Cardiorenal Medicine

Review Article

Cardiorenal Med 2024;14:581–587
DOI: 10.1159/000541876

Received: July 5, 2024
Accepted: October 4, 2024
Published online: October 7, 2024

Hypertension in Cardiovascular and Kidney Disease: Recent Trends – Treating Two Diseases as One

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Keywords
Hypertension · Chronic kidney disease · Cardiovascular disease

Abstract

Background: Hypertension and chronic kidney disease (CKD) are closely interlinked pathophysiologic states, such that high blood pressure (BP) is an independent risk factor for disease progression in both adult and pediatric patients with kidney disorders and progressive decline in kidney function can conversely lead to worsening BP control. ***Summary:*** Hypertension in CKD is not only associated with GFR loss, but increases cardiovascular risk, which is the leading source of mortality and morbidity in this population. Given this complex relationship between hypertension, CKD, and CVD, an optimal management of BP in CKD is mandatory to break an established vicious pathophysiological cycle that leads to adverse outcomes. ***Key Messages:*** New promising molecules for the treatment of CKD, with interesting mechanisms, particularly regarding their pathophysiological interactions with arterial hypertension, are available or under development and in the very next future they may change the way we treat high BP in CKD patients.

Introduction

Chronic kidney disease (CKD) is the most common cause of secondary hypertension, while hypertension is a major risk factor for CKD development and progression: hypertension is an independent risk factor for ESKD and regardless of nephropathy, elevated blood pressure (BP) values worsen eGFR decline. Prevalence of hypertension in patients affected by CKD is 80–85% depending on GFR: from 65% in patients in stage 2 growing up to 95% in the latter stages [1]. CV outcome in patients with CKD get consistently worsened since hypertension and CKD are mutually supportive in the pathophysiology of both renal and CV damage [2].

In the last decade, research led to the development of many drugs for CKD treatment that lower BP as side effect, acting on pathophysiological abnormalities that

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magnify both renal and cardiovascular disease when coexisting hypertension and CKD. In this paper, we will discuss about the recent trends in treatment of both hypertension and CKD, exploring new therapeutics horizons.

Pathophysiology

Renin-Angiotensin-Aldosterone System

The classical vision of RAA system described a consequential cleavage of Angiotensinogen in Angiotensin 1 and Angiotensin 2, which finally stimulates Aldosterone secretion and vasoconstriction. This paradigm is outdated since we know that Angiotensin 1 can undergo multiple cleavage pathways in order to generate at least 6 hormones (AngII, Ang 1-9, Ang 1-7, AngIII, AngA, Alamandine) that target at least 6 receptors (PRR, AT1R, AT2R, AT4R, Mas, Mrgd) expressed in several organs and tissues including smooth muscle, endothelium, heart, brain, kidney, adrenal gland, and adipose tissue. AT1R stimulation leads to vasoconstriction, Na reabsorption, aldosterone secretion, inflammation, fibrosis. By contrast, AT2R, AT4R, MASR and MRGDR stimulation leads to vasodilation through improved nitric oxide (NO) syntesis, natriuresis, inhibition of both inflammation and fibrosis [3].

In 2020, Brown et al. [4] showed a spectrum of incomplete suppression of aldosterone that worsen across the severity of hypertension, while only a small percentage of patients reached the threshold for the diagnosis of Primary Hyperaldosteronism.

Mineralocorticoid receptor (MR) is expressed by several nonepithelial cells, including miocardiocytes, adipocytes, podocytes, inflammatory cells, fibroblasts, endothelial cells and vascular smooth muscle cells. Aldosterone stimulation on these tissues activation of MR has been proved to promote myocardial hypertrophy, fibrosis and post-infarction remodeling in the heart, VSMC contraction, induction of VSMC osteogenic phenotype, endothelial disfunction, promotion of M1 differentiation of macrophages in atherosclerotic lesions and inflammation in the vascular system, renal interstitial fibrosis, podocyte autophagy and downregulation of the expression of nephrin, podocin, podoplanin and podocalyxin.

However, not all patients affected by these lesions show high plasma aldosterone levels, which could justify an overactivation of mineralocorticoid receptor. In 2008, Shibata et al. [5] showed that RAC1 – a member of the Rho family of small GTPases involved in many signal transduction pathways – upregulates the expression of MR and enhances nuclear shuttling of activated MR but, above all, could activate MR in absence of Aldosterone. RAC1 activation has been subsequently related to the development of podocyte foot process effacement and slit diaphragm remodeling, development of proteinuria and myocardial hypertrophy.

