COMMENTARY

Do angiotensin II type 1 receptor blockers have molecular effects?

Shin-ichiro Miura and Keihiro Saku

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Angiotensin II (Ang II) type 1 (AT₁) receptor blockers (ARBs) are highly selective for the AT₁ receptor and block the deleterious effects of Ang II.¹ Many ARBs are available for clinical use worldwide. Recent clinical and basic studies have shown that not all ARBs have the same effects and some benefits conferred by ARBs may not be class effects, but rather molecular effects.² However, it is still controversial whether each ARB has molecular effects in a clinical setting.

In this issue of *Hypertension Research*, Tsutamoto *et al.*³ have reported that replacing candesartan with olmesartan decreased the left ventricular mass index (LVMI) without changing blood pressure (BP) in patients with essential hypertension. This study indicated that ARBs did not all have the same effects on LVMI. Each ARB has been shown to have unique molecular effects in basic experimental studies, and these effects may be because of small differences in the molecular structure of each ARB.² Although olmesartan and candesartan have common molecular structures (biphenyl tetrazol and imidazol groups), olmesartan contains a hydroxyl group in addition to an α -carboxyl group in the imidazol ring, whereas candesartan only has an α -carboxyl group. The hydroxyl group and carboxyl group of olmesartan are important for tightly binding to AT₁ receptor and for strong inverse agonism against inositol phosphate production.⁴ The inverse agonism of olmesartan was stronger than that of candesartan.⁵

The structure of olmesartan might be associated with the differential effects of olmesartan and candesartan on LVMI. In contrast, mechanical stress activates AT₁ receptor (activation of extracellular signal-regulated protein kinases (ERKs)) independent of Ang II, and this activation can be inhibited by candesartan.^{6,7} Zou *et al.*⁶ also examined pressure overload on the heart by constricting the transverse aorta of adult male angiotensinogen knockout mice. Although treatment with candesartan did not reduce BP, candesartan significantly attenuated the development of cardiac hypertrophy.⁶ In addition, olmesartan also blocked mechanical stress-induced ERKs activation through AT₁ receptor.⁸ There may be no difference in the blockade of mechanical stress-induced ERKs activation between olmesartan and candesartan. On the basis of those experimental studies, olmesartan and candesartan offered similar benefits for mechanical stress-induced ERKs activation, but there was a different clinical outcome in the Tsutamoto's study.³ In contrast, there was a similar clinical outcome among ARBs, even though ARBs have different benefits on the basis of experimental studies. The presence of molecular effects for each ARB, according to experimental studies, does not necessarily reflect the clinical outcome. It is still controversial whether each ARB has unique molecular effects in a clinical setting, even though there are several differences among ARBs in experimental studies.

Recently, many studies have provided new insights regarding the renin-angiotensin system (RAS), such as the homo- and hetero-oligomerization of Ang II receptors,^{9,10} AT₁ receptor-associated protein,¹¹ AT₂ receptor-interacting protein¹² and Ang-(1–7)

through the catalytic activity of angiotensin-converting enzyme-2 (ACE2).¹³ In the RAS, besides Ang II, other bioactive RAS fragments, such as Ang III, Ang IV and Ang-(1–7), have recently been characterized. ACE2 is the main enzyme responsible for the conversion of Ang II to Ang-(1–7).¹³ Ang-(1–7) binds to a G protein-coupled receptor Mas.¹⁴ In particular, Ang-(1–7) is interesting because of its selectivity, which may be due to the absence of phenylalanine in the C-terminal position of Ang II, which is important for binding to and activating the AT₁ receptor. Iwai and Horiuchi have reviewed it in great detail and concluded that the classic ACE–Ang II–AT₁ receptor axis acts as a 'devil,' whereas the ACE2–Ang-(1–7)–Mas axis acts as an 'angel' in the RAS.¹⁵ This point of view is critical for the assessment of Tsutamoto's results. Tsutamoto *et al.*³ have observed that replacing candesartan with olmesartan decreased plasma Ang II without changing plasma aldosterone. Although they did not analyze plasma levels of Ang-(1–7), they suggested that plasma levels of Ang-(1–7) may be increased in association with the decrease in Ang II after replacement, because a previous report indicated that olmesartan increased ACE2 expression in association with an increase in plasma Ang-(1–7) after myocardial infarction in rats.¹⁶ However, in the rats, olmesartan also increased plasma Ang II levels and ACE2 mRNA increased in the heart. As local expression of the RAS components in the heart is independent of the systemic RAS, cardiac ACE2 levels may not directly influence plasma levels of Ang-(1–7). In addition, Takeda *et al.*¹⁷ reported that treatment with candesartan also increased ACE2 mRNA and decreased angiotensinogen mRNA in the rat heart. It is not easy to

