Editorial Comment

The Earlier, the Better

Hideyasu KIYOMOTO[1)] and Hirofumi HITOMI[1)]

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Recent trends of antihypertensive treatment converge on "the lower, the better" and "beyond hypertension." According to the JSH 2004 Guideline, the target level of blood pressure control was reduced to 130/85 mmHg, and the importance of attaining this target even by multi-drug combination therapy was emphasized. Also, with the recent increase in the interest in metabolic syndrome, antihypertensive therapy in consideration of favorable effects on insulin resistance and metabolism has begun to be recommended rather than simple antihypertensive therapy, leading to the recognition of the efficacy of renin-angiotensin (RA) system antagonists, particularly angiotensin II receptor blockers (ARB) (*1*). However, no consensus has been established as to when aggressive antihypertensive therapy should be initiated to control the blood pressure at an optimal level.

In our previous experiment using rats with type II diabetes mellitus, temporary suppression of the RA system in an early stage of nephropathy was obviously shown to suppress subsequent renal disorders even after discontinuation of the treatment (*2*). This study suggested that early intervention with ARB in a pre-diabetic stage may prevent the subsequent occurrence or progression of nephropathy. In addition, the initiation of the use of RA system antagonists before the onset of diabetes mellitus (time when metabolic syndrome is observed) was recommended with the concept of "never too early to treat" (*3*). All large scale clinical studies, such as the ALLHAT (*4*), LIFE (*5*), and CHARM (*6*) showed significant suppression of the occurrence of diabetes mellitus by RA system inhibitors. Therefore, early intervention with RA system inhibitors from the viewpoint of "beyond hypertension" is important for the prevention of diabetic nephropathy.

Recently, the TROPHY study attracted wide attention by reporting that early intervention of hypertension suppresses the subsequent progression of hypertension itself (*7*). In this study, candesartan or placebo was administered for 2 years in the prehypertension stage preceding stage I hypertension. Then, only placebo in both groups was used for 2 more years. The investigators of the TROPHY study evaluated the frequency of the progression to stage I hypertension and the future cardiovascular risk. This clinical study may be considered to have been influenced by the epoch-making report on basic research by Nakaya *et al*. published in 2001 (*8*). They had also previously evaluated in our journal the possibility of prevention of nephrosclerosis by RA system blocking early after the onset of hypertension with angiotensin-converting enzyme (delapril) or ARB (candesartan) in SHRSP/Izm rats (*9*).

"Developmental activity of the renin-angiotensin system during the 'critical period' modulates later L-NAME–induced hypertension and renal injury" by Ishiguro *et al*. (*10*) appeared in this issue is a very important basic research that supports the evidence shown by the TROPHY study (*7*). This elegant study demonstrated the involvement of the endothelial function in RA system blocking at the onset of hypertension and the mechanism of prevention of the occurrence or progression of hypertension using an NO synthesis inhibitor (L-NAME). Furthermore, their paper has a marked impact on not only the estimation of initial lesions of organ disorders due to angiotensin II by continuous administration but also evaluating its reciprocal effect opposite to the effect of ARB in addition to simply evaluating the effect of the antihypertensive agent. Particularly, as shown in Fig. 3 in their paper (*10*), vascular and glomerular damage was clearly reduced by temporary administration of candesartan in the developmental

From the [1)]Division of Nephrology and Dialysis, Department of CardioRenal and CerebroVascular Medicine, Faculty of Medicine, Kagawa University, Kagawa, Japan.

Address for Reprints: Hideyasu Kiyomoto, M.D., Ph.D., Division of Nephrology and Dialysis, Department of CardioRenal and CerebroVascular Medicine, Faculty of Medicine, Kagawa University, 1750–1 Ikenobe Miki-cho, Kita-gun, Kagawa 761–0793, Japan. E-mail: kiyo@kms.ac.jp

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period compared with reference drugs including calcium antagonists and vasodilators, indicating the efficacy of ARB on renal disorders, that is "beyond hypertension." Moreover, the suppression of oxidative stress and increase in aldosterone due to L-NAME by temporary administration of candesartan were surprising findings.

A point that could be strongly emphasized in this editorial comment is the authors inform clinicians that prompt suppression of the RA system from an early stage is extremely important in a condition showing enhanced RA activities, as shown in the scheme of Fig. 10 of Ishiguro *et al*. (*10*). For example in the clinical setting, renovascular hypertension in youth and adolescence has been untreated for a long period until decreases in renal function appear, and even if renal arterioplasty was successfully performed, its effects on renal function or hypertension might be limited. As a result, permanent medication is likely to become necessary after intervention (*11*). Unimproved renal function or hypertension directly leads to a poor survival state (*12*). Therefore, as their paper suggests, clinicians may be encouraged to treat early hypertension by accepting the concept, "the earlier, the better," as their approach to hypertensive patients.

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