RAC1 is activated by several stimuli including cytokines, growth factors, AngII, ET-1, mechanical stress, oxidative stress, glucose, and sodium [6]. In CKD, all these triggers are magnified and lead to a continuous stimulation of RAC1 that overactivates MR.

In conclusion, overproduction of AngII stimulates both aldosterone synthesis and RAC1 activation which, in turn, over activates MR. BP increases due to AT1R and MR stimulation, damaging blood vessels and glomeruli. Hypertension enhances kidney sclerosis, boosted by MR overactivation, which produces more AngII [7]. Although simplistic, this loop exemplifies that hypertension in CKD is not only a harmful condition sustained by renin-angiotensin-aldosterone system (RAAS) hyperactivation, but an epiphenomenon of tissue fibrosis.

NO and GMP Signaling

NO is a vasodilator that counteracts the action of vasoconstrictive mediators, mainly ET-1, but its hypotensive effect is not solely achieved through the relaxation of smooth muscle cells. NO activates a signaling cascade mediated by cGMP which, in the kidney, mediates the inhibition of renin secretion, the modulation of the expression of luminal NHE3, NKCC, ENaC, and of the Na/K-ATPase on the basolateral side.

Furthermore, the NO-sGC-cGMP pathway exerts complex hemodynamic effects acting as a physiological antagonist of angiotensin II in the modulation of intrarenal vasculature [8]. The levels of NO are reduced in patients with high oxidative stress, such as patients affected by CKD or metabolic syndrome due to the formation of radicals that react with NO forming biologically inactive compounds. Hypertensive milieu constitutes a prototype of oxidative stress in animal models and, therefore, is supposed that the dysregulation of the NO-cGMP signaling pathway plays an important role in the genesis and maintaining of arterial hypertension and both renal and cardiovascular damage [9].

Endothelins

Endothelins are a family of small vasoactive peptides produced mainly by endothelial cells. There are three distinct endothelin peptides (ET-1, ET-2, and ET-3) that act on 2 receptors (ETAR and ETBR). ETAR activation triggers the contraction of vascular smooth muscle cells

and mesangial cells, the effacement in podocytes, the proliferation and migration of immune cells, the stimulation of AngII secretion; moreover, it directly stimulates extracellular matrix production and tissueal fibrosis. ETBR appears to be a counter regulator of ETAR.

The hypertensive effects of ET-1 are driven by direct effects on renal vasculature and interaction with the RAAS. The expression ratio ETAR:ETBR in the human renal artery is approximately 90:10, and approximately 92:8 in the renal vein. ETAR activation triggers vasoconstriction, especially in the efferent arteriole, leading to glomerular hypertension and hyperfiltration, enhanced by AngII which secretion is triggered by ETAR activation [10].

Immune System

Anomalies and hyperactivation of the immune system have been reported in hypertensive rodents, but it is still unclear whether this relationship is causal or consequential. It has been hypothesized that the milieu of the hypertensive phenotype activates the immune system, which in turn perpetuates and exacerbates hypertension in a vicious cycle. Both innate and adaptative parts of the immune system have been shown to be involved in hypertension.

First, it should be noted that immune cells are biologically involved in the neurohormonal system. Receptors for angiotensin have been demonstrated to be expressed in monocytes, macrophages, granulocytes, B and T lymphocytes. T cells can synthesize all components of the RAAS, such as autocrine hormones that enhance the expression of TNF and IL-17. Macrophages and dendritic cells also possess the MR, whose stimulation by aldosterone promotes the secretion of proinflammatory cytokine and the differentiation into the M1 macrophage phenotype [11]. Moving from these observations, many experimental proofs have been produced.

Monocyte-macrophage cells of hypertensive patients overexpress some Toll-like receptor (TLR) family receptors, and this condition has been proved to be reverted when reaching an adequate BP control. In hypertensive rodents, antagonism of TLR 4 and TLR 9 – which are activated by damage-associated molecular patterns released by damaged cells – reduces BP and counteracts pathological mechanisms mediating vascular, cardiac, and renal organ damage.

