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COMMENTARY

How important is it to control nocturnal hypertension with angiotensin II type 1 receptor blockers?

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Better blood pressure (BP) control is associated with remarkable clinical benefits with regard to cardiovascular (CV) and renal protection. Patients with chronic kidney disease (CKD) are at significantly higher risk of CV disease (CVD),[1] and patients with overt proteinuria as well as albuminuria without a reduction in the estimated glomerular filtration rate (eGFR) are also at significantly higher risk.[1] In addition, proteinuria or albuminuria itself should be a target for reducing hard end points. Angiotensin II (Ang II) type 1 (AT_1) receptor blockers (ARBs) are highly selective for the AT_1 receptor and block the deleterious effects of Ang II.[2] ARBs clearly decrease proteinuria and protect the kidneys.[3] A nocturnal increase in BP on ambulatory monitoring is superior to office BP for predicting a worsening of albuminuria in elderly individuals with type 2 diabetes.[4] Non-dippers have been shown to have a greater risk of CV than dippers. With regard to morning BP, morning hypertension (HT) can lead to progressive target organ damage and trigger CV events.[5] It is still controversial whether treatment with ARB is more effective for all types of HT, such as nocturnal and morning HT, or in patients with albuminuria compared with conventional therapy without ARBs in patients with CKD.

In this issue of *Hypertension Research*, Yanagi *et al.*[6] reported that add-on therapy with the ARB olmesartan improves the ambulatory BP profile by preferential reduction of the nighttime BP, with the concomitant inhibition of renal injury in hypertensive patients with CKD, although the mean levels of systolic BP/diastolic BP (SBP/DBP) at night after treatment in the olmesartan group (121/70 mm Hg) were comparable to the values in the non-ARB group (124/70 mm Hg) according to the ambulatory BP profile. In addition, there were significant positive associations between the after-treatment/baseline (A/B) ratio of nighttime SBP and that of the urinary protein excretion rate (UPCR), and between the A/B ratio of nighttime SBP and that of the urinary albumin excretion rate (UACR). The decreases in UPCR and UACR were at least in part dependent on the reduction of nighttime SBP, as ARBs dilate efferent arterioles directly, in addition to their BP-lowering effects, and reduce intraglomerular pressure. Consequently, ARBs decrease UPCR and prevent the progression of renal dysfunction.

Recent clinical and basic studies have demonstrated that not all ARBs have the same effects and some benefits conferred by ARBs may be molecule-specific effects, rather than class effects.[7] Olmesartan significantly decreased BP, proteinuria and the rate of change of reciprocal serum creatinine in a randomized, placebo-controlled multicenter clinical trial, ORIENT (Olmesartan Reducing Incidence of End stage Renal Disease in Diabetic Nephropathy Trial).[8] Although the renoprotective effects of ARBs may be class effects, the present study clearly showed that the reduction of nighttime SBP by olmesartan is critical for inducing a renoprotective effect. Olmesartan has been reported to exert a longer-lasting BP-lowering effect due to the fact that its structure contains a characteristic 'double-chain domain'.[9] Although olmesartan was added in the morning in this study, some ingenuity may also be required to achieve the target nighttime BP, such as the administration of an antihypertensive agent at bedtime. Olmesartan has been shown to improve the altered ambulatory BP profile in CKD even when it is administered only once in the morning.[10] Thus, olmesartan add-on treatment might also be useful in this respect. Moreover, there was a trend toward a decrease in the A/B ratios of morning SBP and DBP in the olmesartan add-on group compared with the non-ARB group, although the differences were not significant. Antihypertensive treatment with a target morning BP of $<135/85$ mm Hg leads to more effective protection than conventional antihypertensive treatment based on the office BP.[10]

Yanagi *et al.*[6] also analyzed the effects of olmesartan add-on therapy on markers of inflammation, the renal renin-angiotensin system, oxidative stress and fibrosis. Interestingly, the A/B ratio of urinary type IV collagen, which is an important marker for renal injury, after treatment in the olmesartan add-on group was significantly suppressed compared with that in the non-ARB group. Although the ratio of urinary type IV collagen to creatinine was not identified as a factor that was associated with a low eGFR in a cross-sectional community-based study,[11] the excretion of urinary type IV collagen has been shown to be increased in diabetic patients with albuminuria.[12] As treatment with other ARBs, such as telmisartan, has also been shown to significantly reduce urinary protein and type IV collagen,[13] and as

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valsartan lowered UAER more effectively than amlodipine in patients with type 2 diabetes,[14] Yanagi *et al.*[6] confirmed this ability of ARBs. They found a significant positive relationship between the A/B ratio of nighttime SBP and that of urinary type IV collagen.[6] This finding is very important for explaining why the reduction of nighttime SBP was associated with a decrease in proteinuria or albuminuria and subsequently induced renal protection.

Another important issue raised by Yanagi *et al.*[6] was that the percentage of angiotensin converting enzyme inhibitor (ACEI) prescribed in the non-ARB group (57%) was about fourfold greater than that in the olmesartan add-on group (14%),[6] as ACEI also hass a role in protecting against renal dysfunction.[15] Although the authors explain that UPCR and UACR after treatment in ACEI (−) patients was greater than that in ACEI (+) patients in the non-ARB group, which also supports the notion that ACEI has renoprotective effects in hypertensive CKD patients, further investigation will be needed to resolve this issue.

In conclusion, clinical trials, including that of Yanagi *et al.*,[6] have shown that ARBs decrease UPCR and UACR with a reduction of urinary type IV collagen. Importantly, olmesartan induced a reduction of nighttime SBP. The benefits conferred by ARBs may be class effects, and we must be careful when comparing their results and interpreting their clinical impact.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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