-value (paired *t*-test) showing the change in SBP/DBP/PR from baseline to week 24 (± 2 weeks).

Significant reduction in PR vs. baseline was observed with nebivolol at 12 and 24 weeks in participants with baseline PR of 70–79 and ≥ 80 beats/min (both $P < 0.001$); the maximum reduction in PR from baseline was seen in participants with a baseline PR of ≥ 80 beats/min (**Table 2**, **Supplementary Fig. 1)**. A significant reduction in SBP and DBP at weeks 12 and 24 compared with baseline was also observed with nebivolol in all baseline PR groups (all $P < 0.001$) (**Table 2**, **Supplementary Fig. 2)**.

In the unadjusted GLM analysis, time-averaged SBP and DBP at week 24 were similar among both baseline PR groups and posttreatment PR reduction groups (**Tables 3** and **4**). The unadjusted time-averaged SBP at 24 weeks was not significantly different within the baseline PR groups or the posttreatment PR reduction groups (**Fig. 1A and B**, **Tables 3** and **4**), but the unadjusted time-averaged DBP was significantly different within both groups ($P < 0.001$) (**Fig. 1C and D**, **Tables 3** and **4**). When adjusted for age, sex, obesity, diabetes mellitus, cardiovascular disease, mode of prescription, mean daily dose of nebivolol, and baseline BP, the difference in time-averaged SBP and DBP at 24 weeks was not significant within the baseline PR groups (**Tables 5** and **6**), but was significant in the posttreatment PR reduction groups (**Fig. 2**, **Tables 7** and **8**), with the exception

Table 3. Difference between time-averaged BP at week 24 and baseline BP according to baseline PR group

Parameters	Baseline PR (beats/min)			*P*-value[a]
	< 70 (*n* = 192)	70–79 (*n* = 319)	≥ 80 (*n* = 569)	
SBP (mmHg)				
Baseline	139.81 ± 18.00	142.90 ± 15.41	145.50 ± 17.28	< 0.001
Time-averaged	130.24 ± 13.08	131.38 ± 13.50	131.25 ± 14.10	0.645
Difference	−9.57 ± 18.19	−11.52 ± 17.01	−14.25 ± 18.37	0.006
DBP (mmHg)				
Baseline	78.39 ± 12.64	84.82 ± 11.98	85.95± 12.68	< 0.001
Time-averaged	74.13 ± 10.06	77.27 ± 9.48	77.41 ± 10.25	< 0.001
Difference	−4.27 ± 12.85	−7.55 ± 11.29	−8.54 ± 12.66	< 0.001

Data are presented as mean ± standard deviation. Difference is calculated as "Time-Averaged Data − Baseline Data."
BP, blood pressure; PR, pulse rate; SBP, systolic blood pressure; DBP, diastolic blood pressure.
[a]*P*-value (analysis of covariance) calculated for the time-averaged SBP and DBP and the difference between baseline and follow-up, with the mean daily dose of nebivolol as covariate.

