Original Research

Safety of the Up-titration of Nifedipine GITS and Valsartan or Low-dose Combination in Uncontrolled Hypertension: the FOCUS Study

Jeong Bae Park, MD, PhD[1]; Joon-Han Shin, MD[2]; Dong-Soo Kim, MD, PhD[3]; Ho-Joong Youn, PhD[4]; Seung Woo Park, MD, PhD[5]; Wan Joo Shim, MD, PhD[6]; Chang Gyu Park, MD, PhD[7]; Dong-Woon Kim, MD, PhD[8]; Hae-Young Lee, MD, PhD[9]; Dong-Ju Choi, MD, PhD[10]; Se-Joong Rim, MD, PhD[11]; Sung-Yun Lee, MD, PhD[12]; Ju-Han Kim, MD, PhD[13]; and on behalf of the FOCUS Investigators

[1]Division of Cardiology, Cheil General Hospital, Dankook University College of Medicine, Seoul, South Korea; [2]Division of Cardiology, Ajou University Hospital, Gyeonggi, South Korea; [3]Division of Cardiology, Inje University Pusan Paik Hospital, Busan, South Korea; [4]Division of Cardiology, The Catholic University of Korea, Seoul St. Mary's Hospital, Seoul, South Korea; [5]Department of Medicine, Sungkyunkwan University School of Medicine, Samsung Medical Center, Seoul, Korea; [6]Division of Cardiology, Korea University Anam Hospital, Seoul, South Korea; [7]Division of Cardiology, Korea University Guro Hospital, Seoul, South Korea; [8]Division of Cardiology, Chungbuk National University Hospital, Chungbuk, South Korea; [9]Division of Cardiology, Seoul National University Hospital, Seoul, South Korea; [10]Division of Cardiology, Seoul National University Bundang Hospital, Gyeonggi, Seoul, South Korea; [11]Division of Cardiology, Gangnam Severance Hospital, Seoul, South Korea; [12]Division of Cardiology, Inje University IlsanPaik Hospital, Gyeonggi, South Korea; and [13]Division of Cardiology, Chonnam National University Hospital, Gwangju, South Korea

ABSTRACT

Purpose: Doubling the dose of antihypertensive drugs is necessary to manage hypertension in patients whose disease is uncontrolled. However, this strategy can result in safety issues. This study compared the safety and efficacy of up-titration of the nifedipine gastrointestinal therapeutic system (GITS) with up-titration of valsartan monotherapy; these were also compared with low-dose combinations of the two therapies.

Methods: This prospective, open-label, randomized, active-controlled, multicenter study lasted 8 weeks. If patients did not meet the target blood pressure (BP) after 4 weeks of treatment with low-dose monotherapy, they were randomized to up-titration of the nifedipine GITS dose from 30 mg (N30) to 60 mg or valsartan from 80 mg to 160 mg or they were randomized to receive a low-dose combination of N30 and valsartan 80 mg for another 4 weeks. BP variability was assessed by using the SD or the %CV of the short-term BP measured at clinic.

Findings: Of the 391 patients (20~70 years with stage II or higher hypertension) screened for study inclusion, 362 patients who had 3 BP measurements were enrolled. The reduction in the mean systolic/diastolic BP from baseline to week 4 was similar in both low-dose monotherapy groups with either N30 or valsartan 80 mg. BP variability (SD) was unchanged with either therapy, but the %CV was slightly increased in the N30 group. There was no significant difference in BP variability either in SD or %CV between responders and nonresponders to each monotherapy despite the significant difference in the mean BP changes. The up-titration effect of nifedipine GTS from 30 to 60 mg exhibited an additional

Accepted for publication February 25, 2016.
http://dx.doi.org/10.1016/j.clinthera.2016.02.025
0149-2918/$ - see front matter

BP reduction, but this effect was not shown in the up-titration of valsartan from 80 to 160 mg. Although the difference in BP was obvious between high-dose nifedipine GTS and valsartan, the BP variability was unchanged between the 2 drugs and was similar to the low-dose combinations. There was a low rate of adverse events in all treatment groups. In addition, escalating the dose of either nifedipine GITS or valsartan revealed a similar occurrence of adverse effects with low-dose monotherapy or the low-dose combination.

Implications: Compared with up-titration of the angiotensin receptor blocker valsartan, up-titration of the calcium channel blocker nifedipine GITS provided no additional increased safety concerns and revealed better mean reductions in BP without affecting short-term BP variability. ClinicalTrials.gov identifier: NCT01071122. (*Clin Ther.* 2016;38:832–842) © 2016 The Authors. Published by Elsevier HS Journals, Inc.

Key words: angiotensin receptor blocker, antihypertensive agents, BP variability, calcium channel blocker, hypertension, safety.

