Calcium channel blocker in patients with chronic kidney disease

Shoko Ohno · Akira Ishii · Motoko Yanagita · Hideki Yokoi

Received: 26 June 2021 / Accepted: 24 October 2021 / Published online: 8 November 2021
© The Author(s) 2021

Abstract
Background Chronic kidney disease (CKD) is involved in a progressive deterioration in renal function over the years and is now a global public health problem. Currently, reducing the number of patients progressing to end-stage renal failure is urgently necessary. Hypertension and CKD interact with each other, and good control of blood pressure (BP) can improve CKD patients' prognosis. With the current global trend for more strict BP control, the importance of BP management and the need for medication to achieve this strict goal are increasing. Calcium channel blockers (CCBs), which target voltage-dependent calcium channels, are frequently used in combination with renin–angiotensin–aldosterone system inhibitors for CKD patients because of their strong BP-lowering properties and relatively few adverse side effects. Calcium channels have several subtypes, including L, N, T, P/Q, and R, and three types of CCBs, L-type CCBs, L-/T-type CCBs, and L-/N-type CCBs, that are available. Nowadays, the new functions and effects of the CCBs are being elucidated.

Conclusion We should use different types of CCBs properly depending on their pharmacological effects, such as the strength of antihypertensive effects and the organ protection effects, taking into account the pathophysiology of the patients. In this article, the role and the use of CCBs in CKD patients are reviewed.

Keywords Calcium channel blocker · Hypertension · Chronic kidney disease

Introduction

Chronic kidney disease (CKD) causes a progressive deterioration in renal function over a long period and has become a worldwide public health problem [1]. More than 13 million people have been estimated to suffer from various stages of CKD in Japan, with more than 340,000 people undergoing dialysis treatment. The growing number of dialysis patients put a strain on the healthcare economy. Currently, CKD is an emerging epidemic and reducing the number of patients progressing to end-stage renal disease is urgently needed.

Hypertension is a common cause of CKD, and since CKD leads to hypertension, hypertension and CKD strongly influence each other. Hypertension is present in approximately 80% of patients with CKD [2]. Hypertension in CKD patients has several causes, and the first is impaired sodium excretion, which causes an increase of extracellular fluid volume. The second is activation of the renin–angiotensin–aldosterone system (RAAS), the third is stimulation of the sympathetic nerve system and the resulting direct persistence of vasoconstriction, and the fourth is calcification of arterial vessels. There are numerous other factors in CKD patients influencing hypertension.

Blood pressure (BP) control is effective in preventing complications including cardiovascular disease (CVD). Particularly, CVD is a major cause of morbidity and mortality in patients with CKD. Therefore, one of the aims of BP control for CKD patients is to prevent CVD. Furthermore, lowering BP can slow the rate of renal disease progression. The GFR reduction rate slows down by a good BP control [3, 4]. Therefore, effective management of hypertension is essential for the management of CKD. In addition, the concept of diabetic kidney disease (DKD) has been proposed, and the involvement of nephrosclerosis as a background factor for DKD is attracting attention [5]. Blood pressure control is also important in diabetic patients for protecting renal function.
Calcium channel blockers (CCBs), which target voltage-dependent calcium channels, are frequently used in combination with RAAS inhibitors for CKD patients because of their strong BP-lowering properties and relatively few adverse side effects [6, 7]. In Japan, CCBs are commonly used as the first-line medication for hypertension, along with RAAS inhibitors and diuretics. There are several subtypes of calcium channels, such as L, N, T, P/Q, and R [8, 9]. CCBs include L-type CCBs, L-/T-type CCBs, and L-/N-type CCBs, which can be used in hypertensive patients depending on their pharmacological function [10].

In this article, we reviewed the localizations and roles of calcium channels and the effects of CCBs on CKD patients.

**Guidelines for BP treatment for CKD patients**

Various societies in different countries have developed their own guidelines related to hypertension. They have not established common BP targets and optimal BP goals for CKD patients. The guideline of Kidney Disease Improving Global Outcomes (KDIGO) indicates that the target BP for hypertensive and CKD patients should be < 120 mmHg systolic, when tolerated [11]. A Report of the International Society of Hypertension on 2020 Global Hypertension Practice Guidelines recommends a strict BP goal of 130/80 mmHg as a diagnosis of hypertension in adults with CKD [12]. Recent trends call for strict BP control. This may be due to the influence of several trials such as SPRINT (Systolic Pressure Intensive Trial) [13]. The same trend can be seen in the Japanese guidelines.

