

Real-world efficacy and safety of nebivolol in Korean patients with hypertension from the BENEFIT KOREA study

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Objective: The efficacy and safety of nebivolol in patients with hypertension is well established, but its effect in Asian patients with essential hypertension in the real world has not been studied.

Methods: Adult South Korean patients with essential hypertension, with or without comorbidities, were enrolled to participate in this prospective, single-arm, open, observational study; 3011 patients received nebivolol either as monotherapy or add-on therapy. Changes in SBP, DBP and heart rate (HR) at 12 and 24 weeks were evaluated. Subgroup analysis for BP changes in newly diagnosed (*de novo*) patients and those receiving other antihypertensives at study entry were also conducted.

Results: Nebivolol significantly decreased mean SBP and DBP at 12 and 24 weeks compared with baseline ($P < 0.0001$). A significant reduction in HR was also observed at 12 and 24 weeks ($P < 0.0001$). The reductions of SBP and DBP were notably greater when nebivolol was used as monotherapy in *de novo* patients ($P < 0.0001$) and as add-on therapy to existing antihypertensives (angiotensin II receptor blockers, angiotensin-converting enzyme inhibitors and calcium channel blockers; $P < 0.0001$). Majority of the reported adverse events were mild; the most common adverse events were dizziness (1.3%), headache (1.0%) and dyspnea (0.9%).

Conclusion: Despite the limitations associated with observational studies, this real-world study in Asian patients with essential hypertension with and without comorbidities, demonstrated the efficacy and safety of once daily nebivolol, either as monotherapy or add-on therapy.

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Keywords: add-on therapy, Asian, combination therapy, essential hypertension, monotherapy, nebivolol

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ADR, adverse drug reaction; ARB, angiotensin II receptor blockers; BP, blood pressure; CCB, calcium channel blocker; ESC, European Society of Cardiology; ESH, European Society of Hypertension; HR, heart rate; RAS, renin-angiotensin system; RCT, randomized

controlled trial; SADR, serious adverse drug reaction; SAE, serious adverse event; SD, standard deviation

INTRODUCTION

Hypertension, characterized by persistent high blood pressure (BP), is the most common modifiable risk factor for all-cause mortality and morbidity worldwide, and is associated with an increased risk of cardiovascular events and kidney disease [1,2]. Worldwide, approximately one in four adults has hypertension [2]. Raised BP is also increasing in trend in Asia, particularly in low-income and middle-income countries; three quarters or more of the rise is attributable to population growth and aging [3], as well as adoption of unfavorable lifestyles [4]. In Korea, although age-standardized mean BP levels and the prevalence of hypertension has showed minimal changes over the last 10 years, the number of people with hypertension has been increasing from 7.6 million in 1998 to over 11 million in 2016 [5].

Management of hypertension constitutes nonpharmacological (lifestyle modification) and pharmacological interventions, which include different classes of antihypertensive medications given as monotherapy or combination therapy [6]. The 2018 European Society of Cardiology (ESC)/European Society of Hypertension (ESH) hypertension guidelines state that all five major classes of antihypertensive drugs

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[angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), beta-blockers, calcium channel blocker (CCBs) and diuretics] are equally effective; some are preferred or less preferred depending on specific clinical conditions [6]. The ESC/ESH guidelines recommend the use of beta-blockers as an add-on for the treatment of hypertension in specific conditions, including for heart rate control, symptomatic angina, postmyocardial infarction, heart failure with reduced ejection fraction, and as an alternative to ACEIs or ARBs in younger women with hypertension who are planning pregnancy or of child-bearing potential [6]. However, the use of beta-blockers as monotherapy or in combination with other agents for initial therapy in hypertension has not been supported, primarily because of unfavorable outcomes observed in studies with once-daily atenolol (a nonvasodilating, second-generation beta blocker) in combination with thiazide diuretics [4,7]. Nonvasodilating beta-blockers have suboptimal effect in controlling BP, a reduced effect on left ventricular hypertrophy, and unfavorable hemodynamics and metabolic effects [8]. In contrast, third-generation beta-blockers – carvedilol, labetalol and nebivolol – have vasodilatory properties and demonstrate a more favorable effect on metabolic and hemodynamic parameters, with fewer side effects [4,9,10].

Nebivolol is a third-generation vasodilatory β_1 -adrenergic receptor antagonist, which induces nitric oxide-mediated vasodilatory effects via β_3 receptor agonism [11]. Nebivolol has been shown to have similar or better treatment response and BP control compared with other antihypertensives or their combinations, with significantly better tolerability [11]. Nebivolol was also effective in reducing SBP and DBP in patients with hypertension as an add-on to or as a fixed-dose combination with other antihypertensive agents [12–17]. Furthermore, in patients with hypertension with comorbidities, nebivolol has been reported to be lipid neutral, did not produce detrimental metabolic effects, and demonstrated a potentially positive effect on HDL cholesterol [18–20].

Although the efficacy and safety of nebivolol in patients with hypertension is well established, its effect in a primarily Asian population has not been investigated in a large-scale study so far. The BENEFIT KOREA study (BENefits after 24 weeks of NEbivolol administration For essential hypertension patients with various comorbidities and treatment environments in KOREA) evaluated the efficacy and safety of nebivolol in Asian patients with essential hypertension in a real-world setting. In this article, we present some of the results from this study.

METHODS

Study design and participants

This open, noncomparative, noncontrolled, prospective, single-arm, multicenter, observational study was conducted at 66 sites in South Korea from 1 July 2015 to 23 March 2017. 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 Institutional Review Board/independent ethics committee(s).

