Section A-Research paper

Understanding emerging trendsin the Management of hypertension in chronic kidney disease: A Systematic review

Dr. Zubia Ghouse[1], Mayank Patel[2],Dr. Shilpi Agarwal[2], Dr Rajiv Singhal[3], Dr. Gaurav Agarwal*[2]

[1]New Vision University, Tbilisi, Georgia

[2]Shikhar Institute of Pharmacy, Budaun, (U.P) India

[3]Maharishi Markandeshwar Institute of Medical Sciences and Research, Sadopur, Haryana, India

*Corresponding Author:

Dr Gaurav Agarwal [M.Pharm, Phd]

Director, Shikhar institute of Pharmacy, Sheikhupur, Budaun, (U.P.) India, 243601

ORCID Id: 0000-0002-9485-8563

Abstract. Chronic kidney disease is becoming more generalglobally and is very much linked to the occurrenceof cardiovascular disease (CVD). A lot of people with CKD feel hypertension (HTN), which is both a source and a result of the condition.

According to the most recent hypertension recommendations, individuals with well-known CKD and/or diabetes with albuminuria should aim for a blood pressure (BP) goal of less than 130/80 mmHg. People suffering from CKD who have blood pressure more than 130/80 mmHg must change their lifestyles and use many antihypertensive drugs.In persons with CKD, managing HTN is important since it reduces the risk of CVD and decreases the disease's course.As a result, knowing the data used to develop these guidelines is critical for deciding how to effectively care for particular patients.Non-pharmacological treatment can help to decrease blood pressure (BP) in populations with CKD, but they are not enough alone to remain BP under control.Patients withhypertension and CKD may need a mix of antihypertensive medicines to attain their desired blood pressure. Before beginning therapy, it is important to consider the extra BP-independent renoprotective and/or cardio-protectiveaction that some pharmaceuticals give. In future, new treatments may improve

therapy. Moreover, meeting BP objectives, lowering CVD risk, and delaying the course of CKD all require a personalised and evidence-based treatment approach.

Key Words: Chronic kidney disease, Hypertension, Albuminuria, Antihypertensive medicines, Novel therapy

Abbreviations:BP; Blood Pressure, , HTN; Hypertension, eGFR; Estimated Glomerular Filtration, CKD; Chronic Kidney Disease, ARBs; Angiotensin Receptor Blockers,CCBs; Calcium Channel blockers, GLP-1-RA; SGLT2i; Sodium-Glucose co-Transporter 2, Glucagon-like Peptide-1 Receptor Agonists, CVD; Cardiovascular disease,RAAS; Renin-Angiotensin-Aldosterone System

Introduction

Chronic kidney disease is clinically manifested as lowered kidney function (an expected [eGFR] <60mL/min/1.73m2) or kidney damage, most commonly evidenced by proteinuria lasting 3 months (1, 2).CKD is a progressively more prevalent condition that affects 10-15% of the global population and is significantly linked with cardiovascular disease (CVD) (3).Hypertensionis both a well-known risk factor and a result of CKD, which affects a vast number of individuals with CKD (4).According to the ESC/ESH (European Society of Cardiology and the European Society of HTN), HTN is defined as a blood pressure lies in the range of ≥140/80mmHg which affects ~30% of the common adult population and approximately 90% of individualswith CKD (5). Indeed,individuals with CKD have a much high risk of heart failure, stroke or peripheral artery disease, and myocardial infarction than the non-CKD populationand as is to be anticipated, the cardiovascular risk increases as kidney function decreases (6, 7).Hence, individuals with advanced CKD have a high probability of dying from any cardiovascular events than from kidney disease that has not yet reached the end stage (ESKD) (8).

In this regard, various pieces of evidence have shown that both eGFR and the urine albumin/creatinine ratio (ACR) are freedisease factors of mortality in the common population.In this context of CKD, lower GFR and higher ACR are linked with a greater danger ratio for all-cause and cardiovascular disease death (9).Therefore, HTN is a determinant of CKD development and also a significant risk factor for cardiovascular diseases. According to the latest European Hypertension guiding principle, the BP cut-off for the cure of HTN in CKD is >140/90 mmHg, with a suggested goal of 130-140 mm of Hg systolic and 70-80 mmHg diastolic BP (10).Therefore, decreasing blood pressure (BP) to prescribed levels represents crucial management of CKD.