The Japanese Society of Nephrology published the evidence-based clinical practice guideline for CKD in 2018. The BP target for CKD patients is different according to the presence or absence of diabetes. The BP target is < 130 mmHg and < 80 mmHg for systolic and diastolic, respectively if diabetes is complicated. In contrast, if there is no diabetes nor albuminuria, BP targets are < 140 mmHg and < 90 mmHg for systolic and diastolic, respectively. If there is no diabetes but an albumin excretion rate of ≥ 30 mg/24 h, the BP targets are < 130 mmHg and < 80 mmHg for systolic and diastolic, respectively. For elderly people over 75 years of age, the recommended BP targets are < 150 mmHg and < 90 mmHg for systolic and diastolic, respectively.

The Japanese Society of Hypertension published the guideline for the management of hypertension in 2019. BP targets are < 130 mmHg and < 80 mmHg for systolic and diastolic, respectively, in CKD patients with proteinuria. Over 75 years old CKD patients without proteinuria, BP targets are < 140 mmHg and < 90 mmHg for systolic and diastolic, respectively [14].

**Pharmacological management of hypertension for CKD patients**

Pharmacological management is important to treat hypertension, reach the target BP goals, and manage BP more effectively. The medications can be effective in reducing urinary protein, slowing the renal function aggravation, and preventing various events including CVD. More than one drug may be required in patients with treatment-resistant hypertension [7, 15], and this is especially true in patients with CKD. The selection of an appropriate antihypertensive regimen for CKD patients is discussed in this review.

RAAS inhibitors ACEI/ARB should be the first-line treatment to manage hypertension for CKD patients with proteinuria/albuminuria according to the Japanese Society of Hypertension Guidelines [14]. Several meta-analyses and RCTs have shown that RAAS inhibitors slow the progression of CKD and reduce mortality [16]. Furthermore, RAAS inhibitors show a more renal protective effect by reducing proteinuria. However, RAAS inhibitors should be administered with caution in patients with CKD stages 4 and 5, as they may cause renal function deterioration and hyperkalemia. CCBs and thiazide diuretics are also recommended for CKD patients.

Susantitaphong et al. reported that dual RAAS blockade therapy reduced both BP and albuminuria [17]. However, dual therapy often increases the risk of hyperkalemia and acute kidney injury [18, 19]. The combination therapy of ACEi and ARB is not recommended in preventing renal function deterioration in current guidelines.

Mineralocorticoid receptor antagonists (MRAs) in addition to ACEi or ARB reduce both BP and albuminuria in CKD patients with albuminuria. More recently, one of the MRAs, finerenone, was reported to improve renal outcomes—renal failure, eGFR reduction of more than 40%, and death from renal causes—of diabetic nephropathy patients with albuminuria, in addition to reducing albuminuria [20]. Conversely, an increased risk of hyperkalemia exists when MRAs are prescribed in addition to ACEi and ARBs for CKD patients; MRAs should also be carefully administered in CKD patients with caution for hyperkalemia.

**CCB in the pharmacological management of hypertension**

KDIGO’s 2021 guidelines recommend CCBs along with RAAS inhibitors and thiazide diuretics for cardiovascular disease prevention in primary hypertension [11]. When
starting antihypertensive therapy, it is recommended to begin with 1 or more drugs among RAAS inhibitors, CCB, and thiazide-like diuretic. In the report of International Society of hypertension on 2020 Global hypertension practice Guideline, CCBs are recommended as a first-line drugs in hypertensive patients with a history of stroke, as are RAAS inhibitors and diuretics [12]. About hypertensive patients with CKD, RAS-inhibitors are recommended as a first-line drug because they reduce albuminuria in addition to BP control, and CCBs and diuretics are mentioned as agents that can be added further. The guideline also mentioned that during pregnancy, dihydropyridine calcium channel blockers (DHP-CCBs) (nifedipine (not in capsule form), nicardipine) are the first choice, along with methyldopa and beta-blockers (labetalol). Moreover, in breastfeeding patients, long acting CCBs are preferred. Thus, in clinical practice, CCB are frequently used and have a wide range of indications.

For CKD patients, the evidence-based clinical practice guideline for CKD of the Japanese Society of Nephrology states the following. RAS inhibitors are recommended for CKD patients complicated with DM. RAS inhibitor is also first choice, if there is no diabetes but proteinuria of 0.15 g/gCr or more. On the other hand, RAS inhibitors, CCB, and thiazide diuretics are recommended for patients without DM with proteinuria of less than 0.15 g/gCr.