Male and female patients aged 19 years or older diagnosed with essential hypertension (previously or at study entry) who had signed the written informed consent form for their voluntary participation were eligible to participate in the study. These patients could be newly diagnosed at study entry and not receiving any antihypertensives, or previously diagnosed and receiving other antihypertensive medications, could switch one of the antihypertensive medications to nebivolol or use nebivolol as an add-on therapy. Patients were not included if they had hypersensitivity to nebivolol substance; a history of bronchospasm or bronchial asthma; metabolic acidosis; bradycardia [heart rate (HR) <60 bpm]; second-degree and third-degree atrioventricular block; acute heart failure, cardiogenic shock, or episodes of decompensated heart failure requiring intravascular inotropic therapy; uncontrolled severe heart failure; hypotension (SBP <90 mmHg); severe peripheral circulatory disturbances; sick sinus syndrome including sinoatrial block; untreated pheochromocytoma; hepatic insufficiency; impaired liver function; chronic heart failure who had severe renal insufficiency (serum creatinine $\geq 250 \mu\text{mol/l}$); rare hereditary problems of galactose intolerance, the Lapp-lactase deficiency or glucose-galactose malabsorption; were pregnant women or nursing mothers; or had participated in other clinical trial within the last 3 months. Concomitant therapy of nebivolol with calcium channel antagonists (verapamil HCL, diltiazem), class I antiarrhythmic (quinidine, hydroquinidine, cibenzoline, flecainide, disopyramide, lidocaine, mexiletine, propafenone), and centrally acting antihypertensives (clonidine, guanfacine, moxonidine, methyl dopa, rilmenidine) was prohibited during the study period.

Assessments were recorded at three patient visits during the study period – baseline visit (0 week), and follow-up visits at 12 (± 2) and at 24 (± 2) weeks. At the baseline visit, the captured parameters included demographics (age, sex, height, weight, waist size), medical history (past medical history and present medical history within 6 months), history of previous antihypertensive drugs, administrative status of nebivolol, concomitant medications, blood parameters [glucose (HbA1c and fasting blood sugar), total cholesterol, triglyceride, HDL cholesterol, LDL cholesterol, and other tests when done], and BP measurement. Of the laboratory test results collected, the values assessed as adverse events were recorded in the safety analysis. At follow-up visits, weight and waist size, administrative status of nebivolol, concomitant medications, laboratory tests, BP measure and safety assessment were documented.

Measurement of blood pressure, pulse rate and heart rate

BP measured based on guidelines from Korean Society of Hypertension [10], was in accordance with the ESC/ESH guidelines. All participating centers were checked for compliance and the settings for BP measurement at the initiation meeting. BP was measured when patients were in stable state with 5 min rest. The mean seated cuff BP was measured twice within 1-min interval using upper arm sphygmomanometer; either manual or automated device was permitted. BP measurements were recorded and presented as an average of two measurements. Pulse rate reading

generated by automated device or pulse rate measured for 15 s before manual measurement multiplied by 4 were regarded as the pulse rate per minute. HR was measured by electrocardiography.

Selection and timing of treatment dose for each patient was conducted in compliance with routine medical practice. The decision to switch therapy, and the equivalent drug and dosage for switching was determined by physician discretion to achieve better BP control or because of side effect of the existing drugs (range 1.25–10 mg; indicated therapeutic dose of nebivolol is 5 mg once-daily).

Study outcomes

The primary efficacy end point in the BENEFIT KOREA study was change in SBP and DBP after 12 and 24 weeks of nebivolol treatment as monotherapy or add-on therapy. The secondary efficacy end points presented here are change from baseline in pulse rate and HR after 12 and 24 weeks compared with baseline. Other secondary end points, which were assessed are not presented in this article. Additionally, we performed a subgroup analysis of the primary efficacy in subpopulations of patients who were newly diagnosed with essential hypertension at study entry (*de novo*); taking other monotherapy antihypertensive at study entry who switched to nebivolol during the study (monotherapy switch); taking one or two other antihypertensives [including CCBs, RAS blockers (ARBs or ACEIs) and diuretics] at study entry who received add-on nebivolol during the study (add-on therapy). Post hoc subgroup analysis of the primary efficacy was also done based on age, sex and baseline BMI. Safety was assessed by recording adverse events and monitoring vital signs (excluding body temperature and respiratory parameters) at each visit.

Statistical analysis

Assuming a standard deviation (SD) in mean SBP change from baseline after 6 months of treatment to be 8.27 based on the width of the 95% confidence interval on paired *t* test

of 0.56 (± 0.28) at a 5% significance level, it was estimated that a sample size of 3352 participants would be needed.

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.

All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, North Carolina, USA). Quantitative data were statistically analyzed using paired *t*-test.

RESULTS

Participants disposition and baseline characteristics

Data for 3250 participants was available from 66 sites across South Korea; data for 3140 participants was included in the safety population. From the safety population, 129 participants whose SBP and DBP were not recorded at baseline or at 12 (± 2 weeks) or 24 weeks (± 2 weeks) were excluded, resulting in 3011 participants included in the efficacy population (Fig. 1). Of the 3250 total participants, 3011 (92.7%) completed the study (Fig. 1).

Baseline demographic and clinical characteristics of the safety population are summarized in Table 1. The mean age of study participants was 63.5 ± 12.9 years; 52.7% of the participants were at least 65 years old and 40.4% were women. Among the study participants, 96.1% had cardiocerebrovascular risk factors of which 50.5% had dyslipidemia and 28.9% had diabetes mellitus (Table 1); 89.1% had past medical history, and 77.8% were receiving concomitant treatment with other antihypertensives (Table 1); and 83.0% also took other concomitant medications including antihyperlipidemic agents (65.7%), anticoagulants, antiplatelet and thrombolytic agents (61.4%) and drugs for angina pectoris (32.4%).

The mean total treatment duration of nebivolol was 172.5 ± 46.4 days. The mean daily treatment dose of