INTRODUCTION

Although hypertension is the most pervasive risk factor for cardiovascular diseases, its control rate is not very high. Many guidelines have been introduced to increase the control rate.[1,2] Except for special cases, most of the guidelines suggest starting medication as monotherapy and increasing the dose or prescribing a low-dose combination. Studies show that the low-dose combination is more effective than increasing the dose of a single drug.[3–5] In practice, however, only a few studies have compared the antihypertensive effects and adverse effects of switching angiotensin receptor blockers (ARBs) and calcium channel blockers (CCBs) from low to high doses; these agents are recommended as primary drugs in most of the guidelines.[6–8] In addition, only a few studies have compared the antihypertensive effects and adverse effects of high doses of a single drug versus combination therapy.[9,10]

The previous FOCUS study[6] found that, compared with the combination of a high-dose nifedipine gastrointestinal therapeutic system (GITS) and valsartan, the low-dose combination of nifedipine GITS plus valsartan or high-dose nifedipine was more effective in improving peripheral (brachial) hemodynamics, thereby lowering central and peripheral blood pressure (BP). However, few studies have shown the effects of the low-dose combination on BP variability; this variability is known to be related to cardiovascular morbidity and mortality, independent from mean BP and frequency of adverse effects caused by powerful BP reductions produced by step-by-step increases in dose.[11,12]

Although the average BP is adopted for treatment decisions in a practical way, there is a wide fluctuation in BP, which changes with every beat. Therefore, when there is too much difference between the first and second BP levels, the average BP is calculated by measuring it a third time and deriving the mean value of the second and third measurements. However, BP is also affected by sympathetic drive, arterial or cardiopulmonary reflex, and arterial stiffness. For the beat-to-beat BP variability, the sympathetic nervous system and psychological factors are considered crucial, as well as the difference caused by depressed baroreflex function.[13,14] Baroreflex dysfunction is caused by physical and emotional stimuli and changes in respiration, as well as rhythmic changes in the central autonomic drive. Because short-term BP variability is determined by various hemodynamics, independent from the mean BP, the cardiovascular risks are increased; therefore, its importance is being recognized in clinical settings. A meta-analysis found that amlodipine, a CCB, has a beneficial effect on long-term BP variability.[15] The long-acting diuretic agents amlodipine and indapamide were repeatedly found to reduce BP variability, and their combination is expected to show better effects.[16]

The CCBs exhibit very strong and dose-dependent antihypertensive effects. However, a higher dose results in more adverse effects, commonly peripheral edema, which is a dose-limiting effect that restricts drug adherence.[4] Usually, it is recommended to use rational combination with different mechanisms to improve BP control and, if BP is not clinically controlled with low doses, use of a drug combination is recommended rather than an increase in dose because of the increase in adverse effects. For ARBs, when their dose is increased, the BP-lowering effect is relatively lower but is safe from adverse effects, compared with other drugs. Thus, the 2 drugs vary in terms of adverse effects and efficacy of up-titration.

In the present multicenter, randomized, active-controlled study, patients with stage II or higher hypertension and patients who did not reach target

BP with an initial low dose of 2 agents were recruited. We compared the safety and efficacy of up-titration of nifedipine GITS versus up-titration of valsartan monotherapy, which were compared with low-dose combinations of the 2 therapies.

PATIENTS AND METHODS

This study was a national, prospective, open-label, randomized, active-controlled trial. The antihypertensive effects and adverse effects of high-dose nifedipine GITS 60 mg (N60) or valsartan 160 mg (V160) versus nifedipine GITS 30 mg plus valsartan 80 mg (N30 + V80) were compared in patients with higher than moderate hypertension whose BP was inadequately controlled by low-dose nifedipine GITS 30 mg (N30) or low-dose valsartan 80 mg (V80) alone. Patients were recruited from 17 study centers in South Korea between March 2010 and February 2012. The study protocol was approved by the institutional review board of each center, and it was conducted in accordance with the ethical principles of the Declaration of Helsinki and Good Publication Practice guidelines. All of the patients provided written informed consent before entry into the study.

Study Population

Eligible patients were aged 20 to 70 years with stage II or higher hypertension (diastolic BP [DBP] $\geq$100 mm Hg and/or systolic BP [SBP] $\geq$160 mm Hg) and who were either treatment naive or had not used an ARB or a CCB. There was no washout period. Major exclusion criteria included severe hypertension (DBP $\geq$120 mm Hg and/or SBP $\geq$200 mm Hg), evidence of secondary hypertension, history of cardiovascular or cerebrovascular disease within the previous 12 months, type 1 diabetes, chronic kidney disease (serum creatinine level $\geq$1.7 mg/dL), severe gastrointestinal disease, hepatic and biliary disease, or concomitant use of any cytochrome P-450 3A4 inhibitor or inducer.

Study Design

After an initial screening visit, all eligible patients were randomized at baseline to receive N30 or V80. After 4 weeks of treatment, patients who did not reach the target BP of <140/90 mm Hg (<130/80 mm Hg in patients with diabetes) were further randomized to receive either N30 + V80 or up-titration of monotherapy (N60 or V160) for 4 weeks. Low-dose combination groups were drawn from both the N30 and V80 groups (28 patients from the N30 group and 38 patients from the V80 group). Patients meeting the target BP remained on low-dose monotherapy for 4 weeks. Brachial SBP and DBP were measured by using the Omron HEM-7080IT-E (Omron, Kyoto, Japan) device at 3-minute intervals. Pulse pressure was calculated as the difference between SBP and DBP. Clinical BP variability was calculated as the short-term BP variability; the SD of SBP was calculated 3 times at 1- to 2-minute intervals, and the %CV was calculated by dividing the SD by the mean.

Statistical Analysis

Statistical analyses were performed by using SAS version 9.1.3 (SAS Institute, Inc, Cary, North Carolina). Data are presented as mean (SD), unless otherwise specified. Baseline characteristics were compared by using a 2-sample t test and Pearson's χ^2 test, as appropriate. Changes were expressed as the difference between week 4 and baseline and between week 8 and week 4. The main comparisons were performed by using ANCOVA with the covariates. The safety analysis was conducted on all patients who had taken at least 1 dose of the study drug. All of the tests were bilateral using $\alpha = 0.05$; the exception was the stepwise method, which was bilateral using $\alpha = 0.15$.