Furthermore, it has been proved that high extracellular fluid tonicity triggers the activation of Nod-like receptors which, in hypertensive cavies, are overexpressed in the kidney, blood vessels, heart, hypothalamus, and amygdala. In murine models of hypertension induced by ATII infusion or DOCA + sodium load, it has been demonstrated that blocking costimulation prevents and reverts

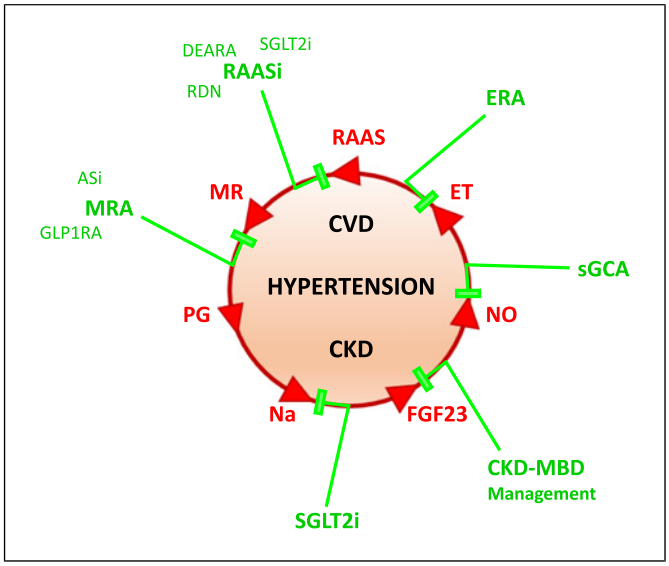

Fig. 1. Hypertension, CVD, and CKD merge in a self-perpetuating cycle sustained by physiological and biological alterations. New drugs lower BP by targeting altered mechanism, breaking the vicious cycle. ASi, aldosterone synthase inhibitors; CKD-MBD, chronic kidney disease-mineral bone disease; DEARA, dual endothelin angiotensin receptor antagonists; ERA, endothelin receptor antagonists; ET, endothelin; FGF23, Fibroblasts Growth Factor 23; GLP1RA, GLP1 receptor agonists; MR, mineralocorticoid receptor; MRA, mineralocorticoid receptor antagonists; Na, sodium; NO, nitric oxide; PG, prostaglandins; RAAS, renin-angiotensin-aldosterone system; RAASi, RAAS inhibitors; RDN, renal denervation; sGCA, soluble guanylate-cyclase activators SGLT2i, sodium-glucose cotransporter 2 inhibitors.

hypertension [12]. In 2014 Trott et al. [13] studied the response to a sodium load in CD4-knockout/CD8+ rodents, in CD4+/CD8-knockout rodents compared to WT cavies treated with angiotensin, demonstrating that CD4 knockout and WT models showed a comparable sodium retention, while CD8-cavies showed a nearly complete sodium overload excretion.

FGF23

A key role in the pathophysiology of organ damage in CKD is played by Fibroblast Growth Factor-23 (FGF-23). Recent data highlighted the significant effects of FGF-23 in the development of myocardial hypertrophy, cardiac fibrosis, and ventricular dysfunction through the specific activation of the Fibroblast Growth Factor receptor in myocardial tissue [14].

FGF-23 has been associated with hypertension through various mechanisms. First, several studies proved that FGF-23 increases aldosterone secretion not only through RAAS but directly and, conversely, aldosterone appears to

stimulate the bone secretion of FGF-23, since MR is expressed in the bone [15]. Furthermore, FGF-23 increases the reabsorption of Sodium in the distal tubule promoting the expression of sodium-chloride cotransporter (NCC) [16].

New Therapeutic Horizons

Guidelines suggest as first therapeutic approach the nonpharmacological treatment, which consists of dietetic treatment, physical activity, cessation of smoke and elimination of hypertensive substances such as caffein and licorice. ACE inhibitors counteract RAAS by blocking ACE, thus reducing ATII formation. ARBs are AT1 receptor antagonists, primary developed to avoid ACE inhibitors side effects such as cough and angioedema, caused by the inhibition of the degradation of bradykinin. ACE and ARBs remain the cornerstone of hypertension treatment in CKD patients (Fig. 1) but new promising drugs are appearing.

MR Antagonists

In the large RCTs FIGARO, FIDELIO, and in the pooled analysis FIDELITY, finerenone mildly reduced systolic blood pressure (SBP) and, notably, the more severe was hypertension, the greater was the effect on BP [17]. Esaxerenone is currently approved in Japan for the treatment of arterial hypertension. In several clinical trials showed a significant antihypertensive effect, in particular decreased nocturnal BP in all patients, with a more consistent effect in the more severe non-dipper phenotypes [18].

Aldosterone Synthase Inhibitors

Aldosterone Synthase (AS, CYP11B2) Inhibitors (ASI) inhibit the production of aldosterone in the glomerulosa zone of the adrenal cortex improving BP control in people with treatment resistant hypertension. In 2023, two novel ASIs, baxdrostat and lorundrostat, demonstrated efficacy in lowering SBP in patients with resistant hypertension in phase 2 trials BrigHTN and Target-HTN. In 2024, a phase 2 trial investigated the efficacy of the novel high affinity ASI BI 690517 in patients with proteinuric CKD (eGFR 30–90 mL/min, UACR 200–5,000 mg/g) treated with RAASi, with and without empagliflozin [19].