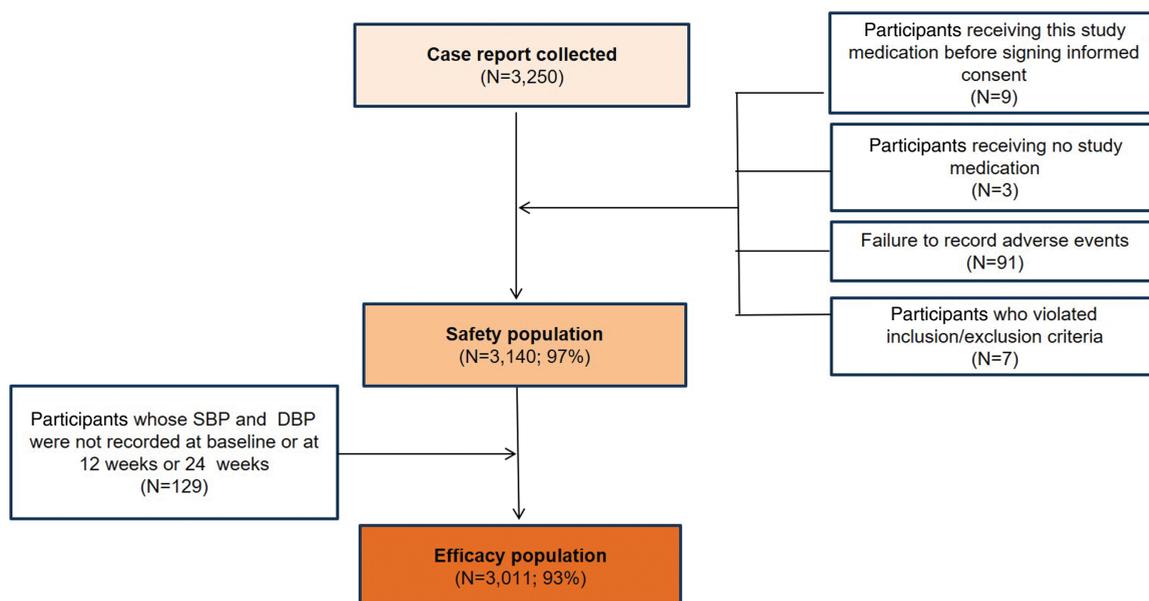


FIGURE 1 Patient disposition BENEFIT KOREA study.

TABLE 1. Baseline demographic characteristics of BENEFIT KOREA study participants (safety population)

Variable	Total
Male [N (%)]	1871 (59.6)
Age, years [mean (SD)]	63.5 (12.9)
Less than 65 years [N (%)]	1485 (47.3)
Cardiocerebrovascular risk factors present [N (%)]	3017 (96.1)
Details on cardiocerebrovascular risk factors	
Male ≥ 45 years; female ≥ 55 years	2707 (89.7)
Current smoker	472 (15.6)
BMI at least 25 kg/m ² , or waist circumference > 90 cm (male) or >80 cm (female)	1128 (37.4)
Dyslipidemia	1524 (50.5)
Impaired fasting glucose or glucose tolerance	57 (1.9)
Family history of early cardiocerebrovascular disease (male <55 years, female <65 years)	153 (5.1)
Diabetes mellitus	872 (28.9)
Medical history present [N (%)]	2798 (89.1)
Details on medical history	
Diseases of circulatory system	
Coronary artery diseases (angina pectoris or myocardial infarction)	1449 (51.8)
Heart failure	275 (9.8)
Peripheral vascular disease	70 (2.5)
Others (atrial fibrillation, cerebral infarction, cardiac hypertrophy, etc.)	630 (22.5)
Endocrine, nutritional and metabolic diseases	1758 (62.8)
Concomitant treatment with antihypertensives prior/current to a switch/addition of nebivolol [N (%)]	2444 (77.8)
Details on concomitant antihypertensives	
Calcium antagonists	1328 (54.3)
Angiotensin II receptor antagonists	1307 (53.5)
Diuretics	578 (23.7)
ACE inhibitors	225 (9.2)
Alpha blockers	33 (1.4)
NA	12 (0.5)

nebivolol was 4.5 ± 1.0 mg (range 1.25–10.0 mg); the majority (2415 participants; 76.9%) received an average daily dose of 5 mg, whereas 718 participants (22.9%) received an average daily dose of less than 5 mg and 7

participants (0.2%) received an average daily dose of more than 5 mg.

Primary efficacy of nebivolol

In the efficacy population, a significant decrease was observed in mean SBP and DBP at 12 weeks (10.2 ± 19.9 mmHg; $P < 0.0001$ and 6.0 ± 13.6 mmHg; $P < 0.0001$, respectively) versus baseline. Similar significant reductions were also observed for SBP and DBP at 24 weeks (11.0 ± 20.6 mmHg; $P < 0.0001$ and 6.6 ± 13.8 mmHg; $P < 0.0001$) compared with baseline (Table 2).

Secondary efficacy of nebivolol

A statistically significant decrease in pulse rate was observed after nebivolol treatment at 12 weeks (7.4 ± 13.3 times/min; $P < 0.0001$) and 24 weeks (8.0 ± 13.7 times/min; $P < 0.0001$) compared with baseline (Table 2). Similarly, a statistically significant decrease was observed in HR after nebivolol treatment at 12 weeks (6.4 ± 13.5 beats/min; $P < 0.0001$) and 24 weeks (6.3 ± 13.5 beats/min; $P < 0.0001$) compared with baseline (Table 2).

Subgroup analysis

Statistically significant decreases in SBP and DBP from baseline at 12 and 24 weeks were observed in all subpopulations analyzed ($P < 0.0001$), except in participants taking concomitant diuretics with add-on nebivolol therapy (Fig. 2a and 2b). The reductions in SBP and DBP were notably greater in study participants who were newly diagnosed with hypertension and received nebivolol as first therapy (de novo) and in participants in whom nebivolol was added-on to existing RAS blockers (either ARBs or ACEIs), CCBs and combination of a RAS blocker and a CCB (add-on). Significant reductions in SBP and DBP from baseline at 12 and 24 weeks were also observed in all age, sex and baseline BMI groups (Supplementary Tables 1–3, <http://links.lww.com/HJH/B173>).

TABLE 2. Efficacy of nebivolol in patients with essential hypertension (efficacy population): blood pressure, pulse rate, heart rate

	SBP (mmHg)			DBP (mmHg)		
	N	Mean ± SD	P value ^a	N	Mean ± SD	P value ^a
Primary efficacy						
Baseline	2880	141.5 ± 18.3		2878	82.8 ± 13.3	
12 weeks (±2 weeks)	2880	131.3 ± 15.3		2878	76.8 ± 11.4	
Mean change from baseline	2880	- 10.2 ± 19.9	<0.0001	2878	- 6.0 ± 13.6	<0.0001
Baseline	2641	141.4 ± 18.5		2640	82.7 ± 13.4	
24 weeks (±2 weeks)	2641	130.5 ± 15.0		2640	76.1 ± 11.0	
Mean change from baseline	2641	- 11.0 ± 20.6	<0.0001	2640	- 6.6 ± 13.8	<0.0001
Pulse rate (beats/min)						
Heart rate						
Baseline	2371	79.8 ± 13.9		212	76.6 ± 15.5	
12 weeks (±2 weeks)	2371	72.4 ± 11.8		212	70.2 ± 13.7	
Mean change from baseline	2371	- 7.4 ± 13.3	<0.0001	212	- 6.4 ± 13.5	<0.0001
Baseline	2158	79.6 ± 13.8		151	77.4 ± 16.3	
24 weeks (±2 weeks)	2158	71.6 ± 11.6		151	71.1 ± 13.8	
Mean change from baseline	2158	- 8.0 ± 13.7	<0.0001	151	- 6.3 ± 13.5	<0.0001

^aPaired t-test; P value < 0.05 was considered significant.

