Benefits of Prestroke Use of Angiotensin Type 1 Receptor Blockers on Ischemic Stroke Severity

Nobukazu Miyamoto, MD, PhD,* Yasutaka Tanaka, MD, PhD,* Yuji Ueno, MD, PhD,* Ryota Tanaka, MD, PhD,† Nobutaka Hattori, MD, PhD,* and Takao Urabe, MD, PhD*

Background: There is a general agreement that the stroke prevention benefit of antihypertensive agents is mainly based on their blood pressure lowering properties. The aim of this retrospective study was to assess the benefits of angiotensin type 1 receptor blockers (ARBs) used before the onset of ischemic stroke. *Methods:* Data were obtained between April 2007 and March 2009 using the discharge statistics of the neurologic service at Juntendo hospital. We retrieved the demographic and clinical characteristics of stroke patients and functional status upon discharge assessed by the modified Rankin Scale (mRS) and Barthel index (BI). *Results:* We enrolled 151 patients. Patients treated with ARBs were less often treated with a calcium channel blocker (CaB)/angiotensin-converting enzyme inhibitor (ACEI). They often had diabetes and showed better outcomes than the non-ARB group. Logistic regression analysis indicated that in patients with a mRS score of 0 to 2, older age ($P < .007$) was associated with severe outcomes, while the factor of pretreatment with ARB ($P < .014$) was associated with better outcomes. For patients with BI scores of more than 75, older age ($P < .015$) and large artery atherosclerosis ($P < .035$) were associated with severe outcomes. Logistic regression analysis identified the factor of pretreatment with ARB ($P < .020$) to be associated with better outcomes. *Conclusions:* ARB is widely used in patients with hypertension and cardiovascular disease, and our results further support this indication. **Key Words:** Acute ischemic stroke—angiotensin type 1 receptor blocker—Barthel index—modified Rankin Scale—severity.

Hypertension (HT) is the leading modifiable risk factor for stroke.[1] Lowering blood pressure (BP) with the use of drugs of different modes of action substantially reduces stroke frequency.[2,3] However, there is debate about the merits and demerits of various classes of antihypertensive agents for stroke prevention.[4] Although the general consensus is that BP lowering is the most important factor in the stroke prevention benefit conferred by antihypertensive treatment, there is evidence that certain classes of antihypertensives may confer the clinical benefits in stroke prevention through additional mechanisms.[5]

Several clinical trials showed beneficial effects by reducing morbidity and mortality in cardiovascular diseases, improved renal outcomes in both hypertensive and nonhypertensive patients, delays in the onset of diabetes in hypertensive patients, and reduced stroke rates in primary and secondary stroke prevention.[6,7] Recent clinical studies, such as the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET),[8] the Jikei Heart Study,[9] and Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS),[10] have indicated that blockade of the renin-angiotensin system (RAS) is important in preventing stroke. The overall evidence provided by randomized controlled trials supports the conclusion that angiotensin

From the *Departments of Neurology, Juntendo University School of Medicine, Tokyo; and †Juntendo University Urayasu Hospital, Chiba, Japan.

Received August 5, 2010; revision received September 23, 2010; accepted September 28, 2010.

Address correspondence to Takao Urabe, MD, PhD, Department of Neurology, Juntendo University School of Medicine, 3-1-3 Hongo, Bunkyou-ku, Tokyo 113-0033, Japan. E-mail: t_urabe@juntendo.ac.jp.

1052-3057/$ - see front matter

doi:10.1016/j.jstrokecerebrovasdis.2010.09.011

type 1 receptor blockers (ARBs) and angiotensin-converting enzyme inhibitor (ACEIs) are equally protective against the risk of cardiovascular events and all-cause mortality in patients belonging to a wide range of conditions characterized by a high cardiovascular risk. Moreover, Reboldi et al[11] reported that the risk of stroke was 8% lower with angiotensin II receptor blockers than ACEIs in a metaanalysis. Compared with other antihypertensives like diuretics, ACEIs, or beta-blockers, ARB achieves a similar reduction in arterial tension measures, which means that the benefits observed in the population taking ARB are not only related to arterial tension regulation but to additional protective mechanisms.