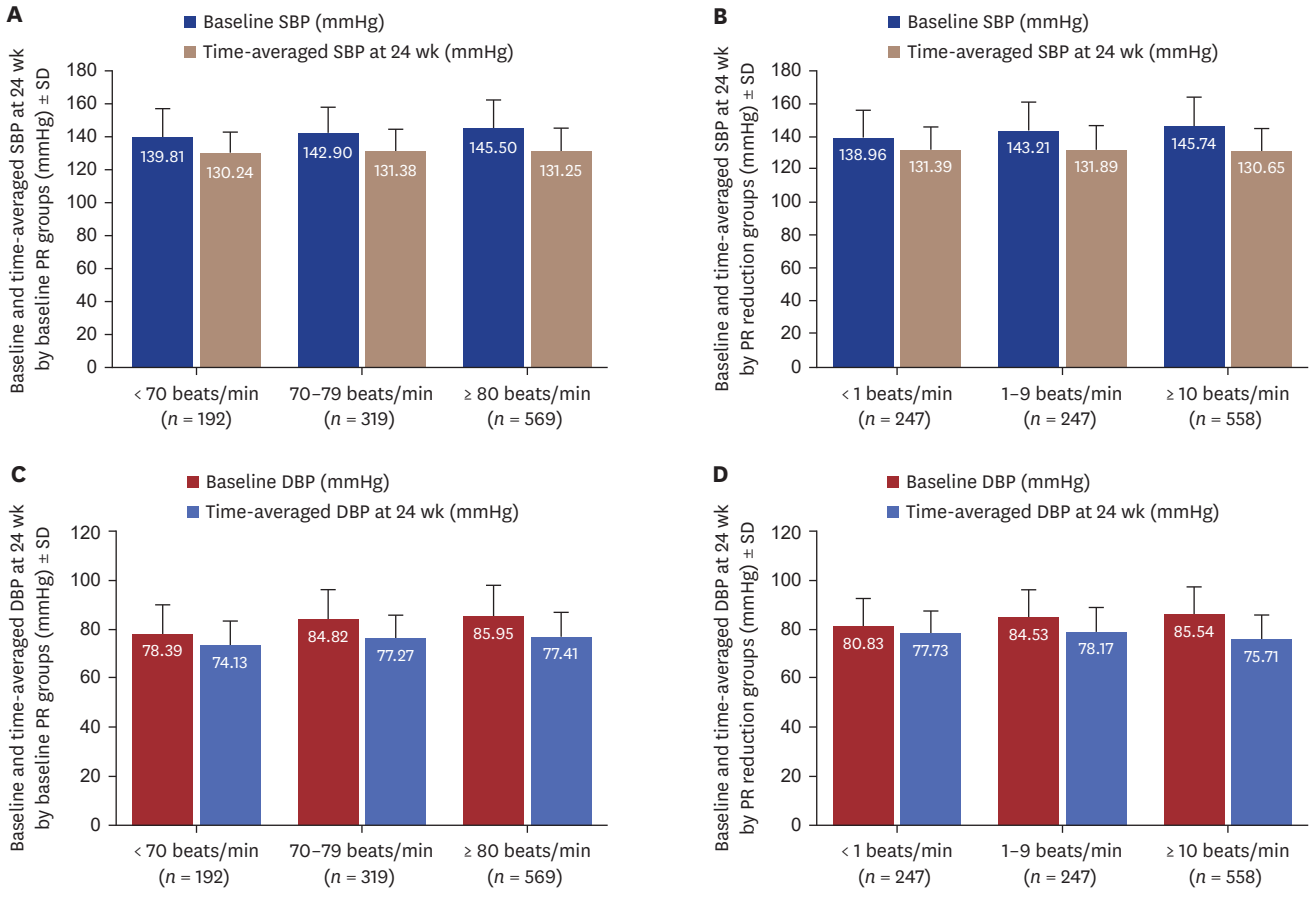


Fig. 1. Baseline and time-averaged SBP by (A) baseline PR groups and (B) posttreatment PR reduction groups. Baseline and time-averaged DBP by (C) baseline PR groups ($P < 0.001$) and (D) posttreatment PR reduction groups ($P < 0.001$).
SBP, systolic blood pressure; DBP, diastolic blood pressure; PR, pulse rate; SD, standard deviation.

Table 4. Difference between time-averaged BP at week 24 and baseline BP according to posttreatment PR reduction groups

Parameters	Post treatment PR reduction (beats/min)			*P*-value[a]
	< 1 (*n* = 247)	1–9 (*n* = 247)	≥ 10 (*n* = 558)	
SBP (mmHg)				
Baseline	138.96 ± 16.12	143.21 ± 16.95	145.74 ± 16.96	< 0.001
Time-averaged	131.39 ± 13.76	131.89 ± 14.43	130.65 ± 13.36	0.455
Difference	−7.57 ± 17.09	−11.31 ± 16.84	−15.08 ± 18.72	< 0.001
DBP (mmHg)				
Baseline	80.83 ± 11.80	84.53 ± 12.77	85.54 ± 12.87	< 0.001
Time-averaged	77.73 ± 9.63	78.17 ± 10.32	75.71 ± 10.04	< 0.001
Difference	−3.11 ± 11.67	−6.36 ± 11.70	−9.83 ± 12.41	< 0.001

Data are presented as mean ± standard deviation. Difference is calculated as "Time-Averaged Data − Baseline Data."
BP, blood pressure; PR, pulse rate; SBP, systolic blood pressure; DBP, diastolic blood pressure.
[a]*P*-value (analysis of covariance) calculated for the time-averaged SBP and DBP and the difference between baseline and follow-up, with the mean daily dose of nebivolol as covariate.

of adjusted time-averaged SBP in the group with posttreatment PR reduction of 1–9 beats/min vs. the group with posttreatment PR reduction of < 1 beats/min which was not significant.