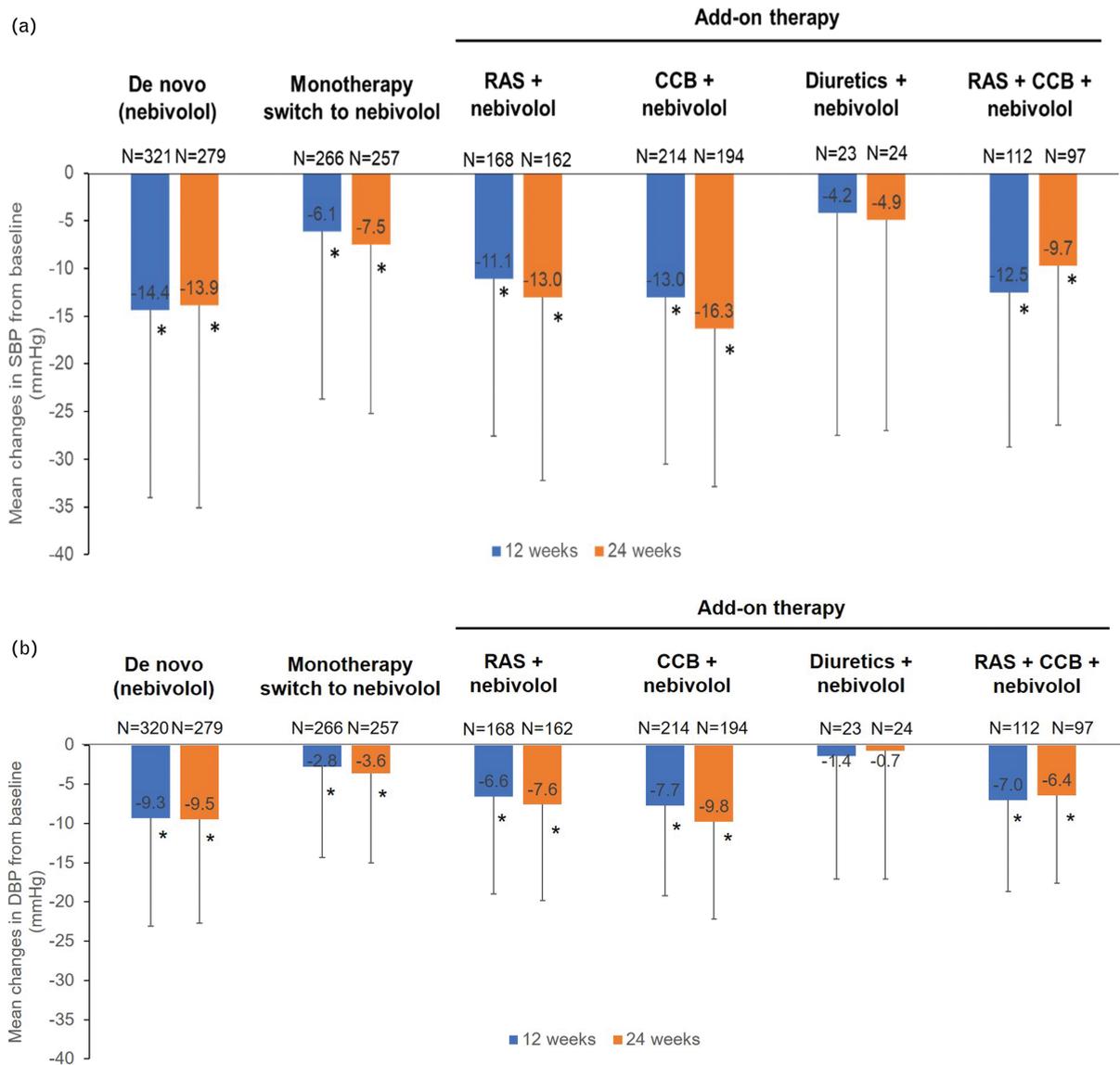


FIGURE 2 (a) Mean changes in SBP from baseline at 12 weeks and 24 weeks in *de novo* patients and patients with prior and concomitant antihypertensives. * $P < 0.0001$, paired t test. (b) Mean changes in DBP from baseline at 12 and 24 weeks in *de novo* patients and patients with prior and concomitant antihypertensives. * $P < 0.0001$, paired t test. CCBs, calcium channel blockers; RAS, renin-angiotensin system (includes angiotensin II receptor blockers [ARBs] and angiotensin-converting enzyme inhibitors [ACEIs]).

Safety

During the study period, 14.4% participants reported adverse events. Majority of the adverse events were mild and moderate. The incidence of adverse events during the study is summarized in Table 3. The most common adverse events reported were dizziness (1.3%), headache (1.0%) and dyspnea (0.9%). The most common adverse drug reactions (ADRs) reported in this study based on investigators judgement included dizziness (0.2%) and bradycardia (0.2%). Further information on the ADRs can be found in Table 3. A total of 119 serious adverse events (SAEs) were reported in 110 participants (3.5%); the most common SAEs reported were chest pain (0.4%), dyspnea (0.2%) and chest discomfort (0.2%). The most common serious adverse drug reactions (SADRs) based on investigators judgement included dyspnea (0.1%) and bradycardia (0.1%). Three participants died during the study period because of events unrelated to the study

drug (progression of lung cancer, septic shock with peritonitis, and esophageal cancer). Sixty-three participants discontinued treatment because of adverse events.

DISCUSSION

To our knowledge, the BENEFIT KOREA study is the largest observational study of beta-blockers for hypertension in Asia, which is particularly important in light of increasing prevalence of hypertension and the rapid population aging in Asia [21]. Our real-world data demonstrate that once daily neбиволл, as monotherapy or combination, significantly reduced SBP and DBP in Korean patients with essential hypertension, with an acceptable safety profile.