RESULTS

Of the 391 subjects screened for inclusion, 362 subjects were randomized to receive low-dose monotherapy, including 181 patients for the N30 group and 181 patients for the V80 group for 4 weeks (Figure). After 4 weeks, 203 patients who did not reach their target BP level were randomized to receive up-titration or the low-dose combination for additional 4 weeks.

Baseline Characteristics

As shown in Table I, there were no differences in BP or demographic characteristics between the 2 low-dose treatment groups.

Effects of Low-dose ARB or CCB on BP Variables

After 4 weeks, SBP/DBP were both significantly decreased by –21.1 (14.3)/–11.8 (8.9) mm Hg in the N30 group and by –18.7 (15.9)/–10.5 (9.9) mm Hg in the V80 group (both, $P < 0.001$) (Table II). When BP variability was measured according to SD or %CV of

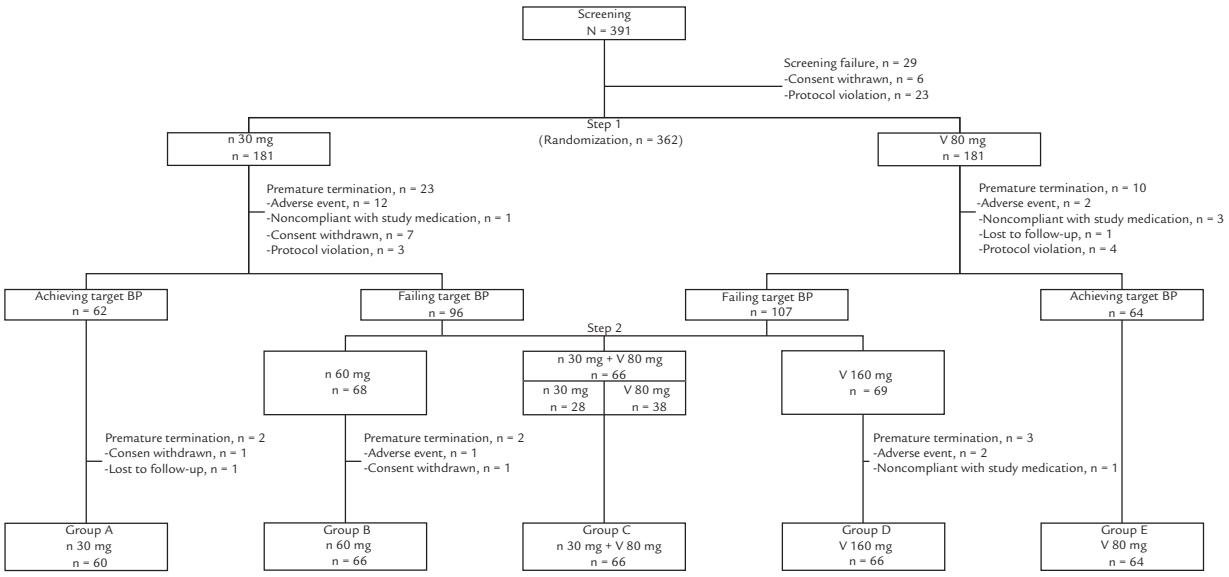

Figure. Study design. After screening, the first randomization to low-dose monotherapy was performed with either nifedipine (N) gastrointestinal therapeutic system (GITS) 30 mg or valsartan (V) 80 mg. Patients not meeting the target blood pressure (BP) level (<140/90 mm Hg or <130/80 mm Hg for those with diabetes) for 4 weeks underwent a second randomization to up-titration of monotherapy or a low-dose combination for the remaining 4 weeks.

SBP, there was no difference in the 2 low-dose groups, and the BP response and control rate were similar. In the nifedipine low-dose, 30-mg group, younger men with higher triglyceride levels were more likely to be nonresponders (Table III). However, in the valsartan low-dose 80-mg group, men with a lower functioning kidney were more likely to be nonresponders. Despite the decrease in BP, neither group exhibited much difference in short-term BP variability.

Up-titration Effect of Nifedipine GTS and Valsartan on BP Variables After an Additional 4 Weeks of Treatment

In the N60 group in which nifedipine was increased from 30 mg (ie, low-dose nifedipine GTS and valsartan group) in week 4 to 60 mg in week 8, an additional BP decrease was recorded (from 149.7 [10.2] mm Hg to 138.5 [9.4] mm Hg; $P < 0.01$) (Table IV). However, for the V160 group, in which valsartan was increased from 80 to 160 mg, there was no additional decrease in BP (from 149.9 [10.0] mm Hg to 146.9 [15.6] mm Hg). For the nifedipine up-titration group, BP decreased by –11.1 (11.6) mm Hg and for the valsartan up-titration group, it was decreased by –3.1 (13.4) mm Hg; the difference was statistically significant ($P < 0.01$). In the low-dose combination group, there was a decrease in BP from 151.1 (13.7) mm Hg to 136.5 (15.1) mm Hg ($P < 0.01$). However, although there was an obvious difference between the groups, there was no difference in BP variability measured with SD or %CV of SBP.

