Impact of Visit-to-Visit Variability and Systolic Blood Pressure Control on Subsequent Outcomes in Hypertensive Patients With Coronary Artery Disease (from the HIJ-CREATE Substudy)

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Although visit-to-visit variability in systolic blood pressure (BP) is a strong predictor of stroke, the impact on subsequent major adverse cardiac events (MACEs) in patients with coronary artery disease (CAD) in terms of secondary prevention remains unclear. The aim of this study was to clarify the prognostic significance of visit-to-visit variability in systolic BP on subsequent MACE in hypertensive patients with CAD. In the Heart Institute of Japan Candesartan Randomised Trial for Evaluation in Coronary Artery Disease, a total of 2,049 hypertensive patients with CAD were enrolled. Incidence of MACEs in addition to biochemistry tests and office BP were determined during follow-up. Achieved BP was defined as the mean value of systolic BP in patients who did not experience MACE and the mean value of systolic BP before MACE in those who experienced MACE during follow-up. In the present study, 1,734 patients had multiple follow-up visits (≥3 times) until their final follow-up. During a median follow-up of 4.2 years, the primary outcome occurred in 317 patients (18.3%). Visit-to-visit variability of systolic BP was defined as the SD. Participants were divided into equal quartiles based on the mean systolic BP during follow-up and visit-to-visit variability of systolic BP, respectively. Although there was no relation between visit-to-visit variability of systolic BP and the incidence of MACE, the highest quartile based on mean systolic BP showed a significant relation with subsequent MACE. In conclusion, in hypertensive patients with CAD, inadequate BP control is a strong predictor of subsequent MACE, whereas visit-to-visit variability of systolic BP is not. **© 2015 Elsevier Inc. All rights reserved.** **(Am J Cardiol 2015;116:236−242)**

Hypertension is an established and important risk factor for various cardiovascular diseases (CVDs).[1−3] Evidence from clinical trials indicates the beneficial effects of various classes of blood pressure (BP)-lowering regimens on cardiovascular event rates in hypertensive patients.[4−8] Previous studies reported significant correlations between the incidence of CVD and various hypertension indexes, such as systolic BP, diastolic BP, and mean BP.[9] The prognostic value of BP is based mainly on measurements of mean systolic BP and guidelines for diagnosis and treatment focus only on underlying mean BP measurements.[10] Recent studies suggest that visit-to-visit BP variability is a simple surrogate marker that predicts stroke, myocardial infarction, cardiovascular events, and all-cause mortality, independent of mean BP.[5,9,10] It has been known that BP variability reflects stiffness of blood vessels, sympathetic nerve activation, class effect of antihypertensive agents, and other patient characteristics.[11] Recent studies demonstrated that visit-to-visit BP variability was an important index for stroke and coronary event prediction independent of mean systolic BP.[12,13] Previous studies reported an association of end-organ damage,[14−16] cardiovascular events,[17,18] or all-cause mortality[5] with BP variability. In contrast, some studies showed that BP variability was inferior to mean systolic BP for predicting the cardiovascular outcomes in hypertensive patients.[19−22] To the best of our knowledge, there are no sufficient data regarding the correlation between cardiovascular events and BP variability in patients with coronary artery disease (CAD). The aim of this study was to evaluate the prognostic significance of visit-to-visit systolic BP variability in hypertensive patients with CAD in terms of secondary prevention.

Methods

This study was designed as a part of the Heart Institute of Japan Candesartan Randomised Trial for Evaluation in Coronary Artery Disease (HIJ-CREATE).[23] The design and methods of the HIJC-CREATE have been described previously.[23] Briefly, HIJ-CREATE was a multicenter, prospective, randomized, controlled study that compared the effects of candesartan-based therapy with those of non−angiotensin receptor blocker (ARB)-based standard therapy on major

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adverse cardiac events (MACEs) in 2,049 hypertensive patients with CAD recruited from June 2001 to April 2004. BP was measured using a standard cuff mercury sphygmomanometer after 5 minutes of rest in the sitting position. Hypertension was defined as systolic BP ≥140 mm Hg, diastolic BP ≥90 mm Hg, or history of having received treatment for hypertension at the time of enrollment. Titration of antihypertensive agents was performed to reach the target BP of <130/85 mm Hg. The HIJ-CREATE included specifically targeted hospitalized patients with CAD and hypertension aged 20 to 80 years. The protocol required coronary angiography to be performed for the diagnosis of CAD when patients were enrolled. The primary end point of the HIJ-CREATE was the time to first MACE (composite of cardiovascular death, nonfatal myocardial infarction, unstable angina, heart failure, stroke, and other cardiovascular events requiring hospitalization). Participants were followed by hospital doctors or other general practitioners. Incidence of end point events in addition to biochemistry tests and office BP was determined during the scheduled visits at 6, 12, 24, 36, 48, and 60 months through contact with each patient or through access to certificates issued by administrative authorities if necessary. Cardiovascular death was defined as death due to myocardial or cerebral infarction or documented sudden cardiac death. Unstable angina was defined according to the Braunwald criteria.[24] Heart failure was defined on the basis of symptoms (such as dyspnea), clinical signs (such as rales or ankle edema), and the need for treatment with diuretics, vasodilators, or antihypertensive drugs. Stroke was defined as a new focal neurologic deficit of vascular origin lasting 24 hours. Stroke was further classified as the result of intracranial hemorrhage, ischemia (if results of computed tomography or magnetic resonance imaging were available), or uncertain cause. Other cardiovascular events include peripheral artery diseases, dissecting aneurysm of the aorta, and increased size of aortic aneurysm.

