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COMMENTARY

Multifunctional L/N- and L/T-type calcium channel blockers for kidney protection

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Chronic kidney disease (CKD) increases the risk of cardiovascular disease (CVD) and end-stage kidney disease (ESKD) in accordance with its severity.[1] Furthermore, recent studies have revealed that proteinuria and albuminuria in CKD are risk factors for both ESKD and CVD. Accordingly, reductions in proteinuria and albuminuria are associated with a trend in reduced kidney death and cardiovascular events. These findings support the novel concept that high albuminuria/proteinuria alone should be targets for reduction and represent significant end points, similar to the treatment aims for high blood pressure (BP), high blood glucose and high low-density lipoprotein cholesterol. Thus albuminuria/proteinuria reduction is one of the most important surrogate goals for hypertension treatment, because it reduces both kidney death and CVD. Therefore, in 2012, the Kidney Disease: Improving Global Outcomes organization recommended the classification of patients according to albuminuria as well as glomerular filtration rate (GFR).[1] The reduction of albuminuria while maintaining GFR is important to prevent progression to ESKD and the occurrence of cardiovascular events in patients with CKD.

It has been well established that blockade of the renin–angiotensin system (RAS) with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (ARBs) inhibits the progression of CKD, including diabetic nephropathy, and these drugs are recommended as first-line treatment for diabetes and CKD.[2] Despite the use of maximal doses of these agents, intractable hypertension commonly persists, particularly in patients with CKD, highlighting the need for additional medication.

Large clinical trials have demonstrated that the combination of RAS inhibitors and the calcium channel blocker (CCB) amlodipine is more effective than thiazide diuretics for reducing cardiovascular and kidney events in high-risk patients. The GUARD study demonstrated that although treatment with the angiotensin-converting enzyme inhibitor benazepril and a diuretic resulted in a greater reduction in albuminuria compared with the benazepril and amlodipine group, the decline in GFR was slower in the benazepril plus amlodipine group than the benazepril plus hydrochlorothiazide group in hypertensive type 2 diabetic patients with albuminuria.[3] Furthermore, the ACCOMPLISH trial demonstrated that the combination of benazepril and amlodipine is superior to the combination of benazepril and hydrochlorothiazide for reducing cardiovascular events and the progression of CKD in patients with hypertension who are at high risk for such events.[4] In addition, in the CKD subgroup, a slower decline in estimated GFR (eGFR) was observed in the benazepril plus amlodipine group ($1.6\,ml\,min^{-1}\,1.73\,m^{-2}$) than the benazepril plus hydrochlorothiazide group ($-2.3\,ml\,min^{-1}\,1.73\,m^{-2}$; $P=0.001$).[4] A CKD subanalysis of the OSCAR study involving elderly patients showed that, compared with ARB alone at an increased dose, combination therapy with an ARB and CCB resulted in better BP control and a low incidence of CVD.[5] Accordingly, CCBs are widely used[6,7] and are generally recommended as the drug to be combined with an RAS inhibitor in high-risk populations, including diabetic patients with CKD.

Several clinical studies have shown that the addition of a CCB to ARB effectively reduces BP and urinary protein excretion. Although systemic BP is a significant contributor to the development of nephropathy, the role of intraglomerular pressure is also a critical factor. However, the mechanism of the kidney-protective action of CCBs may be considered multifactorial. Calcium channels are classified into several subtypes, namely L-, N-, T-, P/Q- and R-types, based on electrophysiological and pharmacological properties.[8] Table 1 shows the distributions of each calcium channel and the clinical significance of their blockade. L-type calcium channels are widely distributed in the smooth muscle cells of peripheral arteries. Thus blockade of L-type calcium channels dilates the systemic vasculature and substantially reduces BP. N-type channels are located in brain cells, and T-type channels are found in the sinus node and brain. Regarding the intrarenal distribution of calcium channel subtypes, L-type calcium channels are present in only afferent arterioles, whereas the T-type calcium channel is present in both afferent and efferent arterioles, and the N-type calcium channel is present in the nerve terminals along these arterioles.[8] Therefore, CCBs that block not only L-type but also T- or N-type calcium channels may exert kidney-protective effects by dilating the efferent arteriole and protecting the glomerulus from hyperfiltration injury.