Results demonstrated a significant reduction in UACR with BI 690517 which was up to −39% (CI −50 to −26). In terms of BP control, BI 690517 demonstrated a significant reduction in SBP only at the maximum dosage of 20 mg in monotherapy (−4.94 mm Hg [CI −9.44 to −0.43]), while, if empagliflozin was added, SBP reduction was significant at any dosage, reaching −8.25 mm Hg [CI −13.40 to −3.09]. The EASi-KIDNEYTM is an ongoing phase 3 trial which will further elucidate the impact of ASIs and clarify their safety profile before FDA approval.

SGLT2 Inhibitors

SGLT-2 inhibitors (SGLT2I) inhibit sodium and glucose reabsorption in the proximal convoluted tubule, increasing sodium excretion. Natriuresis could explain the antihypertensive effect of gliflozins, although other mechanisms have been identified, such as the reduction of sympathetic tone and modulation of the RAAS secondary to the restoration of tubuloglomerular feedback [20].

In a meta-analysis [21] of 6 randomized clinical trials, SGLT-2 inhibitors significantly reduced 24-h ambulatory SBP and diastolic blood pressure (DBP) by −3.76 mm Hg (CI, −4.23 to −2.34) and −1.83 mm Hg (CI −2.35 to −1.31), respectively. Furthermore, compared to placebo, reduced night-time SBP by −2.61 mm Hg (CI, −3.08 to −2.14). These results were confirmed in another larger and more recent meta-analysis comprising 111 clinical studies and over 100,000 patients [22]. Based on 24-h ambulatory measurement, the average reduction in SBP induced by SGLT-2 inhibitors was −4.39 mm Hg (95% CI −5.4 to −3.3) during the day and −2.41 mm Hg (95% CI −3.3 to −1.5) during the night. Furthermore, SGLT2i show a kaliuretic effect which could be useful to avoid hypopotassic diet and/or the withdrawal of RAASi.

GLP1 Receptor Agonists and Tirzepatide

In large RCTs, GLP1 receptor agonists (GLP1RA) proved to improve cardiovascular and renal outcomes in patients affected by type 2 diabetes mellitus and to have a mild antihypertensive effect. A meta-analysis of 60 clinical studies [23] proved that treatment with GLP1RA leads to a reduction of SBP ranging from −1.84 mm Hg (95% CI: −3.48 to −0.20) to −4.60 mm Hg (95% CI: −7.18 to −2.03).

This effect seems not only related to weight loss: it has been demonstrated that the treatment with GLP1RA reduces SNS activity through the antagonism of GLP1R in the brain and the carotid body, decreases vascular smooth cells tone and enhances natriuresis by inhibiting the sodium-hydrogen antiporter 3 (NHE3) [24].

A novel combination drug tirzepatide has recently been approved in the USA. Tirzepatide combines agonists of both GLP1 and GIP receptors, demonstrating exceptional results in weight loss and glycemic control and, moreover, a reduced risk of progression of kidney disease compared to insulin glargine in a subset of patients with CKD [25].

In a post hoc analysis of 5 pivotal clinical trials [26], tirzepatide exhibited a significant reduction in SBP (from −2.8 to −11.5 mm Hg), with a dose dependent effect.

To sustain the hypothesis that the antihypertensive effect is not driven only by weight loss, it should be noted that the correlation between the reduction in BP and weight loss was significant but weak (r = 0.18–0.22, $p < 0.001$). This result suggests that the antihypertensive effect may be in part independent by weight loss, thus justifying the differences in terms of BP reduction observed compared to GLP-1 receptor agonists alone. Thus, the most significant reductions in SBP were noted in the group with the highest baseline category (>140 mm Hg), whereas those in the lowest quartile of baseline SBP category (<122 mm Hg) did not experience any additional decrease in SBP. An ongoing multicentre clinical trial (TREASURE-CKD, ClinicalTrials.gov identifier NCT05536804) will evaluate efficacy of tirzepatide specifically in individuals with CKD, with and without Diabetes.

Endothelin Receptor Antagonists and Dual Endothelin-Angiotensin Receptors Antagonists

In 2022, the dual endothelin receptor antagonist (ERAs) aprocitentan demonstrated to be efficacy in reducing BP in individuals with resistant hypertension, along with a remarkable safety profile, in patients affected by proteinuric CKD (GFR 15–60 mL/min) [27]. In 2023, endothelin receptor antagonists gained renewed attention in the nephrological field due to the remarkable effect of the novel dual endothelin-angiotensin receptor antagonist sparsentan in the treatment of FSGS and IgA nephropathy.