In this study, 3 sets of analyses were conducted to evaluate BP variability, one for standard deviation of systolic BP, the second for coefficient of variation (CV), and the third for variation independent of mean (VIM).[15,25,26]

The study protocol was approved by the institutional review board or ethics committee. All participating patients provided written informed consent. Patient enrollment was carried out according to the principles of the Declaration of Helsinki.

Continuous data that could be assumed to have a normal distribution were presented as means ± SD, whereas continuous data that could not be assumed to have a normal distribution were summarized as median values (twenty-fifth and seventy-fifth percentiles). The 4 groups were compared using analysis of variance, the Kruskal-Wallis test, the Wilcoxon rank-sum test, or the chi-square test, depending on the characteristics of the data. A multivariable Cox proportional hazards model was used to calculate the hazard ratios and 95% confidence intervals with consideration of clinically plausible interactions. The proportional hazards assumption was confirmed by the log (−log survival function). Two-tailed p values <0.05 were considered significant. Correlations were assessed using Pearson's or Spearman's methods, as appropriate. Statistical analysis was conducted at an independent statistical data center (Medical TOUKEI Corporation, Tokyo, Japan) using SPSS 15.0 (SPSS Inc., Chicago, Illinois) and SAS 9.1.3 (SAS Institute Inc., Cary, North Carolina).

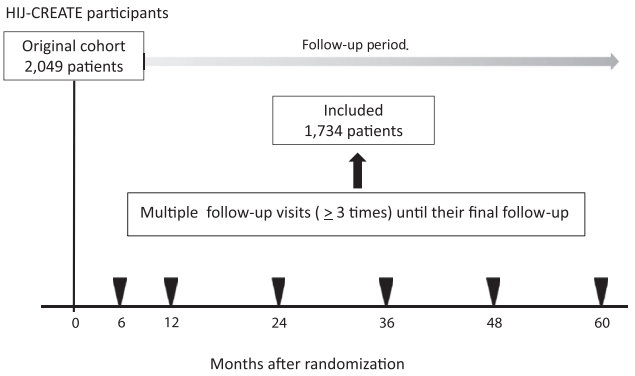

Figure 1. Flow diagram of the analysis in this HIJ-CREATE substudy. Of 2,049 patients in the original cohort, 1,734, who underwent BP measurements during at least 3 different visits, were included.

Results

From June 2001 to April 2004, a total of 2,049 patients were randomized in the HIJ-CREATE. Of them, we limited the present analysis to patients in the HIJ-CREATE who underwent BP measurements on at least 3 different visits. As a result, a total of 1,734 patients were included in this study (Figure 1). Patient characteristics are summarized in Table 1. The patients' characteristics of this study by quartile of SD of systolic BP are also provided in Table 1. The participants in the highest quartile of the SD of systolic BP were characterized as more likely to be women, of advanced age, and have higher systolic and diastolic BP at baseline. In addition, participants in the highest quartile of SD of systolic BP were more likely to have peripheral artery disease and receive β blockers. Conversely, statin therapy was provided less frequently for this group than the other quartiles. The correlation between the visit-to-visit variability of systolic BP and mean of systolic BP before the occurrence of MACE was weak but significant in the group as a whole (Figure 2).

During a median follow-up of 4.2 years, the primary outcome occurred in 317 patients (18.3%). After adjustment for age, gender, and mean diastolic BP, Cox proportional hazard analysis revealed that indexes of BP variability were not associated with MACE, whereas mean of systolic BP was (Table 2, Figure 3).

Discussion

In this study, we showed that BP variability was not associated with subsequent cardiovascular events in hypertensive patients with CAD. Elevated mean systolic BP during the follow-up period had a close relation with the incidence of MACE. Advanced age, female gender, higher systolic and diastolic BP, a lower prevalence of dyslipidemia, and a higher incidence of peripheral artery disease were associated with increased variability of systolic BP.

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