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

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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 BP reduction, but this effect was not shown in the

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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;▮:▮▮▮–▮▮▮) © 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