Safety Variables

During the low-dose monotherapy phase, 70 adverse effects were reported by 46 (25.4%) patients in the N30 group and 41 AEs reported by 32 (17.7%) patients in the V80 group, including 12.7% and 3.9% of patients in the respective groups who had potentially treatment-related AEs (Table V). During the low-dose combination and high-dose monotherapy phase, 7 (10.6%) patients experienced 7 AEs in the N30 + V80 group, 7 (10.5%) patients experienced 9 AEs in the N60 group (1 serious event of muscle strain, unrelated to the study drug), and 11 (16.2%) patients experienced 16 AEs in the V160 group.

Table I. Baseline characteristics of the first randomization with low-dose nifedipine 30 mg versus valsartan 80 mg. Unless otherwise indicated, values are given as mean (SD).

Characteristic	Nifedipine 30 mg (n = 181)	Valsartan 80 mg (n = 181)	*P*
Male sex, no. (%)	117 (64.6)	114 (63.0)	0.7428
Age, y	48.2 (10.2)	49.4 (9.5)	0.2640
Weight, kg	71.7 (12.9)	71.2 (13.6	0.7230
Height, cm	167.2 (9.0)	165.4 (9.1)	0.0614
Body mass index, kg/m^2	25.5 (3.3)	25.9 (3.7)	0.3228
Duration of hypertension, y	2.5 (4.3)	2.6 (5.2)	0.8478
Dyslipidemia	23 (12.7)	20 (11.1)	0.6260
Diabetes mellitus	11 (6.1)	9 (5.0)	0.6454
Hematocrit, %	41.6 (2.6)	41.4 (2.6)	0.6559
Fasting glucose, mg/dL	106.8 (26.2)	106.4 (19.6)	0.8901
Total cholesterol, mg/dL	223.9 (36.4)	225.6 (35.6)	0.6581
HDL-C, mg/dL	44.6 (21.8)	43.8 (23.5)	0.7202
Triglyceride, mg/dL	147.1 (118.4)	157.4 (171.4)	0.5072
LDL-C, mg/dL	93.2 (55.5)	96.1 (55.8)	0.6164
Serum creatinine, mg/dL	0.9 (0.2)	0.9 (0.3)	0.8813
Baseline bBP			
bSBP, mm Hg	162.6 (11.8	161 (10.7)	0.1577
bDBP, mm Hg	102.4 (8.4)	101 (8.9)	0.1124
bPP, mm Hg	60.2 (12.7)	60 (13.1)	0.8679
bHR, beats/min	73.5 (10.8)	74.1 (10.8)	0.5758
Previous antihypertensive treatments	32 (17.7)	35 (19.3)	0.6847

bBP = brachial blood pressure; bDBP = brachial diastolic blood pressure; bHR = brachial heart rate; bPP = brachial pulse pressure; bSBP = brachial systolic blood pressure.

Potential treatment-related AEs occurred in 1.5%, 4.5%, and 5.8% of patients in the N30 + V80, N60, and V160 groups, respectively. Most of the AEs were mild to moderate in intensity.

DISCUSSION

This prospective, open-label, randomized, active-controlled 8-week study explored the safety and efficacy of up-titration of nifedipine GITS versus up-titration of valsartan monotherapy. In addition to the previous FOCUS study that reported an increasing average central and peripheral BP reduction by doubling the dose of nifedipine GITS,[6] the present study is the first to focus on safety by using a stepwise up-titration of nifedipine GITS and BP variability, known to be an independent predictor of cardiovascular mortality. The main findings of the study, compared with up-titration of the ARB valsartan, are as follows: (1) up-titration of the CCB nifedipine GITS produced no additional increased safety concerns; and (2) despite better BP reduction, up-titration of the CCB nifedipine GITS produced no change in short-term BP variability.

BP Variability and Drug Treatment

Among the major classes of antihypertensive drugs, only CCBs lowered the BP variability by using the SD of 24-hour BP monitoring.[13,16–18] A large BP variability is expected if BP is drastically reduced; thus, this CCB effect disappears when the BP variability is calculated as the %CV, which is SD divided by the mean BP.[13,16,17] SD is preferred over %CV for the

Table II. Changes in mean (SD) blood pressure (BP) and BP parameters after 4 weeks in patients treated with a low dose of nifedipine or valsartan.

Variable	Nifedipine 30 mg (n = 181)				Valsartan 80 mg (n = 181)			
	Baseline	4 Weeks	Change	*P*	Baseline	4 Weeks	Change	*P*
Baseline bBP								
bSBP, mm Hg	162.7 (11.9)	141.6 (14.7)	-21.1 (14.3)	<0.0001	161.0 (10.7)	142.3 (16.3)	-18.7 (15.9)	<0.0001
bDBP, mm Hg	102.4 (8.4)	90.7 (10.4)	-11.8 (8.9)	<0.0001	101.0 (8.9)	90.5 (11.9)	-10.5 (9.9)	<0.0001
bPP, mm Hg	60.3 (12.9)	50.9 (10.0)	-9.4 (11.3)	<0.0001	60.0 (13.1)	51.8 (11.1)	-8.2 (11.2)	<0.0001
bHR, beats/min	73.4 (10.9)	75.8 (9.9)	2.4 (9.5)	0.0008	74.1 (10.8)	74.2 (10.6)	0.1 (9.6)	0.8706
BP variability								
SD of clinical SBP	3.66 (2.61)	3.84 (2.45)	0.18 (3.12)	0.4453	4.05 (2.99)	4.00 (2.44)	-0.05 (3.60)	0.8400
%CV of clinical SBP	2.25 (1.57)	2.71 (1.65)	0.46 (2.03)	0.0028	2.51 (1.83)	2.81 (1.68)	0.29 (2.34)	0.0949
Responder rate, %		119 (67.2)				117 (64.6)		0.6051
Control rate, %		64 (36.2)				68 (37.6)		0.7821

bBP = brachial BP; bDBP = brachial diastolic BP; bHR = brachial heart rate; bPP = brachial pulse pressure; bSBP = brachial systolic BP.