### Calcium channels: physiological roles and pharmacological modification

#### Classification of calcium channels

The voltage-dependent calcium channels are localized in the plasma membrane and are essential for the release of neurotransmitters and hormones [21]. These channels are classified into L-, P/Q-, N-, R-, and T-type subtypes based on their pharmacological and electrophysiological properties. Molecular biological analysis has shown that calcium channels are composed of $\alpha_1$, $\alpha_2/\delta$, $\beta$, and $\gamma$ subunits [22], among which $\alpha_1$ subunits are the most important in defining channel properties (Fig. 1). The $\alpha_1$ subunit genes were cloned and classified into the following three subfamilies based on their sequence similarity: Ca$^{2+}$v1.x, Ca$^{2+}$v2.x, and Ca$^{2+}$v3.x (Fig. 2).

#### Localization of calcium channels in the kidney

In the kidney, several calcium channels are expressed, including Ca$^{2+}$v1.2 ($\alpha_{1C}$), Ca$^{2+}$v1.3 ($\alpha_{1D}$), Ca$^{2+}$v2.1 ($\alpha_{1A}$), Ca$^{2+}$v2.2 ($\alpha_{1B}$), Ca$^{2+}$v3.1 ($\alpha_{1G}$), and Ca$^{2+}$v3.2 ($\alpha_{1H}$). They are classified according to function into L-type (Ca$^{2+}$v1.2,

---

**Fig. 1** Structure of calcium channel. The voltage-dependent calcium channels are localized in the plasma membrane and are essential for the release of neurotransmitters and hormones. These channels are classified into L-, P/Q-, N-, R-, and T-type subtypes based on their pharmacological and electrophysiological properties. Molecular biological analysis has shown that calcium channels are composed of $\alpha_1$, $\alpha_2/\delta$, $\beta$, and $\gamma$ subunits, among which $\alpha_1$ subunits are most important for defining channel properties. The N-type and L-type structures are shown. The $\gamma$ subunit is deficient in N-type calcium channels.
Ca\textsuperscript{2+},1.2, P/Q-type (Ca\textsuperscript{2+},2.1), and T-type (Ca\textsuperscript{2+},3.1, Ca\textsuperscript{2+},3.2) Ca\textsuperscript{2+} channels [8, 23, 24].

Figure 3 and Table 1 shows the localization of calcium channels in the kidney.

First, the following basic researches have been reported on rats and mice. L-type calcium channel, Ca\textsuperscript{2+},1.2, is expressed in cells of the distal tubules as well as in the outer and inner medullary collecting ducts of a rat kidney by immunohistochemistry [25]. Andreasen et al. examined the nephron localization of Ca\textsuperscript{2+},3.1, T-type calcium channel in rats, and found it to be expressed in the distal convoluted tubules and collecting duct [26]. On the other hand, Poulsen et al. reported that T-type calcium channels, Ca\textsuperscript{2+},3.1 and Ca\textsuperscript{2+},3.2, are expressed in the efferent arterioles of a mouse kidney [27]. Few reports on the localization of calcium channels have explicitly mentioned humans. Hansen et al. reported that L-type (Ca\textsuperscript{2+},1.2), P/Q-type (Ca\textsuperscript{2+},2.1), and T-type (Ca\textsuperscript{2+},3.1, Ca\textsuperscript{2+},3.2) calcium channels are expressed in the human renal artery and dissected intrarenal blood vessels by PCR analysis [28]. Hansen et al. also reported that Ca\textsuperscript{2+},2.1, a P/Q-type calcium channel, contributes functionally to renal blood vessel contraction in humans [29].

Fan et al. demonstrated N-type (Ca\textsuperscript{2+},2.2) calcium channels’ immunoreactivity in rat renal vascular walls, possibly nerves in the adventitia, and in the distal tubules and podocytes [30]. They also reported that the N-type calcium
channel in cultured podocytes was involved in producing reactive oxygen species by angiotensin-II [30]. Previously, we reported that Ca$^{2+}$v2.2 was localized in the glomerulus including podocytes and in distal tubular cells of mouse by immunohistochemical study [31].