Dr S Miura and Professor K Saku are at the Department of Cardiology, Fukuoka University School of Medicine, Fukuoka, Japan; and S Miura is also at the Department of Molecular Cardiology, Cleveland Clinic Foundation, OH, USA.
E-mail: miuras@cis.fukuoka-u.ac.jp

Table 1 Direct comparison of the efficacies of ARBs in clinical trials

Effects	Efficacies
Reducing left ventricular mass ¹⁸	Val > Los
Lowering plasma PAI-1 and MCP-1 ¹⁹	Can > Los
Preventing coronary artery contraction ²⁰	Ex > Can
Preventing coronary restenosis ²¹	Val > Los
Reducing CRP ²²	Olm > Val
Reducing plasma Ad and Glu ²³	Tel > Can
Inhibiting platelet activation ²⁴	Los > Val
Reducing IL-6 and CRP ²⁵	Olm > Tel
Improving Glu and lipid profiles ²⁶	Tel > Olm

Abbreviations: Ad, adiponectin; Angiotensin II type 1 receptor blocker; Can, candesartan; CRP, C-reactive protein; Ex, Exp3174; Glu, glucose; IL-6, interleukin-6; Los, losartan; MCP-1, monocyte chemoattractant protein-1; Olm, olmesartan; PAI-1, plasminogen activator-inhibitor type-1 antigen; Tel, telmisartan; Val, valsartan.

conclude that the difference in the effects of olmesartan and candesartan are due to ACE2 activity. Although we do not yet know whether the benefit is due to a molecular effect, the replacement of candesartan with olmesartan was effective.

Over the past decade, the efficacies of ARBs have been compared and differences have been observed in clinical studies (Table 1). Valsartan is more effective than losartan at reducing LVMI.¹⁸ Candesartan significantly lowered plasma plasminogen-activator inhibitor type-1 and monocyte chemoattractant protein-1.¹⁹ The ARB Exp3174 effectively prevented human coronary artery contraction.²⁰ Valsartan decreased the rate of target lesion revascularization after stenting.²¹ Olmesartan showed a significant reduction of high-sensitive C-reactive protein.²² Changes in serum adiponectin and plasma glucose were significantly greater in a telmisartan group.²³ Losartan significantly reduced human platelet activation.²⁴ These differences in the effects of ARBs are independent of BP lowering. Interestingly, when olmesartan was compared with telmisartan, conflicting data were reported.^{25,26} There were no differences between ARBs with regard to their effects on metabolic parameters, including hemoglobin A1c and adiponectin.²⁵ In contrast, telmisartan was more beneficial for improving glucose and lipid profiles.²⁶

In conclusion, clinical trials, including that of Tsutamoto *et al.*,³ have shown that ARBs have different degrees of benefits. Some effects may be due to molecular effects, whereas most of the benefits conferred by ARBs are class effects. As these trials were relatively small, we must be careful when comparing their results and interpreting their clinical impact, and should also reconsider whether these are molecular effects of ARBs, rather than class effects.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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