Dizziness, headache, chest pain/discomfort, and dyspnea/exertional dyspnea were the most frequently reported AEs in all 3 baseline PR and posttreatment PR reduction groups (**Table 9**). The majority of AEs and ADRs reported were mild in severity. There was no difference

Table 5. Multiple linear regression analysis for time-averaged SBP at week 24 according to baseline PR groups (*n* = 770)

Variables	Parameter estimate (β)	Standard error	*P*-value
Intercept	92.6924	5.6484	< 0.001
Baseline PR group (beats/min)			
< 70 (reference)	-	-	-
70–79	0.6563	1.4426	0.649
≥ 80	0.1927	1.3604	0.887
Age (1 yr)	0.0507	0.0415	0.223
Sex			
1 = Male	0.4753	1.0125	0.639
0 = Female (reference)	-	-	-
Obesity			
1 = Obesity	2.5661	0.9837	0.009
0 = Normal (reference)	-	-	-
Diabetes mellitus			
1 = Yes	0.8956	1.1795	0.448
0 = No (reference)	-	-	-
Cardiovascular diseases			
1 = Yes	−0.3579	1.0940	0.744
0 = No (reference)	-	-	-
Mode of prescription			
1 = De novo or add-on therapy	−2.5736	1.2766	0.044
0 = Switching (reference)	-	-	-
Baseline SBP (1 mmHg)	0.2599	0.0296	< 0.001
Mean daily dose of nebivolol (1 mg)	−0.5178	0.4314	0.230

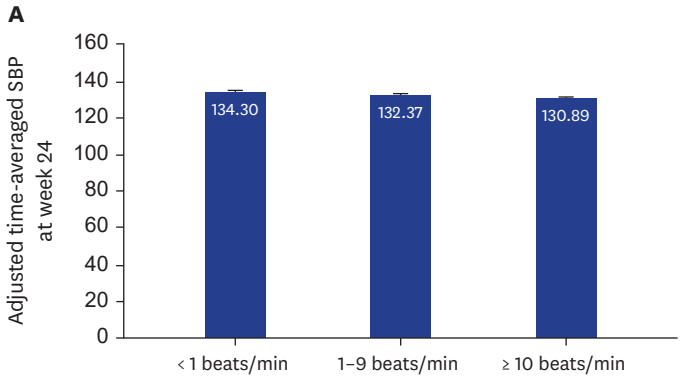
Adjusted for age, sex, obesity, diabetes mellitus, cardiovascular disease, mode of prescription, mean daily dose of nebivolol, and baseline blood pressure (dependent variable: time-averaged SBP).
SBP, systolic blood pressure; PR, pulse rate.

Table 6. Multiple linear regression analysis for time-averaged DBP at week 24 according to baseline PR groups (*n* = 770)