Currently, CCBs are classified into three types, namely L-, L/T- and L/N-types, according to their blocking activities and predominant actions. In clinical practice, amlodipine and nifedipine are classified as L-type CCB,

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Table 1 Localization of Ca channels and clinical significance of their blockade

	L-type	*N-type*	*T-type*
Systemic localization	Skeletal muscle	Nervous system	Heart (sinus node)
	Smooth muscle	Brain	Brain
	Brain, Adrenal		Adrenal
	Pancreas, Retina		Liver
Intrarenal localization	Afferent arterioles	Nerve terminals along afferent and efferent arterioles	Afferent arterioles
	Mesangial cells		Efferent arterioles
			Vasa recta
			Distal tubules
			Cortical collecting duct
			Mesangial cells
Target organs	*Clinical significance of the blocking activity*		
Heart	Contractility ↓	Heart rate ↓	Heart rate ↓
Sympathetic nervous system	Pulse rate ↑	Pulse rate ↓	Pulse rate ↓
Kidney	Glomerular pressure ↑	Glomerular pressure ↓	Glomerular pressure ↓
Adrenal			Aldosterone synthesis ↓

whereas cilnidipine is classified as L/N-type CCB. Although benidipine has been observed to exhibit N-type calcium channel blocking activity and azelnidipine has been shown to suppress sympathetic nerve activity in animal models, efonidipine, benidipine and azelnidipine are classified as L/T-type CCBs.

In this issue of the journal, Thamcharoen *et al.*[9] performed a meta-analysis to assess the efficacy of L/N- and L/T-type CCBs in hypertensive patients with proteinuria. They compared the kidney function parameters of two treatment arms: (i) L/N- and L/T-type CCBs as add-on treatment to an RAS inhibitor and (ii) a standard treatment group in which RAS inhibitors with or without other types of antihypertensive medications, including L-type CCBs, were administered. Although no significant difference in systolic and diastolic BP was observed between the two groups, pulse rate was significantly decreased in the group administered L/N- and L/T-type CCBs as add-on therapy. L/N- and L/T-type CCB add-on therapy resulted in significant reductions in albuminuria/proteinuria and improved eGFR compared with the standard therapy. Interestingly, in the subgroup analysis, the efficacy of L/N- and L/T-type CCBs on eGFR and proteinuria were not the same. These CCBs improved eGFR in patients with an eGFR of $>60\,ml\,min^{-1}\,1.73\,m^{-2}$ and microalbuminuria at enrollment, whereas they reduced proteinuria in patients with lower eGFR and macroalbuminuria or overt proteinuria at enrollment. Furthermore, these CCBs had beneficial effects on both eGFR and albuminuria/proteinuria in studies with a longer follow-up duration (>6 months), but no such effects were observed in studies with a shorter follow-up duration ($\leqslant 6$ months). In this regard, recent renal subanalysis of the JATOS trial demonstrated that a 2-year treatment with efonidipine elevated eGFR in elderly hypertensive patients, even when patients had reduced kidney function or diabetes at baseline.[10]