The BP control observed in our study is similar to that reported in RCTs [22–26] as well as real-world studies with neбиволл [19,27–32]. It is important to note that the

TABLE 3. Adverse events with an incidence of at least 0.2% in the safety population and adverse drug reactions with an incidence of at least 0.05% in the safety population

Description ^a	Incidence, N (%)
Any AEs	221 (7.0)
Dizziness	42 (1.3)
Headache	31 (1.0)
Dyspnea	29 (0.9)
Chest pain	23 (0.7)
Chest discomfort	18 (0.6)
Palpitations	12 (0.4)
Dyspnea exertional	11 (0.4)
Dyspepsia	10 (0.3)
Paraesthesia	9 (0.3)
Bradycardia	8 (0.3)
Asthenia	7 (0.2)
Cough	7 (0.2)
Angina pectoris	7 (0.2)
Hyperlipidaemia	7 (0.2)
Any ADRs	22 (0.8)
Dizziness	6 (0.2)
Bradycardia	6 (0.2)
Dyspnea	3 (0.1)
Paraesthesia	3 (0.1)
Headache	2 (0.1)
Heart rate decreased	2 (0.1)

AEs, adverse events; ADRs, adverse drug reactions.
^aMedDRA 20.0.

inherent differences in the study populations and the conduct of an RCT and a real-world study may influence the extent of treatment effects observed. Real-world data in a western population showed that nebivolol, as monotherapy and add-on therapy in patients with hypertension with/without concomitant diabetes mellitus, reduced SBP and DBP by 17.2–25.5 and 8.5–19.0 mmHg, respectively [19,27–29]. Two prospective, randomized open-label, single-center studies in Indian patients with essential hypertension reported a reduction in SBP and DBP of 43.2 ± 1.5 and 18.6 ± 1.3 mmHg, respectively at 24 weeks [30], and 27.7 and 3.5 mmHg, respectively at 12 weeks [31] with nebivolol; the sample size of both studies, however, was small ($n = 30$). In another small, prospective, randomized open-label, single-center study in patients with essential hypertension in Turkey ($n = 40$), nebivolol reduced SBP and DBP by 19.1 and 10.3 mmHg, respectively at 4 months [32]. A larger prospective, open-label, noninterventive study in Filipino adults with hypertension ($n = 1154$) found nebivolol to be effective in reducing SBP and DBP by 28.3 ± 14.9 and 15.5 ± 10.5 mmHg after 60 days of follow-up [33]. The SBP and DBP baseline values of patients reported in these prospective studies are higher (SBP range: 152.8–162.8 mmHg; DBP range: 93.3–98.3 mmHg) than those reported in our study (141.5 ± 18.4 and 82.8 ± 13.3 mmHg, respectively). This may potentially explain the differences observed in the size of treatment effect in our study compared with other prospective studies with nebivolol.

The HR reduction observed in our study was also consistent with that reported in other real-world study of nebivolol in Asian patients with hypertension [30,32,33]. Additionally, in a small subpopulation of patients from the BENEFIT study whose metabolic profile was recorded, no

changes were observed in the blood glucose and HbA1c levels and a neutral/favorable trend in lipid profile was observed with nebivolol treatment (results not described in this article) [34].

Our study also demonstrated the efficacy of nebivolol in controlling BP regardless of age, sex and baseline BMI. Nebivolol efficacy was also observed in *de novo* patients, as well as in patients in whom monotherapy treatment was switched to nebivolol or nebivolol was added on to background antihypertensive therapy. The greatest magnitude of effect was seen when nebivolol was administered as monotherapy in *de novo* patients and as an add-on to existing antihypertensive therapy, which included RAS blockers, CCBs and combination of a RAS blocker and a CCB. The benefit of BP reduction from combination therapy of nebivolol and RAS blockers, CCBs and diuretics has been demonstrated in several studies [12–14,16,35,36]. A similar observation has been reported in phase IV studies of hypertensive patients with comorbidities where the addition of nebivolol to other antihypertensives resulted in a further reduction of DBP versus add-on placebo [37,38]. In a retrospective study of hypertensive patients with inadequate response to initial treatment, the addition of nebivolol to existing monotherapy was associated with better BP control at 2 months after treatment initiation when compared with add-on hydrochlorothiazide, metoprolol and amlodipine [38]. Although the addition of nebivolol to existing diuretic has been demonstrated to significantly reduce SBP and DBP in other studies [13,35,38], we did not observe any significant BP reductions in our study, likely because of the very small number of participants in this subgroup.

The overall incidence of adverse events in this study was relatively low compared with those reported in RCTs and real-world studies [26,29]; incidence rates in other real-world studies of nebivolol were reportedly lower [27,28]. The favorable safety of nebivolol is reflected from the low rates (<0.2%) of typical beta-blocker adverse events (bradycardia, erectile dysfunction, fatigue and weight gain) [39,40] in this study. Older generation of beta-blockers have been associated with higher rates of erectile dysfunction. Interestingly, the detrimental effects on sexual function was also seen with carvedilol, a beta-blocker of the same class as nebivolol [41]. By contrast, nebivolol has not been shown to have any detrimental effects on erectile dysfunction [42,43]. The low incidence of adverse effects observed with nebivolol may be attributed to the high β 1-adrenoceptor selectivity and the hemodynamic benefits of nitric oxide-mediated vasodilatation that nebivolol provides.

Treatment adherence in chronic disease management is important for improving patient outcomes and poor adherence has been shown to be the most important cause of poor BP control [44–47]. The efficacy and simplicity of treatment regimen coupled with good tolerability profile significantly influence patient's adherence and persistence to treatment. A real-world database study by Chen *et al.* [48] reported that nebivolol was associated with higher rates of treatment adherence and persistence in comparison to diuretic. In trials of older patients with chronic heart failure, the proportion of patients reaching the higher target dose

was highest with nebivolol (68%) [49] compared with other beta-blockers (including metoprolol, bisoprolol and carvedilol) [50–52], suggesting higher tolerability of nebivolol, and thus compliance in these patients. New generation beta blockers, carvedilol and nebivolol, had a lower risk of treatment discontinuation compared with atenolol [53]. The findings from these studies suggest that nebivolol, with once-daily dosing and a favorable safety profile, supports treatment adherence for hypertension.