assessment of BP variability for 2 reasons. First, it is invalid to calculate the reduction in BP variability independent of BP level with a robust division as using %CV because some statistical efficacy may be lost.[16] In addition, although prognostic value concerning the %CV of BP is limited in the literature, the SD of 24-hour BP has been frequently reported in various studies on cardiovascular morbidity and mortality.

In the present study, there was no difference in the SD or %CV BP variability between the 2 low-dose groups (ie, the responder and nonresponder groups). Therefore, although there is a substantial decrease in BP, it is assumed that short-term BP variability is not always large. A large BP variability is due to the combination of a person's activities, psychological factors, drug compliance, sympathetic nerve system, and humoral systems. Other than short-term BP variability, there are various forms of BP variability such as mid-term (day-by-day) and long-term (visit-to-visit).[19] For now, long-term BP variability is believed to be related more to prognosis than to other variabilities.[12,20,21] There is currently no standard measurement for BP variability.[22]

The effectiveness of a drug in reducing BP variability is known to be influenced by age, mean BP, and heart rate. CCBs are apparently effective in BP variability because there was much reduction in the average BP.[13,16,23] In this study, although high-dose nifedipine GITS had a much better BP-lowering effect than high-dose valsartan, they had no difference in the SD and %CV of BP due to the difference in mechanisms between the BP variability and beat-to-beat BP variability shown in 24-hour BP. It may signify that its effects cannot be revealed within a short study period (ie, 8 weeks), and we therefore assumed no effect of it. Further studies with lengthier study periods of longer BP variability will be necessary.

Safety of Up-titration of CCBs

A previous study found that, although the BP-lowering effect of both amlodipine and nifedipine (the high-dose CCBs) was evident compared with low doses of the CCBs, edema was found to occur 25% and 15% more in the amlodipine and nifedipine groups, respectively, than in the low-dose amlodipine or nifedipine monotherapy group or the low-dose combination group.[9] In the present study, after 4 weeks of N30 treatment, the dose was increased to 60 mg (N60) for those who did not meet the target

Table III. Responders versus nonresponders after treatment with a low dose of nifedipine gastrointestinal therapeutic system or valsartan for 4 weeks. Unless otherwise indicated, values are given as mean (SD); "changes" indicate changes from baseline to week 4.

	Nifedipine 30 mg (N = 177*)			Valsartan 80 mg (N = 181)		
	Responders (n = 119)	Nonresponders (n = 58)		Responders (n = 117)	Nonresponders (n = 64)	
Characteristic	4 Weeks	4 Weeks	*P*	4 Weeks	4 Weeks	*P*
Male sex, no. (%)	70 (58.8)	44 (75.9)	0.0263	67(57.3)	47 (73.4)	0.0312
Age, y	49.7 (10.1)	45.4 (9.9)	0.0089	49.3 (10.1)	49.5 (8.5)	0.9276
Weight, kg	70.5 (13.7)	73.9 (10.9)	0.1005	70.2 (13.2)	73.0 (14.4)	0.1884
Height, cm	166.3 (9.5)	168.5 (7.7)	0.1185	164.7 (9.1)	166.7 (9.1)	0.1763
Body mass index, kg/m^2	25.3 (3.3)	26.0 (3.2)	0.2254	25.8 (3.6)	26.2 (3.8)	0.4777
Duration of hypertension, y	2.6 (4.6)	2.3 (3.8)	0.6982	2.4 (5.7)	2.8 (4.3)	0.5592
Dyslipidemia	19 (16.0)	3 (5.2)	0.0410	14 (12.0)	6 (9.4)	0.5950
Diabetes mellitus	5 (4.2)	5 (8.6)	0.2995	7 (6.0)	2 (3.1)	0.4956
Hematocrit, %	41.6 (2.5)	41.6 (2.6)	0.9718	41.4 (2.5)	41.5 (2.7)	0.8255
Fasting glucose, mg/dL	106.7 (28.7)	107.1 (20.5)	0.9212	105.1 (15.9)	109.0 (25.3)	0.3023
Total cholesterol, mg/dL	222.7 (35.7)	224.7 (36.4)	0.7243	226.1 (35.6)	224.7 (35.8)	0.8076
HDL-C, mg/dL	45.2 (23.7)	43.1 (17.8)	0.5139	43.7 (23.6)	43.8 (23.5)	0.9839
Triglyceride, mg/dL	131.6 (96.1)	179.2 (151.9)	0.0320	160.5 (205.0)	151.6 (80.7)	0.6783
LDL-C, mg/dL	94.5 (56.1)	89.4 (55.6)	0.5718	95.9 (59.1)	96.6 (49.7)	0.9368
Serum creatinine, mg/dL	0.9 (0.2)	0.9 (0.2)	0.8179	0.8 (0.3)	0.9 (0.2)	0.0054
Baseline bBP						
Changes in bSBP, mm Hg	−27.4 (11.6)	−8.2 (9.8)	<0.0001	−26.6 (11.4)	−4.1 (12.2)	<0.0001
Changes in bDBP, mm Hg	−15.9 (6.1)	−3.2 (7.5)	<0.0001	−15.7 (6.7)	−0.9 (7.2)	<0.0001
Changes in bPP, mm Hg	−11.5 (9.8)	−5.0 (12.8)	<0.0001	−10.9 (10.6)	−3.2 (10.8)	<0.0001
Changes in bHR, beats/min	2.4 (9.2)	2.5 (10.3)	0.9437	0.4 (10.0)	−0.5 (8.8)	0.6687
Blood pressure variability						
Changes in SD of clinical SBP	0.13 (3.08)	0.29 (3.22)	0.2352	−0.37 (3.42)	0.52 (3.86)	0.0540
Changes in %CV of clinical SBP	0.54 (1.99)	0.30 (2.10)	0.9962	0.23 (2.28)	0.41 (2.47)	0.4752
Responder rate, %	119 (100.0)	0	0.0001	117 (100.0)	0	<0.0001
Control rate, %	62 (52.1)	2 (3.5)	<0.0001	67 (57.3)	1 (1.6)	<0.0001