Function of calcium channels on renal microvasculature

The renal microvasculature comprises two major categories: the glomerular capillary and peritubular capillary (PTC). When the arterial blood flow enters the kidney, it gradually

| Table 1 | Localization of calcium channel in the kidney of rats and mice |
|---------|--------------------------------------------------|
| L       | Mesangial cell                                   |
|         | Hansen et al. [39]                               |
| N       | Podocyte                                         |
|         | Fan et al. [30]                                  |
|         | Ohno et al. [31]                                 |
| T       | Mesangial cell                                   |
|         | Hansen et al. [39]                               |
|         | Poulsen et al. [27]                              |
| P/Q     | Mesangial cell                                   |
|         | Hansen et al. [40]                               |

Fig. 4 Alleviation of mesangial expansion and urinary albumin excretion in diabetic Ca$_{2.2}^{-/-}$ mice. A Time course of urinary albumin excretion per milligram creatinine of experimental mice. Urinary albumin excretion of both db/db Ca$_{2.2}^{+/+}$ and db/db Ca$_{2.2}^{+/-}$ mice was lower than that of db/db Ca$_{2.2}^{+/+}$ mice. db/+ +Ca$_{2.2}^{+/-}$ mice (white circles), db/+ +Ca$_{2.2}^{+/-}$ mice (white triangles), db/ + +Ca$_{2.2}^{+/-}$ mice (black circles), db/db Ca$_{2.2}^{+/-}$ mice (black triangles), and db/db Ca$_{2.2}^{+/-}$ mice (black squares). B A glomerulus of mice at 16 weeks of age in each mouse. C Mesangial area was increased in diabetic Ca$_{2.2}^{+/-}$ mice and was suppressed in diabetic Ca$_{2.2}^{+/-}$ mice. This figure is modified from the article [31].
shifts to the smaller arteries and enters the glomerulus capillaries through the afferent arterioles. Post-glomerular blood flow enters the peritubular capillaries (PTCs) that feed the tubules.

L-type calcium channel blockade does not reduce the intraglomerular pressure because the L-type calcium channels are present only in the afferent arterioles. Their blockade mainly dilates the afferent arterioles in a rat kidney [32]. On the other hand, T-type calcium channels are present in both the afferent and efferent arterioles of the rat kidney. Therefore, T-type calcium channel blockade dilates both arterioles and reduces the glomerular capillary pressure, drawing attention to the role of T-type channels in renal protection [33, 34]. However, Thuesen et al. conducted experiments using T-type CC knockout mice and found that deficiency of Ca_{v}3.1 increased renal blood flow (RBF) and deficiency of Ca_{v}3.2 increased glomerular filtration rate (GFR), suggesting that Ca_{v}3.1 is involved in afferent tone and Ca_{v}3.2 influences efferent dilatation [35]. N-type calcium channels are present at the synaptic nerve endings of both the afferent and efferent arterioles [36]. Cilnidipine, an N/L-type calcium channel blocker, ameliorates glomerular hypertension by dilating both the afferent and efferent arterioles in the canine kidney [23]. Since L-type CCBs act on afferent arterioles, cilnidipine improves glomerular hypertension by blocking N-type calcium channels. The reduction of glomerular pressure is one of the important factors in reducing proteinuria in hypertensive patients [37]. To improve glomerular hypertension, controlling the arteriolar resistance, especially in the efferent arterioles, is highly effective [38].

**Function of calcium channels on glomerulus**

Although there are several studies referred to the localization of calcium channels in the blood vessels as above, there exist few reports referred to the localization in glomeruli. Three types of calcium channels, L-type [39], P/Q-type [40], and T-type [39], have been reported to localize in the mesangial cells. Previous reports showed that glomerular podocytes express N-type calcium channels [30, 41].

Konda et al. reported that cilnidipine, an N/L-type CCB, reduces BP and improves glomerular sclerosis in Dahl salt-sensitive rats [42]. Fan et al. also reported cilnidipine suppressed more proteinuria level than amlodipine by inhibiting N-type calcium channel-dependent podocyte injury in spontaneously hypertensive rats/ND mcr-cp (SHR/ND) [30]. Cilnidipine significantly prevented the podocyte injury assessed by desmin staining and restored the glomerular podocin and nephrin expression compared with amlodipine in SHR/ND rats.

We employed mice lacking the N-type calcium channel α1 subunit gene (Ca_{v}2.2−/−) to generate db/db (diabetic) and Ca_{v}2.2−/− double mutant mice [31]. In our study, albuminuria and glomerular histological changes were significantly alleviated in diabetic Ca_{v}2.2−/− mice (Fig. 4). In cultured podocytes, depolarization-dependent calcium responses were decreased by ω-conotoxin, a Ca_{v}2.2-specific inhibitor. Furthermore, the reduction of nephrin by transforming growth factor-β (TGF-β) in podocytes was abolished with ω-conotoxin. These results suggest that Ca_{v}2.2 inhibition exerts renoprotective effects against the progression of diabetic nephropathy, partly by protecting podocytes.