The neuroprotective mechanism of angiotensin type 1 (AT1) blockade has been extensively investigated. Walther et al[12] observed a smaller infarct area after occlusion of the middle cerebral artery (MCA) in AT1-deficient mice. Moreover, Iwai et al[13] showed that valsartan, an ARB, reduced the ischemic area after MCA occlusion in wild-type mice. These results suggest a role for AT1 stimulation in the development of brain ischemic lesions, and that blocking this activity decreases ischemia by lowering BP and possibly via other mechanisms.

The possible benefits of treatment with ARB before stroke are not clear at present. In this study, we assessed the potential benefits of prestroke use of ARB. In particular, we hypothesized that ARB use before stroke was associated with a less severe stroke as reflected by the functional status upon discharge from the hospital, as assessed by the modified Rankin Scale (mRS) and Barthel index (BI).

Patients and Methods

Patients

The study encompassed 487 Japanese patients with stroke who were admitted to Juntendo University Hospital between April 2007 and March 2009 and who visited the hospital within 24 hours after the stroke onset. Brain computed tomographic (CT) scans and/or brain magnetic resonance imaging (MRI) and electrocardiography were performed in all patients. We excluded patients with cerebral hemorrhage and transient ischemic attack (TIA). TIA was defined as transient focal neurologic symptoms lasting <24 hours and no high-intensity lesion on diffusion-weighted MRI.

We retrieved the following data for each patient: 1) demographics; 2) risk factors for stroke (e.g., HT, diabetes mellitus, hyperlipidemia, the Trial of Org 10172 in Acute Treatment [TOAST] classification[14] of sources of cardioembolism (CE), and history of TIA and smoking) as reported by the patient and his/her family; 3) vital signs at presentation BP; 4) blood glucose profile and lipid profile on admission; 5) medications upon admission, with particular attention to antiplatelets, anticoagulants, antihypertensives, and statins (we did not collect information about the duration of medication use, daily use, or compliance); 6) stroke mechanism, after completing the diagnostic evaluation, according to TOAST criteria; 7) duration of hospitalization; 8) the baseline NIH Stroke Scale (NIHSS) score,[15] which was recorded by stroke-trained neurologists certified in the application of NIHSS at admission and upon discharge; and 9) functional status upon discharge, as assessed by a mRS score of 0 to 2 and a BI score of more than 75,[15] which assessed assistance-free daily activity. To evaluate the functional status at discharge according to the different antihypertensives, we excluded patients who were not taking any antihypertensive medications and those with a mRS score >1 at stroke onset (Fig. 1). When the patients recovered to the functional stage from the assistance-free stage, they would be discharged from the hospital to their homes. Therefore, the endpoint of the trial was discharge from the hospital.

Ethical Consideration and Statistical Analysis

The protocol of this retrospective study was approved by the Human Ethics Review Committee of the Juntendo University School of Medicine. The data were analyzed using SPSS (v 17.0; SPSS, Chicago, IL). All values were expressed as mean ± standard deviation (SD). Statistical analysis was performed using the Chi-square test for categorical variables, the t test for parametric analysis, and the Mann–Whitney U test for nonparametric analysis. All variables with a $P < .2$ on univariate analysis were entered into multiple logistic regression analysis. A 2-sided $P < .05$ was considered statistically significant.

Results

Overall, 487 patients with acute stroke were admitted to Juntendo University during the study period. We

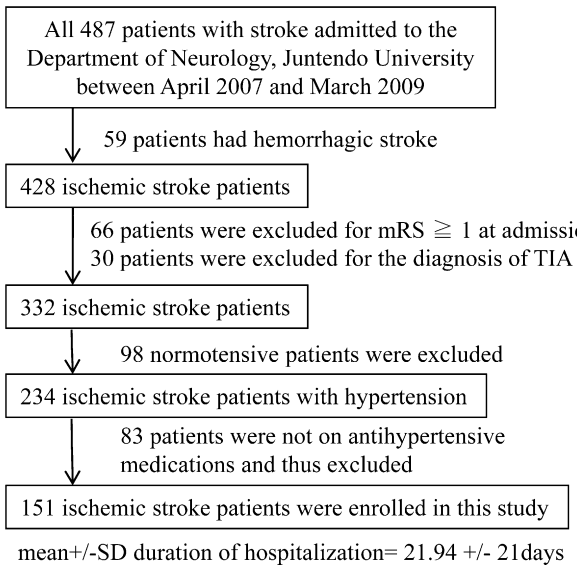

Figure 1. *Flow chart describing enrollment of patients with stroke in the present study.*