A phase 2 trial involving ERAs in CKD explored the effectiveness of the new selective endotelin A receptor antagonist zibotentan in combination with SGLT-2i (dapagliflozin) on top of standard treatment in patients with proteinuric CKD. Patients treated with zibotentan plus dapagliflozin experienced a higher reduction in UACR and BP (SBP −7.6 mm Hg [CI −10.3 to −4.9]; DBP −5.4 mm Hg [CI −7.1 to −3.7]) [28]. A future phase 3 clinical trial (ClinicalTrials.gov identifier NCT06087835) will provide more comprehensive data about the longer-term efficacy and safety of zibotentan and dapagliflozin on clinical kidney outcomes.

Renal Denervation

Renal sympathetic denervation (RDN) is a minimally invasive procedure which uses radiofrequency, ultrasounds or alcohol to destroy renal plexus, approached with a catheter through renal artery wall, to reduce sympathetic stimulation in the kidney and, consequently, BP. Many studies were performed in the past, providing encouraging but unconclusive evidence due to many limitations. Furthermore, there is a safety concern due to the use of iodinated contrast agent use, especially in patients with reduced GFR.

Recently, the RADIANCE Clinical Trial Program (US ablation) and the SPYRAL HTN (RF ablation) Clinical Trials demonstrated renal denervation efficacy in reducing BP at 6 months against sham controls in both home and office measurements [28, 29], and a cost-effectiveness analysis concluded that RDN performed with catheter-based radiofrequency can be a cost-effective strategy for uncontrolled hypertension.

However, in the cited trials eGFR <45 mL/min/1.73 m^3 is an exclusion criterion. Trials performed on CKD patients aimed to assess effects on eGFR, aiming to nephroprotection as primary endpoint. Even if these studies have several limitations, such as the absence of a sham-control group, suggest that in CKD renal denervation can be a safe procedure and could even be nephroprotective. The RDN-CKD trial (ClinicalTrials.gov identifier NCT04264403), is an ongoing prospective, double-blind, sham-controlled, multicentric feasibility study which aims to determine the efficacy of RDN in patients with CKD stage 3a or 3b.

Soluble Guanylate Cyclase Activator

Avenciguat (BI-685509) is a potent, orally active sGC activator. It restores cyclic guanosine monophosphate (cGMP) levels and enhances the functionality of NO pathways. A recent pooled analysis of two phase 2b trials assessed efficacy of avenciguat in reducing albuminuria in CKD patients with or without diabetes [30]. In terms of BP control, this analysis revealed a reduction in BP in the avenciguat treatment groups compared to the placebo group during the first 4 weeks. Over the 20-week treatment period with either placebo or avenciguat, the mean changes from baseline in SBP and DBP for the avenciguat groups at 1 mg, 2 mg, and 3 mg TID were −25.4 mm Hg (95% CI, −29.4 to −21.3), −23.0 mm Hg (95% CI, −27.4 to −18.6), and −20.4 mm Hg (95% CI, −24.6 to −16.2), respectively. New Phase 3 trials are expected to demonstrate the drug's efficacy on renal outcomes. It remains a promising new molecule for the treatment of CKD, with interesting mechanisms, particularly regarding its pathophysiological interactions with arterial hypertension.

Conclusion

RASi (ACEi or ARB) should be used in patients with CKD to treat hypertension and to reduce the burden of associated cardiovascular risk. The evidence for use of RASi in patients with mild increased albuminuria is lower in quality than in severely increased albuminuria. Despite the availability of RASi and some other classes of BP-lowering

drugs that are effective and safe, there are still many CKD patients who do not have optimal BP control. New promising molecules for the treatment of CKD, with interesting mechanisms, particularly regarding their pathophysiological interactions with arterial hypertension are available or under development and in the very next future they may change the way we treat high BP in CKD patients.

Conflict of Interest Statement

We have read and understood Karger policy on disclosing conflicts of interest and declare that we have none.

Funding Sources

No funding was received.

Author Contributions

Antonio De Pascalis and Giuseppe Cianciolo conceived of the presented idea. Alessandro Tomassetti, Daniele Vetrano, and Edoardo Tringali contributed to the drafting of the work, the elaboration of the figure and the review of the literature. Luca Di Lullo, Marcello Napoli and Gaetano La Manna supervised this work. All authors contributed to the final manuscript.

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