CCBs are widely-used antihypertensive drugs and a large body of human evidence supports their pleiotropic effect. L-type CCB is the most widely prescribed drug worldwide and has the longest history. Recently, however, the renal protective effects of new types of T-type and N-type CCBs have received more attention [43, 44].

Clinical studies reported that L-/T-type CCB (benidipine) is superior to treatment with L-type CCB (amlodipine) in decreasing urinary albumin excretion and plasma aldosterone level [45–47]. In the JATOS trial, a large-scale clinical trial evaluating the optimal target BP in elderly hypertensive patients, the renal subanalysis showed that efonidipine, T-/L-type CCB, improved eGFR in patients with proteinuria [48].

N-/L-type CCBs have also been reported to have renal protective effects. Konoshita et al. reported that cilnidipine, an N/L-type CCB, leads to less activation of RAAS in hypertensive patients than does amlodipine, and that UAE with cilnidipine administration was also significantly lower than that with amlodipine [49]. The CARTER study reported that cilnidipine reduced proteinuria in patients with CKD who were already treated with RAAS inhibitors [50].

**Function of calcium channels on renal tubules**

There are several reports referred to the localization in the tubules. Brunette et al. reported that L-, P/Q- and T-type calcium channels exist in the luminal side of the distal tubules in rabbits, because their channel antagonist, including diltiazem, ω-conotoxin, and mibebradil, decreased Ca^{2+} transport in the absence of sodium [51]. Andreasen et al. showed the nephrin localization of Ca^{2+}_{v}3.1, T-type calcium channels, in the inner medullary collecting ducts, distal collecting ducts and collecting tubules, especially in the apical sites [26]. Sugano et al. investigated the effect of the stereoselective T-type calcium channel blocker R(-)-efonidipine and CKD progression in spontaneously hypertensive rats that had undergone subtotal nephrectomy [52]. They showed that T-type calcium channel blockade has renal protective actions that depend not on hemodynamic changes and on the inhibition of Rho-kinase activity, tubulointerstitial
fibrosis, and epithelial-mesenchymal transitions. Baylis et al. reported that T-/L-type CCBs, mibefradil, resulted in superior nephroprotection including amelioration of proteinuria and glomerular injury, to traditional L-type CCBs, amlodipine, in deoxycorticosterone acetate (DOCA)-salt rats which are the models of high glomerular BP and rapidly developing kidney damage [53]. In contrast, L-type CCBs, amlodipine, failed to improve renal injury. They suggest that amelioration of tubulointerstitial injury may contribute to the nonhemodynamic effect of T-type CCBs. However, the relationship between calcium channels and renal tubules is not fully investigated. Further studies are needed to address these questions.

**Calcium channels in the sympathetic nerve system**

Ino et al. reported that N-type calcium channel α1 subunit knockout (Ca_v1.2−/−) mice that lack the cytosolic portion of the N-type calcium channel are viable and have an almost normal behavior but show a very low sympathetic nerve activity in the atra [54]. Previously, we reported that diabetic Ca_v1.2−/− mice showed low SBP with a marked reduction in urinary catecholamine levels [31]. Yamada et al. showed that Ca_v1.2−/− mice exhibited lower SBP than control mice because of vasodilatation, reduced heart contractile activity, and inhibited sympathetic nerve activity [55]. Recently, it is shown that N-type Ca^{2+} channel is upregulated in the interstitial nerve fibers of obstructed fibrotic kidneys of mouse and ablation of N-type Ca^{2+} channel significantly attenuated the fibrotic changes of the kidneys after UUO partly by the reduction of renal sympathetic nerve activation [56]. The P/Q-type calcium channels are also associated with neurons but may not be with sympathetic nerves. Mutations in P/Q-type calcium channel are involved in neurological disorders, including epilepsy and familial hemiplegic migraine [56].

**The relationship between RAAS system and CCBs**

In L/T type and L/N type CCBs, they are expected to have renoprotective by acting on efferent arteriole dilatation. However, they are reported to be no more effective than RAAS inhibitors. Li et al. reported in their systematic review and meta-analysis that anti-proteinuric effects of T-type CCBs are stronger than L-type CCBs, and do not differ from those of RAS inhibitors [46]. RAAS inhibitors and CCBs are often used in combination. Some reports showed that RAAS inhibitors are effective in reducing edema, a side effect of CCBs, by decreasing capillary hypertension and transcapillary fluid exudation [57, 58]. Jamerson et al. reported that the combination therapy of CCBs and RAAS inhibitors reduces the risk of cardiovascular events [59].