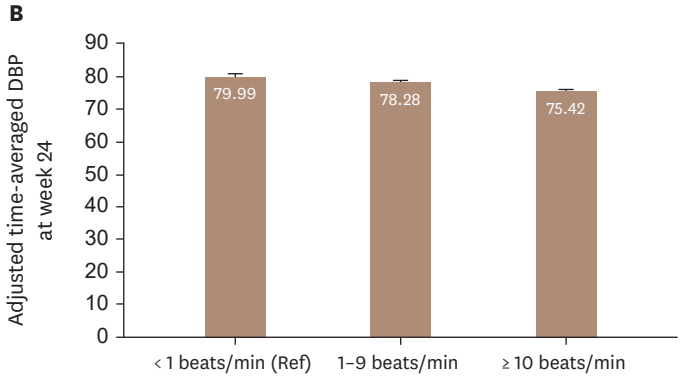
Variables	Parameter estimate (β)	Standard error	*P*-value
Intercept	61.9704	3.7587	< 0.001
Baseline PR group (beats/min)			
< 70 (reference)	-	-	-
70–79	0.9390	0.9871	0.342
≥ 80	0.2541	0.9308	0.785
Age (1 yr)	−0.1025	0.0289	< 0.001
Sex			
1 = Male	0.1815	0.6867	0.792
0 = Female (reference)	-	-	-
Obesity			
1 = Obesity	0.1630	0.6683	0.807
0 = Normal (reference)	-	-	-
Diabetes mellitus			
1 = Yes	−1.4188	0.8016	0.077
0 = No (reference)	-	-	-
Cardiovascular diseases			
1 = Yes	−0.1617	0.7434	0.828
0 = No (reference)	-	-	-
Mode of prescription			
1 = De novo or add-on therapy	−1.9367	0.8640	0.025
0 = Switching (reference)	-	-	-
Baseline DBP (1 mmHg)	0.2707	0.0279	< 0.001
Mean daily dose of nebivolol (1 mg)	−0.0549	0.2910	0.851

Adjusted for age, sex, obesity, diabetes mellitus, cardiovascular disease, mode of prescription, mean daily dose of nebivolol, and baseline blood pressure (dependent variable: time-averaged DBP).
DBP, diastolic blood pressure; PR, pulse rate.

between the baseline PR groups and between the posttreatment PR reduction groups with respect to AEs and ADRs.



				Post-hoc test	Post-hoc test		
Variables	*P*-value for variable	LS means	± SE	Duncan grouping	Bonferroni		
Post-treatment PR reduction group	0.022				< 70 beats/min	70–79 beats/min	≥ 80 beats/min
< 1 beats/min (Ref)		134.30	± 1.17	A		0.4992	0.0186
1–9 beats/min		132.37	± 1.11	A			0.6016
≥ 10 beats/min		130.89	± 0.87	A			
Baseline SBP (1 mmHg)	< 0.001						
Dependent variable: time-averaged SBP; No. of subjects included in model = 750							



				Post-hoc test		Post-hoc test		
Variables	*P*-value for variable	LS means	± SE	Duncan grouping		Bonferroni		
Post-treatment PR reduction group	< 0.001					< 70 beats/min	70–79 beats/min	≥ 80 beats/min
< 1 beats/min (Ref)		79.99	± 0.78	A			0.2013	< 0.0001
1–9 beats/min		78.28	± 0.74	A				0.0007
≥ 10 beats/min		75.42	± 0.58		B			
Baseline DBP (1 mmHg)	< 0.001							
Dependent variable: time-averaged DBP; No. of subjects included in model = 750								

Fig. 2. Generalized linear model for (A) time-averaged SBP and (B) time-averaged DBP at week 24 adjusted for age, sex, obesity, diabetes mellitus, cardiovascular disease, mode of prescription, mean daily dose of nebivolol and baseline BP according to posttreatment pulse rate reduction groups.
SBP, systolic blood pressure; DBP, diastolic blood pressure; LS, least square; SE, standard error.

https://doi.org/10.5646/ch.2025.31.e8

Table 7. Multiple linear regression analysis for time-averaged SBP at week 24 according to posttreatment PR reduction group (n = 750)

Variables	Parameter estimate (β)	Standard error	*P*-value
Intercept	92.5186	5.6232	< 0.001
Posttreatment PR reduction group (beats/min)			
< 1 (reference)	-	-	-
1–9	−1.9339	1.3961	0.166
≥ 10	−3.4148	1.2437	0.006
Age (1 yr)	0.0727	0.0418	0.083
Sex			
1 = Male	0.4953	1.0179	0.625
0 = Female (reference)	-	-	-
Obesity			
1 = Obesity	2.7672	0.9931	0.006
0 = Normal (reference)	-	-	-
Diabetes mellitus			
1 = Yes	0.4877	1.1841	0.681
0 = No (reference)	-	-	-
Cardiovascular disease			
1 = Yes	−0.5518	1.0956	0.615
0 = No (reference)	-	-	-
Mode of prescription			
1 = De novo or add-on therapy	−2.7075	1.2687	0.033
0 = Switching (reference)	-	-	-
Baseline SBP (1 mmHg)	0.2692	0.0300	< 0.001
Mean daily dose of nebivolol (1 mg)	−0.4569	0.4311	0.289

Adjusted for age, sex, obesity, diabetes mellitus, cardiovascular disease, mode of prescription, mean daily dose of nebivolol, and baseline blood pressure (dependent variable, time-averaged SBP).
SBP, systolic blood pressure; PR, pulse rate.