bBP = brachial blood pressure; bDBP = brachial diastolic blood pressure; bHR = brachial heart rate; bPP = brachial pulse pressure; bSBP = brachial systolic blood pressure.
*4 people were excluded due to inaccurate evaluation of responsiveness.

BP, and vasodilatory symptoms such as dizziness, headache, flushing, and palpitation were similar between the treatment groups of 30 and 60 mg. In addition, there was no difference between high-dose valsartan and the low-dose combination of the 2 drugs.[9] It is difficult to explain why there was no increase in the occurrence of adverse effects with N60, which is known to have one of the strongest vasodilation effects among CCBs. Compared with low-dose valsartan, low-dose nifedipine had a higher rate of adverse effects, and it can be assumed that the occurrence of these effects did not increase as the dose increased because the patients were adapting to low-dose nifedipine.

Table IV. Further changes in blood pressure (BP) and BP parameters from 4 to 8 weeks in patients with controlled and uncontrolled disease. Unless otherwise indicated, values are given as mean (SD).

	Group A		Group B		Group C		Group D		Group E	
	Nifedipine 30 mg to >30 mg (n = 60)		Nifedipine 30 mg to >60 mg (n = 66)		Nifedipine 30 mg + Valsartan 80 mg (n = 66)		Valsartan 80 mg to >160 mg (n = 66)		Valsartan 80 mg >80 mg (n = 64)	
Variable	4 Weeks	8 Weeks	4 Weeks	8 Weeks	4 Weeks	8 Weeks	4 Weeks	8 Weeks	4 Weeks	8 Weeks
Brachial BP, mm Hg										
SBP	128.7 (7.5)	130.9 (10.4)	149.7 (10.2)	138.5 (9.4)*	151.1 (13.7)	136.5 (15.1)*	149.9 (10.0)	146.9 (15.6)	126.7 (7.0)	128.7 (12.6)
DBP	81.9 (5.9)	83.2 (8.1)	95.7 (8.3)	89.6 (9.4)*	95.3 (9.6)	86.8 (9.4)*	96.5 (9.5)	94.1 (11.3)†	80.6 (7.5)	81.8 (10.1)
HR, beats/min	74.3 (8.6)	70.2 (8.9)*	76.6 (10.1)	75.5 (11.4)	75.8 (10.1)	75.3 (10.5)	73.5 (11.2)	71.1 (9.4)	75.4 (10.9)	70.3 (9.7)*
BP variability										
SD of SBP	3.59 (2.03)	3.10 (1.78)	4.17 (2.71)	3.81 (2.64)	4.00 (2.62)	3.72 (2.74)	4.21 (2.21)	3.69 (2.13)	3.55 (2.53)	3.78 (2.18)
%CV of SBP	2.78 (1.57)	2.37 (1.33)	2.78 (1.75)	2.76 (1.91)	2.65 (1.70)	2.69 (1.91)	2.80 (1.44)	2.54 (1.52)	2.8 (1.92)	2.92 (1.56)
Responder rate, %	58 (96.7)	54 (90.0)	34 (51.5)	52 (78.8)	31 (47.0)	56 (84.9)	30 (45.5)	37 (56.1)	63 (98.4)	58 (90.6)
Control rate, %	59 (98.3)	47 (78.3)	0	26 (39.4)	0	34 (51.5)	0	16 (24.2)	64 (100)	46 (71.9)

DBP = diastolic BP; HR = heart rate; SBP = systolic BP.
*$P < 0.01$ versus 4 weeks.
†$P < 0.05$ versus 4 weeks.

Table V. Number and percentage of patients with any emergent adverse event (given in brackets) during treatment with the study drug (safety population). The most common emergent adverse events are also presented (frequency ≥2 patients in any group).