Thuesen et al. reported that deficiency of T-type calcium channel, Ca_3.1 or Ca_3.2, do not alter baseline blood pressure levels and Ang II-induced hypertension [35]. However, Ca_3.1, but not Ca_3.2, contributes to aldosterone secretion in mice infused Ang II [35]. Imagawa et al. reported that efonidipine, L/T type CCB, significantly reduces aldosterone synthesis and secretion [60].

N-type calcium channel is expressed in the sympathetic nerve terminals and regulates catecholamines’ release [61]. Therefore, N/L-type CCB reduces plasma catecholamine secretion rate through inhibiting N-type calcium channel [62], and can be less active in RAAS than L-type CCB in animal models [49, 63, 64].

There are still many unanswered questions about CCBs and RAAS inhibitors, and further studies on the effects of combination therapy are necessary.

**Conclusion**

Hypertension and CKD interact with each other, and good BP control can improve CKD patients’ prognosis. Worldwide, BP management is becoming increasingly important with the current trend for more stringent BP control. To achieve this strict goal, the need for medication is increasing. CCBs play a major role in antihypertensive medication. Understanding the types of CCBs, the strength of their antihypertensive effects, the difference in organ protection effects, and using them properly according to the patients and their pathophysiology are necessary. N-/L-type and T-/L-type CCBs can have additional organ-protecting effects in addition to the reliable antihypertensive effect of conventional L-type CCBs. It requires further investigations to clarify the mechanisms of organ-protecting effects of CCBs. Establishing evidence for the effectiveness of various CCBs and establishing guidelines for more effective CCB administration are also necessary.

**Acknowledgements** This study was supported by grants from JSPS KAKENHI (Grant Numbers 20K08633, 21K16189, 20K17278).

**Author contributions** SO, AI, MY, and HY contributed to the conception of this review article. SO and HY wrote the paper. All approved the final version of the article.

**Declarations**

**Conflict of interest** HY has received research grants from Daiichi-Sankyo Company, Mitsubishi Tanabe Pharma Corporation and Baxter, and lecture fees from Mitsubishi Tanabe Pharma Corporation and AstaZeneca. MY has received grants from Astellas Pharma Inc., Kyowa Kirin Corporation, Mitsubishi Tanabe Pharma Corporation, Chugai Pharmaceutical Corporation and Baxter, and research funding from Mitsubishi Tanabe Pharma Corporation, Boeringer Ingelheim Japan, and Boeringer Ingelheim Germany, and lecture fees from Chugai Pharmaceutical Corporation, Kyowa Kirin Corporation, and Mitsubishi Tanabe Pharma Corporation.

© Springer
Ethical approval All animal handling and experimentation was conducted in accordance with the guidelines and with approval of the Animal Experimentation Committee of Kyoto University (MedKyo 2018).

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article’s Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article’s Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/.