Table 8. Multiple linear regression analysis for time-averaged DBP at week 24 according to posttreatment PR reduction group (n = 750)

Variables	Parameter estimate (β)	Standard error	*P*-value
Intercept	62.1119	3.7340	< 0.001
Posttreatment PR reduction group (beats/min)			
< 1 (reference)	-	-	-
1–9	−1.7138	0.9346	0.067
≥ 10	−4.5781	0.8296	< 0.001
Age (1 yr)	−0.0893	0.0289	0.002
Sex			
1 = Male	−0.0026	0.6809	0.997
0 = Female (reference)	-	-	-
Obesity			
1 = Obesity	0.4713	0.6652	0.479
0 = Normal (reference)	-	-	-
Diabetes mellitus			
1 = Yes	−1.5075	0.7921	0.057
0 = No (reference)	-	-	-
Cardiovascular disease			
1 = Yes	−0.2432	0.7336	0.740
0 = No (reference)	-	-	-
Mode of prescription			
1 = De novo or add-on therapy	−2.2094	0.8471	0.009
0 = Switching (reference)	-	-	-
Baseline DBP (1 mmHg)	0.2991	0.0277	< 0.001
Mean daily dose of nebivolol (1 mg)	−0.0383	0.2867	0.894

Adjusted for age, sex, obesity, diabetes mellitus, cardiovascular disease, mode of prescription, mean daily dose of nebivolol, and baseline blood pressure according to the posttreatment PR reduction groups (dependent variable, time-averaged DBP).
DBP, diastolic blood pressure; PR, pulse rate.

https://doi.org/10.5646/ch.2025.31.e8

Table 9. Adverse events with an incidence of ≥ 0.5% and adverse drug reactions with an incidence of ≥ 0.2% in any baseline PR groups or posttreatment PR reduction groups in the safety population