Although the BENEFIT KOREA study is potentially the largest observational study of beta-blockers in Asian patients, it has a few limitations associated with its design. Firstly, the study was a single-arm, noncontrolled study, in which all participants received the study drug, nebivolol. Secondly, a majority of participants included in the study were previously diagnosed with essential hypertension, had combined risk factors or comorbidities, and were receiving antihypertensive drugs. As such, there is a limited generalizability of the study results from this study group of population to those at low-risk hypertension. Thirdly, observational studies in general are associated with certain limitations, such as confounding, selection and information bias, and unreliable inferences about causality [54]. Although RCTs are considered the gold standard for establishing treatment efficacy and safety, the exclusion criteria of RCTs are stringent and result in a homogeneous study population. This limits the generalizability of findings from RCTs to real-world settings [55]. Real-world observational studies conducted in large populations are, therefore needed to validate findings from RCTs [56,57]. Results from such observational studies can supplement RCT data with additional insights on the balance of benefit and risk from the real-world practice [58]. Therefore, despite the limitations enumerated here, the present study provides data that is relevant to routine clinical practice, especially from an Asian population where RCT data on beta-blockers are lacking.

In conclusion, despite the limitations of observational studies, this real-world study in Asian patients with essential hypertension with and without comorbidities, demonstrated the efficacy and safety of once daily nebivolol, either as monotherapy or add-on therapy. Therefore, our study indicates that nebivolol can potentially be used in hypertensive patients with and without comorbidities, alone or in combination with other antihypertensive agents, to achieve better BP outcomes.

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Previous presentations of data from the study

Lee JY, *et al.* Efficacy of Nebivolol monotherapy in the open, noncontrolled, prospective, multicenter observational study in KOREA (BENEFIT-KOREA). Presented at the 27th International Society of Hypertension (ISH) 2018; 20–23 September 2018; Beijing, China [Lee JY, *et al.* *J Hypertens* 2018;36: e229].

Cho EJ, *et al.* Efficacy and safety of vasodilator beta-blocker in elderly hypertensive patients: Result from BENEFIT-KOREA study. Presented at the 27th International Society of Hypertension (ISH) 2018; 20–23 September 2018; Beijing, China [Cho EJ, *et al.* *J Hypertens* 2018;36: e236].

Cho EJ, *et al.* Efficacy and safety of vasodilator beta-blocker in elderly hypertensive patients: Result from BENEFIT-KOREA study. Presented at the American Heart Association (AHA) 2018; 10–12 November 2018; Chicago, USA [Cho EJ, *et al.* *Hypertension* 2018;72:AP336].

Cho KI, *et al.* Effect of nebivolol on gender-different efficacy and safety in Korean patients with hypertension: Result from BENEFIT-KOREA study. Presented at the European Society of Cardiology (ESC) Congress 2018; 25–29 August 2018; Munich, Germany [Cho KI, *et al.* *Eur Heart J* 2018;39 (Suppl 1): 3801].

Kwon SW, *et al.* Effect of nebivolol on lipid and metabolic profiles in Korean patients with hypertension: Result from BENEFIT-KOREA study. Presented at the European Society of Cardiology (ESC) Congress 2018; August 25–29, 2018; Munich, Germany [Kwon SW, *et al.* *Eur Heart J* 2018;39(Suppl 1): 1871].

Shin JH, *et al.* Real world efficacy of nebivolol according to various prescription patterns in the open, noncontrolled, prospective, multicenter observational study in KOREA (BENEFIT-KOREA). Presented at the 28th ESH (European Society of Hypertension) Meeting; 8–11 June 2018; Barcelona, Spain [Shin JH, *et al.* *J Hypertens* 2018;36: e124].

Shin JH, *et al.* Real world efficacy of nebivolol in combination with renin angiotensin system blockade and/or calcium antagonist, a sub-study of prospective, multicenter observational study. Presented at the 29th ESH (European Society of Hypertension) 2019; 21–24 June 2019; Milan, Italy [Shin JH, *et al.* *J Hypertens* 2019;37: e174-e175].

Lee JY, *et al.* Efficacy and safety of nebivolol in the management of hypertension in the elderly: result from BENEFIT-KOREA study. Presented at the 29th ESH (European Society of Hypertension) 2019; 21–24 June 2019; Milan, Italy [Lee JY, *et al.* *J Hypertens* 2019;37: e102].

Conflicts of interest

J.S. has received research grants and honoraria from Borjyung Pharmaceutical, CKD Pharmaceuticals, Hanmi, Menarini, and Sanofi. In the past 24 months G.M. has received speaker fees from Boehringer Ingelheim, Ferrer, Medtronic Vascular Inc, Menarini Int, Merck Healthcare KGaA, Neopharmed-Gentili, Novartis Pharma, Recordati, Sanofi, and Servier. A.M. received honoraria for lectures from Menarini. Y.J.C., G.H., D.W.J., D.K., Y.Y.K. and H.J. have no conflicts of interest. S.W.P. is an employee of A.Menarini Korea Ltd.

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* 2016; 388:1659–1724.
2. Forouzanfar MH, Liu P, Roth GA, Ng M, Birukov S, Marczak L, *et al.* Global burden of hypertension and systolic blood pressure of at least 110 to 115 mmHg, 1990–2015. *JAMA* 2017; 317:165–182.

3. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in blood pressure from 1975 to 2015: a pooled analysis 1479 population-based measurement studies with 19.1 million participants. *Lancet* 2017; 389:37–55.
4. Kim CH, Abelardo N, Buranakitjaroen P, Krittayaphong R, Lim CH, Park SH, et al. Hypertension treatment in the Asia-Pacific: the role of and treatment strategies with nebivolol. *Heart Asia* 2016; 8:22–26.
5. Korean Society Hypertension (KSH); Hypertension Epidemiology Research Working Group Kim HC, Cho MC. Korea hypertension fact sheet 2018. *Clin Hypertens* 2018; 24:13.
6. Williams B, Mancia G, Spiering W, Rosei EA, Azizi M, Burnier M, et al. 2018 ESC/ESH guidelines for the management of arterial hypertension. *J Hypertens* 2018; 36:1953–2041.
7. Warmack TS, Estes MA, Heldenbrand S, Franks AM. Beta-adrenergic antagonists in hypertension: a review of the evidence. *Ann Pharmacother* 2009; 43:2031–2043.
8. National Clinical Guideline Centre (UK). Hypertension: The clinical management of primary hypertension in adults: update of clinical guidelines 18 and 34; 2011 [online]. Available at: <http://www.ncbi.nlm.nih.gov/books/NBK83274/>. (Accessed 8 May 2018)
9. Kallistratos MS, Poulimenos LE, Manolis AJ. Vasodilator α -blockers: a different class of antihypertensive agents? *Future Cardiol* 2014; 10:669–671.
10. Lee HY, Shin J, Kim GH, Park S, Ihm SH, et al. 2018 Korean Society of Hypertension Guidelines for the management of hypertension: part II-diagnosis and treatment of hypertension. *Clin Hypertension* 2019; 25:20.
11. Van Bortel LM, Fici F, Mascagni F. Efficacy and tolerability of nebivolol compared with other antihypertensive drugs: a meta-analysis. *Am J Cardiovasc Drugs* 2008; 8:35–44.
12. Giles TD, Weber MA, Basile J, Gradman AH, Bharucha DB, Chen W, NAC-MD-01 Study Investigators. Efficacy and safety of nebivolol and valsartan as fixed-dose combination in hypertension: a randomized, multicenter study. *Lancet* 2014; 383:1889–1898.
13. Papademetriou V. Comparison of Nebivolol monotherapy versus Nebivolol in combination with other antihypertensive therapies for the treatment of hypertension. *Am J Cardiol* 2009; 103:273–278.
14. Neutel JM, Smith DH, Gradman AH. Adding nebivolol to ongoing antihypertensive therapy improves blood pressure and response rates in patients with uncontrolled stage I-II hypertension. *J Hum Hypertens* 2010; 24:64–73.
15. Weber MA, Basile J, Stapff M, Khan B, Zhou D. Blood pressure effects of combined beta-blocker and angiotensin-converting enzyme inhibitor therapy compared with the individual agents: a placebo-controlled study with nebivolol and lisinopril. *J Clin Hypertens (Greenwich)* 2012; 14:588–592.
16. Vitale C, Marazzi G, Iellamo F, Spoletini I, Dall'Armi V, Fini M, Volterrani M. Effects of nebivolol or irbesartan in combination with hydrochlorothiazide on vascular functions in newly-diagnosed hypertensive patients: the NINFE (Nebivololo, Irbesartan Nella Funzione Endoteliale) study. *Int J Cardiol* 2012; 155:279–284.
17. Cicero AFG, Kuwabara M, Borghi C. A critical review of nebivolol and its fixed-dose combinations in the treatment of hypertension. *Drugs* 2018; 78:1783–1790.
18. Peter P, Martin U, Sharma A, Dunne F. Effect of treatment with nebivolol on parameters of oxidative stress in type 2 diabetics with mild to moderate hypertension. *J Clin Pharm Ther* 2006; 31:153–159.
19. Van Bortel LM. Efficacy, tolerability and safety of nebivolol in patients with hypertension and diabetes: a postmarketing surveillance study. *Eur Rev Med Pharmacol Sci* 2010; 14:749–758.
20. Ayers K, Byrne LM, DeMatteo A, Brown NJ. Differential effects of nebivolol and metoprolol on insulin sensitivity and plasminogen activator inhibitor in the metabolic syndrome. *Hypertension* 2012; 59:893–898.
21. Park JB, Kario K, Wang JG. Systolic hypertension: an increasing clinical challenge in Asia. *Hypertens Res* 2015; 38:227–236.
22. Weiss RJ, Weber MA, Carr AA, Sullivan WA. A randomized, double-blind, placebo-controlled parallel-group study to assess the efficacy and safety of nebivolol, a novel beta-blocker, in patients with mild to moderate hypertension. *J Clin Hypertens (Greenwich)* 2007; 9:667–676.
23. Saunders E, Smith WB, DeSalvo KB, Sullivan WA. The efficacy and tolerability of nebivolol in hypertensive African American patients. *J Clin Hypertens (Greenwich)* 2007; 9:866–875.
24. Greathouse M. Nebivolol efficacy and safety in patients with stage I-II hypertension. *Clin Cardiol* 2010; 33:E20–E27.
25. Punzi H, Lewin A, Lukić T, Goodin T, Wei Chen. Efficacy and safety of nebivolol in Hispanics with stage I-II hypertension: a randomized placebo-controlled trial. *Ther Adv Cardiovasc Dis* 2010; 4:349–357.
26. Weiss RJ, Saunders E, Greathouse M. Efficacy and tolerability of nebivolol in stage I-II hypertension: a pooled analysis of data from three randomized, placebo-controlled monotherapy trials. *Clin Ther* 2011; 33:1150–1161.
27. Cleophas TJ, Agrawal R, Lichtenthal A, Mäkel W, Fici F. Nationwide efficacy-safety study of nebivolol in mildly hypertensive patients. *Am J Ther* 2006; 13:192–197.
28. Schmidt AC, Graf C, Brixius K, Scholze J. Blood pressure-lowering effect of nebivolol in hypertensive patients with type 2 diabetes mellitus: the YESTONO study. *Clin Drug Investig* 2007; 27:841–849.
29. Neutel JM, Giles TD, Punzi H, Weiss RJ, Li H, Finck A. Long-term safety of nebivolol and valsartan combination therapy in patients with hypertension: an open-label, single-arm, multicenter study. *J Am Soc Hypertens* 2014; 8:915–920.
30. Badar VA, Hiware SK, Shrivastava MP, Thawani VR, Hardas MM. Comparison of nebivolol and atenolol on blood pressure, blood sugar, and lipid profile in patients of essential hypertension. *Indian J Pharmacol* 2011; 43:437–440.
31. Johar SK, Bhosle D, Jaybhaye D, Sheikh A. To study the comparative effects of nebivolol and metoprolol on lipid profile in patients of essential hypertension. *Int J Basic Clin Pharmacol* 2015; 4:574–578.
32. Ozyildiz AG, Eroglu S, Bal U, Atar I, Okayk K, Muderrisoglu H. Effects of carvedilol compared to nebivolol on insulin resistance and lipid profile in patients with essential hypertension. *J Cardiovasc Pharmacol Ther* 2017; 22:65–70.
33. Collado FR. An open label, multicenter, noninterventional study of the safety of nebivolol (Nebilet) in the treatment of hypertension in Filipino adult patients: a postmarketing surveillance study. *J Gen Pract (Los Angel)* 2018; 6:631.
34. Kwon SW, Do JY, Hong GR, Kim BK, Hwang WM, Kim SH, et al. Effect of nebivolol on lipid and metabolic profiles in Korean patients with hypertension: result from BENEFIT-KOREA study. *Eur Heart J* 2018; 39 (Suppl 1):1871.
35. Lacourcière Y, Arnott W. Placebo-controlled comparison of the effects of nebivolol and low-dose hydrochlorothiazide as monotherapies and in combination on blood pressure and lipid profile in hypertensive patients. *J Hum Hypertens* 1994; 8:283–288.
36. Punzi HA. Combination therapy with nebivolol/amlodipine is superior to metoprolol/amlodipine in the control of 24-hr ABPM. *J Am Soc Hypertens* 2015; 9:e24.
37. Deedwania P, Shea J, Chen W, Brenner L. Effects of add-on nebivolol on blood pressure and glucose parameters in hypertensive patients with prediabetes. *J Clin Hypertens (Greenwich)* 2013; 15:270–278.
38. Ayyagari R, Xie J, Cheng D, Wu EQ, Huang XY, Chen S. A retrospective study evaluating the tolerability and effectiveness of adjunctive anti-hypertensive drugs in patients with inadequate response to initial treatment. *J Clin Hypertens (Greenwich)* 2018; 20:1058–1066.
39. Weiss R. Nebivolol: a novel beta-blocker with nitric oxide-induced vasodilatation. *Vasc Health Risk Manag* 2006; 2:303–308.
40. Münzel T, Gori T. Nebivolol: the somewhat-different beta-adrenergic receptor blocker. *J Am Coll Cardiol* 2009; 54:1491–1499.
41. Cordero A, Bertomeu-Martinez V, Mazon P, Fácila L, Bertomeu-González V, Conthe P, et al. Erectile dysfunction in high-risk hypertensive patients treated with beta-blockade agents. *Cardiovasc Ther* 2010; 28:15–22.
42. Brixius K, Middeke M, Lichtenthal A, Jahn E, Schwinger RH. Nitric oxide, erectile dysfunction and beta-blocker treatment (MR NOED study): benefit of nebivolol versus metoprolol in hypertensive men. *Clin Exp Pharmacol Physiol* 2007; 34:327–331.
43. Electronic Medicines Compendium (UK). Summary of product characteristics, Nebivolol 5 mg tablets. Available at: https://www.medicines.org.uk/emc/product/1620/smpc#PHARMACODYNAMIC_PROPS. (Accessed 8 May 2019)
44. Corrao G, Zambon A, Parodi A, Poluzzi E, Baldi I, Merlino L, et al. Discontinuation of and changes in drug therapy for hypertension among newly-treated patients: a population-based study in Italy. *J Hypertension* 2008; 26:819–824.