References

1. Levey AS, et al. Chronic kidney disease as a global public health problem: approaches and initiatives—a position statement from Kidney Disease Improving Global Outcomes. Kidney Int. 2007;72(3):247–59.
2. Whaley-Connell AT, et al. CKD in the United States: Kidney Early Evaluation Program (KEEP) and National Health and Nutrition Examination Survey (NHANES) 1999–2004. Am J Kidney Dis. 2008;51(4 Suppl 2):S13-20.
3. Bakris GL, et al. Preserving renal function in adults with hypertension and diabetes: a consensus approach. National Kidney Foundation Hypertension and Diabetes Executive Committees Working Group. Am J Kidney Dis. 2000;36(3):646–61.
4. Jafar TH, et al. Progression of chronic kidney disease: the role of blood pressure control, proteinuria, and angiotensin-converting enzyme inhibition: a patient-level meta-analysis. Ann Intern Med. 2003;139(4):244–52.
5. Afkarian M, et al. Clinical manifestations of kidney disease among US adults with diabetes, 1988–2014. JAMA. 2016;316(6):602–10.
6. Vejikama P, et al. Reno-protective effects of renin-angiotensin system blockade in type 2 diabetic patients: a systematic review and network meta-analysis. Diabetologia. 2012;55(3):566–78.
7. Kario K, et al. Clinical studies on pharmacological treatment of hypertension global hypertension practice guidelines. Hypertension. 2015;73(22):2103–16.
8. Umemura S, et al. The Japanese society of hypertension guidelines for the management of hypertension (JSH 2019). Hypertens Res. 2019;42(9):1235–481.
9. Hiragi S, et al. Association between the size of healthcare facilities and the intensity of hypertension therapy: a cross-sectional comparison of prescription data from insurance claims data. Hypertens Res. 2021;44(3):337–47.
10. Xie X, et al. Renin-angiotensin system inhibitors and kidney and cardiovascular outcomes in patients with CKD: a bayesian network meta-analysis of randomized clinical trials. Am J Kidney Dis. 2016;67(5):728–41.
11. Susantitaphong P, et al. Efficacy and safety of combined vs. single renin-angiotensin-aldosterone system blockade in chronic kidney disease: a meta-analysis. Am J Hypertens. 2013;26(3):424–41. https://doi.org/10.1093/ajh/hps038.
12. ONTARGET Investigators O, Yusuf S, et al. Telmisartan, ramipril, or both in patients at high risk for vascular events. N Engl J Med. 2008;358(15):1547–59.
13. Fried LF, et al. Combined angiotensin inhibition for the treatment of diabetic nephropathy. N Engl J Med. 2013;369(20):1892–903.
14. Bakris GL, Agarwal R, Anker SD, Pitt B, Ruilope LM, Rossing P, et al. Effect of finerenone on chronic kidney disease outcomes in Type 2 diabetes. N Engl J Med. 2020;383(23):2219–29.
15. Moreno DH. Molecular and functional diversity of voltage-gated calcium channels. Annu NY Acad Sci. 1999;868:102–17.
16. Hofmann F, Briel M, Flockner V. Molecular basis for Ca2+ channel diversity. Annu Rev Neurosci. 1994;17:399–418.
17. Hayashi K, et al. Ca2+ channel subtypes and pharmacology in the kidney. Circ Res. 2007;100(3):342–53.
18. Godfraind T. Discovery and development of calcium channel blockers. Front Pharmacol. 2017;8:286.
19. Zhao PL, et al. Tubular and cellular localization of the cardiac L-type calcium channel in rat kidney. Kidney Int. 2002;61(4):1393–406.
20. Andreassen D, et al. The αG-subunit of a voltage-dependent Ca2+ channel is localized in rat distal nephron and collecting duct. Am J Physiol Renal Physiol. 2000;279(6):F997-1005.
21. Poulsen CB, et al. Type voltage-gated calcium channels regulate the tone of mouse efferent arterioles. Kidney Int. 2011;79(4):433–51.
22. Hansen PB, et al. Functional importance of L- and P/Q-type voltage-gated calcium channels in human renal vasculature. Hypertension. 2011;58(3):464–70.
23. Hansen PB. New role of P/Q-type voltage-gated calcium channels: from transmitter release to contraction of renal vasculature. J Cardiovasc Pharmacol. 2015;65(5):406–11.
24. Fan YY, et al. Cilnidipine suppresses podocyte injury and proteinuria in metabolic syndrome rats: possible involvement of N-type calcium channel in podocyte. J Hypertens. 2010;28(5):1034–43.
25. Ohno S, et al. Ablation of the N-type calcium channel ameliorates diabetic nephropathy with improved glycemic control and reduced blood pressure. Sci Rep. 2016;6:27192.
26. Hayashi K, et al. Disparate effects of calcium antagonists on renal microcirculation. Hypertens Res. 1996;19(1):31–6.
27. Ohishi M, et al. Renal-protective effect of T-and L-type calcium channel blockers in hypertensive patients: an Amlodipine-to-Benidipine Changeover (ABC) study. Hypertens Res. 2007;30(9):797–806.
28. Yamamoto E, et al. Benidipine, a dihydropyridine L-type/T-type calcium channel blocker, affords additive benefits for prevention of cardioenal injury in hypertensive rats. J Hypertens. 2010;28(6):1321–9.
35. Thuesen AD, et al. Deficiency of T-type Ca\textsuperscript{2+} channels Ca\textsubscript{a,3.1} and Ca\textsubscript{a,3.2} has no effect on angiotensin II-induced hypertension but differential effect on plasma aldosterone in mice. Am J Physiol Renal Physiol. 2019;317(2):F254–63.

36. Mori Y, et al. Ca\textsuperscript{2+} channel alpha1B subunit (Ca\textsubscript{a,2.2}) knockout mouse reveals a predominant role of N-type channels in the sympathetic regulation of the circulatory system. Trends Cardiovasc Med. 2002;12(6):270–5.