Descriptions[a]	Baseline PR group (beats/min)				Posttreatment PR reduction group (beats/min)			
	< 70 (*n* = 192)	70–79 (*n* = 319)	≥ 80 (*n* = 569)	*P*-value	< 1 (*n* = 247)	1–9 (*n* = 247)	≥ 10 (*n* = 558)	*P*-value
Adverse event	20 (10.42)	39 (12.23)	81 (14.24)	0.1775[b]	29 (11.74)	33 (13.36)	75 (13.44)	0.507[b]
Dizziness	2 (1.04)	4 (1.25)	10 (1.76)		2 (0.81)	3 (1.21)	9 (1.61)	
Headache	1 (0.52)	3 (0.94)	8 (1.41)		1 (0.40)	3 (1.21)	8 (1.43)	
Hypoesthesia	1 (0.52)	-	-		1 (0.40)	1 (0.40)	-	
Chest pain	3 (1.56)	2 (0.63)	1 (0.18)		-	5 (2.02)	1 (0.18)	
Chest discomfort	1 (0.52)	4 (1.25)	1 (0.18)		3 (1.21)	1 (0.40)	2 (0.36)	
Pain	1 (0.52)	-	-		-	1 (0.40)		
Dyspnea	4 (2.08)	1 (0.31)	3 (0.53)		3 (1.21)	3 (1.21)	2 (0.36)	
Vasomotor rhinitis	1 (0.52)	-	-		-	1 (0.40)	-	
Dyspepsia	1 (0.52)	-	3 (0.53)		1 (0.40)	-	3 (0.54)	
Abdominal pain	1 (0.52)	2 (0.63)	2 (0.35)		1 (0.40)	1 (0.40)	2 (0.36)	
Dry mouth	1 (0.52)	-	-		-	-	1 (0.18)	
Colitis	1 (0.52)	-	-		-	1 (0.40)	-	
Dental caries	1 (0.52)	-	-		-	1 (0.40)	-	
Palpitations	1 (0.52)	-	1 (0.18)		-	-	2 (0.36)	
Pharyngeal abscess	1 (0.52)	-	-		-	-	-	
Gout	1 (0.52)	-			-	1 (0.40)	-	
Bile duct stone	-	2 (0.63)			1 (0.40)	1 (0.40)	-	
Limb injury	1 (0.52)				1 (0.40)	-	-	
Acetabulum fracture	1 (0.52)				-	1 (0.40)	-	
Orthostatic hypotension	1 (0.52)		2 (0.35)		-	1 (0.40)	2 (0.36)	
Peripheral arterial occlusive disease	1 (0.52)	-	-		1 (0.40)	-	-	
Adverse drug reaction	3 (1.56)	2 (0.63)	8 (1.41)	1.000[c]	3 (1.21)	3 (1.21)	6 (1.08)	> 0.999[c]
Dizziness	1 (0.52)	-	4 (0.70)		1 (0.40)	-	3 (0.54)	
Headache	-	-	2 (0.35)		-	-	2 (0.36)	
Burning sensation	-	-	1 (0.18)		-	1 (0.40)	-	
Hypoesthesia	-	-	1 (0.18)		-	1 (0.40)	-	
Dyspnea	1 (0.52)	-	-		1 (0.40)	-	-	
Arthralgia	-	-	1 (0.18)		-	1 (0.40)	-	
Hypotension	-	1 (0.31)	-		1 (0.40)	-	-	
Orthostatic hypotension	1 (0.52)	-	-		1 (0.40)	1 (0.40)	-	
Pruritus	-	1 (0.31)	-		0	1 (0.40)	-	

Values are presented as number (%).
PR, pulse rate.
[a]According to MeDRA (Medical Dictionary for Regulatory Activities) ver. 20.0.
[b]*P*-value by χ^2 test showing the difference between the groups of baseline PR < 70 beats/min vs. ≥ 80 beats/min or the groups of posttreatment PR reductions < 1 beats/min vs. ≥ 10 beats/min.
[c]Fisher's exact test showing the difference between the groups of baseline PR < 70 beats/min vs. ≥ 80 beats/min or the groups of posttreatment PR reductions < 1 beats/min vs. ≥ 10 beats/min.

DISCUSSION

In this subanalysis of BENEFIT-KOREA study investigating the impact of PR on the efficacy and safety of nebivolol in participants with hypertension, we found that time-averaged BP at 24 weeks when adjusted for covariates was significantly lower in the posttreatment PR reduction groups, while there was no significant difference in the time-averaged BP among the baseline PR groups.

The predictive value of baseline PR and/or PR reduction on the magnitude of BP reduction with β-blockers has not been studied adequately in hypertension. There are some studies which have investigated β-blockers in the context of the impact of baseline PR and/or PR reduction on cardiovascular outcomes (and not the magnitude of BP reduction) in patients with HF or myocardial infarction, but scarcely in hypertension [20,21,23-27]. In HF, the antagonism

of the overactivated sympathetic nervous system with β-blockers leads to a large effect size, and baseline PR and/or PR reduction with β-blockers has been shown to be associated with improved cardiovascular outcomes [23-27]. But the role of accordant BP reduction has not been defined in these studies. Also, this scenario may not be translatable to hypertension where the sympathetic activity profile and baseline PR can be heterogeneous. Hence, studies are needed to investigate the association between baseline PR or PR reduction with β-blockers and the magnitude of BP reduction specifically in patients with essential hypertension.