45. Gale NK, Greenfield S, Gill P, Gutridge K, Marshall T. Patient and general practitioner attitudes to taking medication to prevent cardiovascular disease after receiving detailed information on risks and benefits of treatment: a qualitative study. *BMC Fam Pract* 2011; 12:59.
46. Krousel-Wood M, Joyce C, Holt E, Muntner P, Webber LS, Morisky DE, *et al.* Predictors of decline in medication adherence: results from the cohort study of medication adherence among older adults. *Hypertension* 2011; 58:804–810.
47. Mazzaglia G, Ambrosioni E, Alacqua M, Filippi A, Sessa E, Immordino V, *et al.* Adherence to antihypertensive medications and cardiovascular morbidity among newly diagnosed hypertensive patients. *Circulation* 2009; 120:1598–1605.
48. Chen S, Macaulay D, Swallow E, Diener M, Farooqui S, Xie J, Wu EQ. Real-world adherence and persistence associated with nebivolol or hydrochlorothiazide as add-on treatment for hypertension. *Curr Med Res Opin* 2014; 30:637–643.
49. Flather MD, Shibata MC, Coats AJ, Van Veldhuisen DJ, Parkhomenko A, Borbola J, *et al.*, SENIORS Investigators. Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). *Eur Heart J* 2005; 26:215–225.
50. Packer M, Fowler MB, Roecker EB, Coats AJ, Katus HA, Krum H, *et al.*, Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) Study Group. Effects of carvedilol on the morbidity of patients with severe chronic heart failure: results of the carvedilol prospective randomized cumulative survival (COPERNICUS) study. *Circulation* 2002; 106:2194–2199.
51. CIBIS-II Investigators and Committees. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomized trial. *Lancet* 1999; 353:9–13.
52. MERIT-HF Study Group. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet* 1999; 353:2001–2007.
53. Choi YJ, Ah YM, Kong J, Choi KH, Kim B, Han N, *et al.* Implication of different initial beta blockers on treatment persistence: atenolol vs new-generation beta blocker, a population-based study. *Cardiovasc Ther* 2016; 34:268–275.
54. Gueyffier F, Cucherat M. The limitations of observation studies for decision making regarding drugs efficacy and safety. *Therapie* 2019; 74:181–185.
55. Price D, Bateman ED, Chisholm A, Papadopoulos NG, Bosnic-Anticevich S, Pizzichini E, *et al.* Complementing the randomized controlled trial evidence base; evolution not revolution. *Ann Am Thorac Soc* 2014; 11:S92–S98.
56. de Simone G, Izzo R, Verdecchia P. Are observational studies more informative than randomized controlled trials in hypertension? Pro side of the argument. *Hypertension* 2013; 62:463–469.
57. Sherman RE, Anderson SA, Dal Pan GJ, Gray GW, Gross T. Real-world evidence - what is it and what can it tell us? *N Engl J Med* 2016; 375:2293–2297.
58. Plueschke K, McGettigan P, Pacurariu A, Kurz X, Cave A. EU-funded initiatives for real world evidence: descriptive analysis of their characteristics and relevance for regulatory decision-making. *BMJ Open* 2018; 8:e021864.