37. Marin R, et al. Systemic and glomerular hypertension and progression of chronic renal disease: the dilemma of nephroclerosis. Kidney Int Suppl. 2005;99:S52–6.

38. Wang T, Takahatake T. Effects of vasopeptidase inhibition on renal function and tubuloglomerular feedback in spontaneously hypertensive rats. Hypertens Res. 2005;28(7):611–8.

39. Hansen PB, et al. Differential expression of T- and L-type voltage-dependent calcium channels in renal resistance vessels. Circ Res. 2001;89(7):630–8.

40. Hansen PB, Jensen BL, Andreasen D, Friis UG, Skott O. Vascular smooth muscle cells express the \(\alpha_{1A}\) subunit of a P/Q-type voltage-dependent Ca\textsuperscript{2+} Channel, and It is functionally important in renal afferent arterioles. Circ Res. 2000;87(10):896–902.

41. Lei B, Nakano D, Fujisawa Y, Liu Y, Hitomi H, Kobori H, et al. N-type calcium channel inhibition with cilnidipine elicits glomerular podocyte protection independent of sympathetic nerve inhibition. J PharmacoL Sci. 2012;119(4):359–67.

42. Konda T, et al. Effects of L/N-type calcium channel antagonist, cilnidipine on progressive renal injuries in Dahl salt-sensitive rats. Biol Pharm Bull. 2006;29(5):933–7.

43. Abe M, Soma M. Multifunctional L/N- and L/T-type calcium channel blockers for kidney protection. Hypertens Res. 2015;38(12):804–6.

44. Sugano N, et al. Mechanistic view of renal protective action of calcium channel blockade. J Pharmacol Sci. 2012;119(4):359–67.

45. Kamon K, et al. Dominant role of N-type Ca\textsuperscript{2+} channels in the luminal membrane of the distal nephron. Hypertens Res. 2011;34(2):268–73.

46. Li X, Yang MS. Effects of T-type calcium channel blockers on kidney injury caused by deoxycorticosterone-salt hypertension in rats. Am J Kidney Dis. 2008;38(6):1292–7.

47. Baylis C, Qiu C, Engels K. Comparison of L-type and mixed L- and T-type calcium channel blockers on kidney injury caused by deoxycorticosterone-salt hypertension in rats. Am J Kidney Dis. 2001;38(6):1292–7.

48. Ino M, et al. Functional disorders of the sympathetic nervous system in mice lacking the \(\alpha_{1B}\) subunit (Ca\textsubscript{a,22}) of N-type calcium channels. Proc Natl Acad Sci USA. 2001;98(9):5323–8.

49. Yamada Y, et al. Inhibition of N-type Ca\textsuperscript{2+} channels ameliorates an imbalance in cardiac autonomic nerve activity and prevents lethal arrhythmias in mice with heart failure. Cardiovasc Res. 2014;104(1):183–93.

50. Mishima K, et al. Attenuation of renal fibrosis after unilateral ureteral obstruction in mice lacking the N-type calcium channel. PLoS ONE. 2019;14(10):e0223496.

51. Messerli FH. Vasodilatory edema: a common side effect of antihypertensive therapy. Curr Cardiol Rep. 2002;4(6):479–82.

52. Messerli FH, Grossman E. Pedal edema—not all dihydropyridine calcium antagonists are created equal. Am J Hypertens. 2002;15(11):1019–20.

53. Jamerson K, et al. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. N Engl J Med. 2008;359(23):2417–28.

54. Imagawa K, et al. Inhibitory effect of efonidipine on aldosterone synthesis and secretion in human adrenocarcinoma (H295R) cells. J Cardiovasc Pharmacol. 2006;47(1):133–8.

55. Hirning LD, et al. Dominant role of N-type Ca\textsuperscript{2+} channels in evoked release of norepinephrine from sympathetic nerves. Science (New York, NY). 1988;239(4835):57–61.

56. Takahara A, et al. Cilnidipine attenuates renal nerve stimulation-induced renal vasoconstriction and antinatriuresis in anesthetized dogs. Jpn J Pharmacol. 1997;75(1):27–32.

57. Konda T, et al. The N- and L-type calcium channel blocker cilnidipine suppresses renal injury in Dahl rats fed a high-sucrose diet, an experimental model of metabolic syndrome. Nephron Physiol. 2005;101(1):p1-13.

58. Konda T, et al. Different effects of L/N-type and L-type calcium channel blockers on the renin-angiotensin-aldosterone system in SHR/Izm. Am J Nephrol. 2009;30(2):155–61.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.