In our study, we found no significant differences in the unadjusted or adjusted time-averaged BP at week 24 vs. baseline between the baseline PR groups, with the exception of unadjusted time-averaged DBP at week 24. We then decided to compare the difference in time-averaged BP among the posttreatment PR reduction groups of < 1, 1–9, and ≥ 10 beats/min. We found that posttreatment PR reduction and not baseline PR is predictive of the magnitude of BP reduction after using nebivolol. A biologically plausible explanation for this could be rooted in the mechanism of action of nebivolol in BP reduction which, unlike other β-blockers, is not solely based on inhibition of sympathetic nervous system [17]. Nebivolol also has an effect on endothelial function independent of sympathetic inhibition [17]. This effect could lead to a decrease in the BP reduction effect size derived from sympathetic antagonism by weakening or diluting the relationship between baseline PR and BP reduction. Furthermore, it is well known that the normal aging process involves slowing down of PR; in some elderly patients, the baseline PR is not necessarily increased despite an overactive sympathetic system due to a difference in the aging process of the sinoatrial node [28]. Hence, baseline PR may not be a good indicator of the activity of the sympathetic nervous system in the BENEFIT-KOREA study population where the mean age was > 60 years; in these patients, PR reduction following β-blocker therapy may be a better indicator of β-blocker efficacy even though it is a posttreatment marker.

To summarize, while overall BP reduction with nebivolol was effective regardless of baseline PR groups in our study, baseline PR may not be an optimal indicator to predict BP reduction efficacy of nebivolol in hypertension. For an individual patient, whether the efficacy of nebivolol is attributable to reduction of PR or sympathetic activity can be speculated only when the posttreatment PR reduction is measured after initiating nebivolol treatment. These findings suggest that nebivolol could be an option for the treatment of hypertension even in a patient with baseline PR < 80 beats/min. Although BP reduction is of critical importance in reducing cardiovascular events, it remains unclear whether PR reduction could improve CV and mortality outcomes in hypertension. Lastly, our postulation could be relevant in a clinical environment—posttreatment PR reduction can potentially be used as a marker for adherence to β-blocker treatment [29].

We believe that one of the strengths of our analysis is that we have evaluated time-averaged BPs with nebivolol treatment rather than BP reduction from baseline at weeks 12 and 24 to account for Wilder principle which proposes that pretreatment values determine posttreatment response [30]. As a result of using time-averaged SBP and DBP values, our analysis is not impacted by baseline BP values.

Our study had several limitations. The BENEFIT-KOREA study was a prospective observational study and here we have reported results from a subanalysis. The associations between PR, reduction in PR, and efficacy of BP response reported in our subanalysis are suggestive and not confirmatory. Also, the sample size of our analysis was not sufficiently

large to exclude false negative results. Large, double-blind, randomized controlled trials are warranted to confirm the predictive value of baseline PR and/or posttreatment PR reduction in the BP-lowering efficacy of conventional as well as vasodilating β-blockers. Additionally, in our study we measure PR with an automated device, or the PR measured for 15 seconds multiplied by 4. PR as measured by automated BP device may also be inaccurate compared with a monitoring method for a longer period. Finally, adherence was not measured in the current study, and the lower PR reduction in the posttreatment group could be the result of poor adherence.

CONCLUSIONS

In this subanalysis in the BENEFIT-KOREA cohort, we have shown that the efficacy of BP response to nebivolol is greater in patients with hypertension with a higher posttreatment reduction in PR, even when adjusted for baseline characteristics (age, sex, obesity, diabetes mellitus, cardiovascular disease, mode of prescription, mean daily dose of nebivolol, and baseline BP). The efficacy of nebivolol for BP reduction seems to be indicated not by baseline PR but by posttreatment PR reduction. These findings suggest the presence of mechanisms of action for nebivolol in addition to sympathetic inhibition which could weaken the relationship between baseline PR and BP reduction.

ACKNOWLEDGEMENTS

The authors thank SeonYoung Nam (D2S) for her assistance in conducting statistical analysis. We would also like to thank Dr. Shilpa Mudgal from In Vivo Communications (Asia) for editorial assistance with this manuscript.

SUPPLEMENTARY MATERIALS

Supplementary Table 1
The list of 66 Institutional Review Board sites

Supplementary Table 2
Concomitant antihypertensives according to baseline PR groups

Supplementary Fig. 1
Mean change in PR from baseline at 12 and 24 weeks according to the baseline PR groups.

Supplementary Fig. 2
Change in (A) SBP and (B) DBP according to baseline PR groups.

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