Diabetic nephropathy is one of the leading causes of ESKD worldwide.[11] Nephropathy progression is largely influenced by intraglomerular pressure, which is controlled by the balance between the afferent and efferent arterioles adjoining the glomerulus. Albuminuria has been found to have a particularly important role in the onset of renal insufficiency or CVD in CKD patients with diabetes mellitus. Intraglomerular pressure varies markedly according to the primary cause of CKD.[12–15] The differences in intraglomerular pressure caused by kidney microcirculation in three major primary diseases of CKD are shown in Figure 1. These changes in intraglomerular pressure affect urinary protein excretion and the development of nephropathy. In diabetic nephropathy in particular, intraglomerular pressure is elevated because of decreased afferent arteriolar resistance, increased efferent arteriolar resistance or both. In addition to angiotensin II, atrial natriuretic peptide and insulin resistance are associated with efferent arteriole resistance in diabetic nephropathy. In contrast, when hypertensive nephrosclerosis is the primary lesion, urinary protein levels are relatively low because the intraglomerular pressure ranges from normal to decreased. Glomerular hypertension causes endothelial, mesangial and podocyte injuries, which ultimately result in glomerulosclerosis and decreases the number of functioning nephrons and further elevates intraglomerular pressure, resulting in a vicious cycle. Thus such alterations in glomerular hemodynamics critically contribute to the pathophysiology of diabetic nephropathy and greatly influence the mode of progression of glomerular damage. Angiotensin II contributes to the development of glomerular hypertension because it constricts efferent arterioles rather than afferent arterioles. Therefore, RAS inhibitors exert beneficial effects on proteinuria and disease progression for patients with glomerular hypertension because RAS inhibitors induce greater decreases in efferent rather than afferent arteriolar resistance with suppression of angiotensin II. Thus combination therapy with L/N- or L/T-type CCBs and RAS inhibitors has beneficial effects via reducing intraglomerular pressure and proteinuria because the mechanism of efferent arteriole dilation by CCBs is different from that of RAS inhibitors.

N-type calcium channels are localized at the nerve endings in the sympathetic and central nervous systems, which regulate the release of neurotransmitters. Thus the inhibition of N-type calcium channels leads to suppression of norepinephrine release in the kidney and would dilate both afferent and efferent arterioles. Furthermore, L/N-type CCB has been clinically demonstrated to be effective for morning hypertension and white-coat hypertension, the latter of which is closely associated with sympathetic nerve activation.[16] Recently, ARB combined with cilnidipine has been reported to attenuate left ventricular remodeling and diastolic dysfunction more effectively than ARB combined with amlodipine in Dahl salt-sensitive rats.[17]

Aldosterone has been demonstrated to cause kidney injury through multiple mechanisms, including tubulointerstitial fibrosis and inflammation, arteriolar sclerosis and glomerular hypertension. T-type but not L-type CCBs have been reported to inhibit aldosterone synthesis and release in cultured adrenal cells. L/T-type CCBs have been shown to reduce not only plasma aldosterone levels but also urinary 8-hydroxy-2'-deoxyguanosine and liver-type fatty acid-binding protein, which are markers of oxidative stress and proximal tubular injury, respectively.[18,19] Therefore, T-type calcium channel blockade also acts to suppress inflammatory processes, the renin–angiotensin–aldosterone system and oxidative stress through modulation of non-hemodynamic processes.

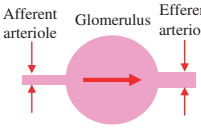
Primary disease	Afferent	Efferent	Intraglomerular pressure	
Nephrosclerosis	Constriction	Constriction		Unchanged to decreased
Chronic glomerulonephritis	Dilation	Unchanged to constriction		Increased
Diabetic nephropathy	Dilation	Constriction		Significantly increased

Figure 1 Characteristics of intraglomerular pressure in three primary chronic kidney diseases. ANP, atrial natriuretic peptide; Ang II, angiotensin II.

L/N- and L/T-type CCBs were shown to exert kidney-protective action by ameliorating glomerular microcirculation via vasodilatory activity on both afferent and efferent arterioles. Therefore, when similar BP levels are attained, L/N- and L/T-type CCBs may be superior to L-type CCBs owing to the complementary antihypertensive action to RAS inhibitors in terms of kidney protection.[9] Although strict BP control is indisputably required, such multifunctional effects of L/N- and L/T-type CCBs appear to be beneficial in terms of preventing CKD progression and cardiovascular events in patients with CKD. However, further studies are needed to determine whether the long-term use of L/N- and L/T-type CCBs can reduce kidney events and cardiovascular morbidity in patients with CKD, because L/N- and L/T-type CCBs were developed in Japan and are only clinically available in East Asian countries, including Japan, South Korea and China.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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