Weeks 1–4	Nifedipine 30 mg (n = 181)	Valsartan 80 mg (n = 181)
All emergent adverse events	46 (25.4) [70]	32 (17.7) [41]
Palpitations	1 (0.6) [1]	2 (1.1) [2]
Constipation	3 (1.7) [3]	1 (0.6) [1]
Gastroesophageal reflux	2 (1.1) [2]	0 (0.0) [0]
Nausea	3 (1.7) [3]	2 (1.1) [2]
Peripheral edema	2 (1.1) [2]	0 [0]
Cystitis	2 (1.1) [2]	0 [0]
Nasopharyngitis	2 (1.1) [2]	2 (1.1) [2]
Dyslipidemia	0 [0]	2 (1.1) [2]
Dizziness	3 (1.7) [3]	2 (1.1) [2]
Headache	16 (8.8) [19]	8 (4.4) [8]
Hypoesthesia	1 (0.6) [1]	2 (1.1) [2]
Flushing	3 (1.7) [3]	0 [0]
Hot flush	5 (2.8) [5]	0 [0]
Serious adverse events	1 (0.6) [2]	1 (0.6) [1]
Drug-related adverse events	23 (12.7) [38]	7 (3.9) [10]

Weeks 5–8	Nifedipine 30 mg + Valsartan 80 mg (n = 66)	Nifedipine 60 mg (n = 67)	Valsartan 160 mg (n = 68)
All emergent adverse events	7 (10.6) [7]	7 (10.5) [9]	11 (16.2) [16]
Upper abdominal pain	0 [0]	0 [0]	2 (2.9) [2]
Peripheral edema	0 [0]	2 (3.0) [2]	0 [0]
Nasopharyngitis	2 (3.0) [2]	0 [0]	2 (2.9) [2]
Headache	1 (1.5) [1]	3 (4.5) [3]	1 (1.5) [1]
Serious adverse events	0 [0]	1 (1.5) [1]	0 [0]
Drug-related adverse events	1 (1.5) [1]	3 (4.5) [4]	4 (5.8) [5]

Study Limitations

One of the limitations of the study was the significant difference in BP reduction between the N60 group and the V160 group. The cause may be that BP variability was more prominent with high BP, although the SD and %CV of BP did not differ between the 2 treatments in this study. In terms of clinical practice, BP fluctuation can differ occasionally; thus, in addition to short-term BP variability in this study, additional studies should be performed, including monitoring of the long-term (visit-to-visit) BP variability, which is more related to cardiovascular risk. Second, this study did no answer why there was no difference in BP variability between the 2 groups. Because short-term BP variability and heart rate variability are both largely affected by the sympathetic nerve system, additional studies on the system are necessary. Third, the research period was relatively short, and the number of participating patients was limited. Clinical studies are therefore needed with a larger cohort of patients, a longer study period, and diverse BP variability parameters.

CONCLUSIONS

Up-titration of nifedipine GITS led to no additional safety concerns compared with up-titration of valsartan or the low-dose combination of the 2, despite strong reductions in BP in these study patients. There was no further change in short-term BP variability.

ACKNOWLEDGMENTS

This research was supported by Bayer Korea Ltd.

Dr Park JB was responsible for study design and management and manuscript drafting.drafting. Drs. Shin J-H, Kim D-S, Youn H-J, Park SW, Shim WJ, Park CG, Kim D-W, Lee H-Y, Choi D-J, Rim S-J, Lee S-Y, Kim J-H performed critical manuscript revisions. Lee H-Y provided initial study analysis. All authors were responsible for concept/design and study/analysis plans. All authors gave final approval for the version to be published. The authors express their sincere appreciation to the collaborators listed below who comprise the FOCUS investigators. Additionally, they are thankful to Ms. Jina Lee for her valuable contribution to the manuscript preparation. The FOCUS Study Group consists of the following individuals: Dong-Ju Choi, Division of Cardiology, Seoul National University Bundang Hospital, Gyeonggi, Korea; Jong-won Ha MD, Division of Cardiology, Severance Hospital, Yonsei University College of Medicine, Seoul, Korea; Hae-Ok Jung MD, Division of Cardiology, The Catholic University of Korea, Seoul St. Mary's Hospital, Seoul, Korea; Dong-Soo Kim, Division of Cardiology, Inje University Pusan Paik Hospital, Busan, Korea; Dong-Woon Kim, Division of Cardiology, Chungbuk National University Hospital, Chungbuk, Korea; Ju-Han Kim, Division of Cardiology, Chonnam National University Hospital, Gwangju, Korea; Hae-Young Lee, Division of Cardiology, Seoul National University Hospital, Seoul, Korea; Sang Chol Lee, Division of Cardiology, Samsung Medical Center, Seoul, Korea; Sung-Yun Lee, Division of Cardiology, Inje University Ilsan Paik Hospital, Gyeonggi, Korea; Chang Gyu Park, Division of Cardiology, Korea University Guro Hospital, Seoul, Korea; Jeong Bae Park MD, Division of Cardiology, Cheil General Hospital, Kwandong University College of Medicine; Seoul, Korea; Seung Woo Park, Department of Medicine, Sungkyunkwan University School of Medicine, Samsung Medical Center, Seoul, Korea; MooYong Rhee MD, Division of Cardiology, Dongguk University Hospital, Goyang-si, Gyeonggi-do, Korea; Se-Joong Rim, Division of Cardiology, Gangnam Severance Hospital, Seoul, Korea; Wan Joo Shim, Division of Cardiology, Korea University Anam Hospital, Seoul, Korea; Joon-Han Shin, Division of Cardiology, Ajou University Hospital, Gyeonggi, Korea; Ho-Joong Youn, Division of Cardiology, The Catholic University of Korea, Seoul St. Mary's Hospital, Seoul, Korea.

CONFLICTS OF INTEREST

As the study sponsor, Bayer Korea assisted the investigators with the study design and produced the final study report (summarizing the collected data). The authors have indicated that they have no conflicts of interest regarding the content of this article.

REFERENCES

1. Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Blood Pressure*. 2013;22:193–278.
2. NICE. Hypertension (CG127): clinical management of primary hypertension in adults. Vol 2015. London: NICE; 2011.
3. Wald DS, Law M, Morris JK, et al. Combination therapy versus monotherapy in reducing blood pressure: meta-analysis on 11,000 participants from 42 trials. *Am J Med*. 2009;122:290–300.
4. Stason WB, Schmid CH, Niedzwiecki D, et al. Safety of nifedipine in patients with hypertension: a meta-analysis. *Hypertension*. 1997;30:7–14.
5. Morgan TO, Anderson AI, MacInnis RJ. ACE inhibitors, beta-blockers, calcium blockers, and diuretics for the control of systolic hypertension. *Am J Hypertens*. 2001;14: 241–247.
6. Park JB, Ha JW, Jung HO, Rhee MY. Randomized trial comparing the effects of a low-dose combination of nifedipine GITS and valsartan versus high-dose monotherapy on central hemodynamics in patients with inadequately controlled hypertension: FOCUS study. *Blood Pressure Monitor*. 2014;19:294–301.
7. Krause T, Lovibond K, Caulfield M, et al. Management of hypertension: summary of NICE guidance. *BMJ*. 2011; 343:d4891.
8. Weber MA, Schiffrin EL, White WB, et al. Clinical practice guidelines for the management of hypertension in the community. *J Clin Hypertens*. 2014;16:14–26.
9. Messerli FH, Oparil S, Feng Z. Comparison of efficacy and side effects of combination therapy of angiotensin-converting enzyme inhibitor (benazepril) with calcium antagonist (either nifedipine or amlodipine) versus high-dose calcium antagonist monotherapy for systemic hypertension. *Am J Cardi*. 2000;86:1182–1187.
10. Ke YN, Dong YG, Ma SP, et al. Improved blood pressure control with nifedipine GITS/valsartan combination versus high-dose valsartan monotherapy in mild-to-moderate hypertensive patients from Asia: results from the ADVISE study, a randomized trial. *Cardiovascular Therapeutics*. 2012; 30:326–332.

11. Parati G, Dolan E, Ley L, Schumacher H. Impact of antihypertensive combination and monotreatments on blood pressure variability: assessment by old and new indices. Data from a large ambulatory blood pressure monitoring database. *J Hyperten*. 2014;32:1326–1333.
12. Rothwell PM, Howard SC, Dolan E, et al. Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension. *The Lancet*. 2010; 375:895–905.
13. Mancia G, Ferrari A, Gregorini L, et al. Blood pressure and heart rate variabilities in normotensive and hypertensive human beings. *Circ Res*. 1983;53:96–104.
14. Floras JS, Hassan MO, Jones JV, et al. Factors influencing blood pressure and heart rate variability in hypertensive humans. *Hypertension*. 1988;11:273–281.
15. Wang JG, Yan P, Jeffers BW. Effects of amlodipine and other classes of antihypertensive drugs on long-term blood pressure variability: evidence from randomized controlled trials. *J Am Soci Hypertens: JASH*. 2014;8:340–349.
16. Zhang Y, Agnoletti D, Safar ME, Blacher J. Effect of antihypertensive agents on blood pressure variability: the Natrilix SR versus candesartan and amlodipine in the reduction of systolic blood pressure in hypertensive patients (X-CELLENT) study. *Hypertension*. 2011;58: 155–160.
17. Pringle E, Phillips C, Thijs L, et al. Systolic blood pressure variability as a risk factor for stroke and cardiovascular mortality in the elderly hypertensive population. *J Hypertens*. 2003;21:2251–2257.
18. Ichihara A, Kaneshiro Y, Takemitsu T, Sakoda M. Effects of amlodipine and valsartan on vascular damage and ambulatory blood pressure in untreated hypertensive patients. *J Hum Hypertens*. 2006;20: 787–794.
19. Parati G, Ochoa JE, Lombardi C, Bilo G. Assessment and management of blood-pressure variability. *Nature Reviews Cardiology*. 2013;10:143–155.
20. Hansen TW, Thijs L, Li Y, et al. Prognostic value of reading-to-reading blood pressure variability over 24 hours in 8938 subjects from 11 populations. *Hypertension*. 2010;55:1049–1057.
21. Mancia G, Bombelli M, Facchetti R, et al. Long-term prognostic value of blood pressure variability in the general population: results of the Pressioni Arteriose Monitorate e Loro Associazioni Study. *Hypertension*. 2007;49:1265–1270.
22. Mena L, Pintos S, Queipo NV, et al. A reliable index for the prognostic significance of blood pressure variability. *J Hypertens*. 2005; 23:505–511.
23. Schillaci G, Verdecchia P, Borgioni C, et al. Lack of association between blood pressure variability and left ventricular mass in essential hypertension. *Am J Hypertens*. 1998;11:515–522.

Address correspondence to: Jeong Bae Park, MD, PhD, Division of Cardiology/Medicine, Cheil General Hospital, Dankook University College of Medicine, 17, Seoae-ro 1-gil, Jung-gu, Seoul, 100-380 Korea (South). E-mail: mdparkjb@gmail.com