The two major goals are as follows:

1) To avoid the incidence of cardiovascular occurrence and the relateddeath and

2) To prevent CKD from progressing to ESKD.

In this context, managing BP in CKD patients has become animportant challenge to improving declined renal functions.Therefore, in this systemic review, we investigate the incidence, therapeutic goals, and research agenda in the treatment of HTN in CKD patients.

Blood Pressure profile in CKD

BPprofiles in CKD individuals havebeen a subject of discussion for years.However, elevated BP profile, so-called HTN in individuals with CKD was defined by two crucial characteristics such as 1)the high prevalence of nocturnal HTN[uncontrolled hidden HTN caused elevations in BP mostly at night]and 2)the real or the apparent HTN (11, 12).The nocturnal BP in CKD patients can be explained as a lower ability to eliminate sodium throughout the day as GFR decreases.Moreover, elevated nocturnal BP has been linked to the preservation of sodium balance throughout the day when renal function declines. In this context, Fukuda et al. have shown a rise in nocturnal BP and sodium dysbalance as GFR declines (13).Similarly, several pieces of evidence have revealed the presence of apparent HTN in individuals with CKD. In this regard, according to Georgianos et al. the incidence of apparent HTN with CKD is up to 40.4%, making it one of the significant risk issues for heart diseases (14).In adding together these two types of HTN,it must be noted thathigh systolic BP is more prevalent in patients with uncontrolled HTN.Most of the risk of developing ESKD seems to be accounted for by anelevated systolic HTN (15, 16).Moreover, evidence has shown that short-time systolic BP fluctuation is widespread in CKD whichmay play an important role in an abrupt increase in cardiovascular risk that occurs as renal function deteriorates (17).

The European Hypertension guidelines indicate a systolic BP range of 130–140 mm of Hg and a diastolic BP range of 70–80 mmHg; however, the cut-off number ofBP for the management of HTN in CKD is>140/90 mmHg (18).The KDIGO (Kidney Disease Improving Global Outcome) commences conference in 2013 advised that BP should be less than 140/90 mmHg in all CKD patients with no proteinuria and less than 130/80 mmHg in those with bothCKD and proteinuria (19).In this regard, severalinternational societies' recommended BP profile range in individuals with CKD and recommended first-line anti-hypertensive treatment which is shown in Table 01.

Society	**BP profile with CKD**	**First line treatment**	**References**
KDIGO (2021)	**SBP <120 mmHg**	**RASi + CCB or RASi + diuretics (mainly loop diuretics)**	**(19)**
ESC (2021)	**<140/90 mmHg**	**RASi + CCB or RASi + diuretics (mainly loop**	**(20)**

		diuretics)	
ISH (2020)	**<130/80mmHg**	**RASi + CCB**	**(21)**
ESC/ESH (2018)	**<140-130/80-70 mmHg**	**RASi + CCB or RASi + diuretics**	**(22)**
ACC/AHA (2017)	**<130/80 mmHg**	**Diuretics, CCBs or RASi**	**(23)**

Table 01- Summary of recent guidelines of BP profile range and recommended anti-hypertensive treatment as per several international societies in CKD.

Understanding pathological hallmarks of HTN in CKD

In CKD-related hypertension, the function of the kidneyis complex because they both cause and are destroyed by hypertension. Typically, BP increases as kidney function declines, and high BP over time speed up the expansion of kidney disease (24, 25). It is well known that the kidney, being an excretory organ, functions as a source of circulating dilators and constrictors and as a component of the sympathetic axis (26).In this regard, several mechanisms can influence the Blood Pressure in patients with CKD including a surplus of intravascular volume (volume dependent), too much excitation of RAAS (Renin Angiotensin aldosterone system), an increase in sympathetic tone and increased arterial stiffness may impeladditional progression ofBP in CKD as shown in (Fig. 01) (27-29).

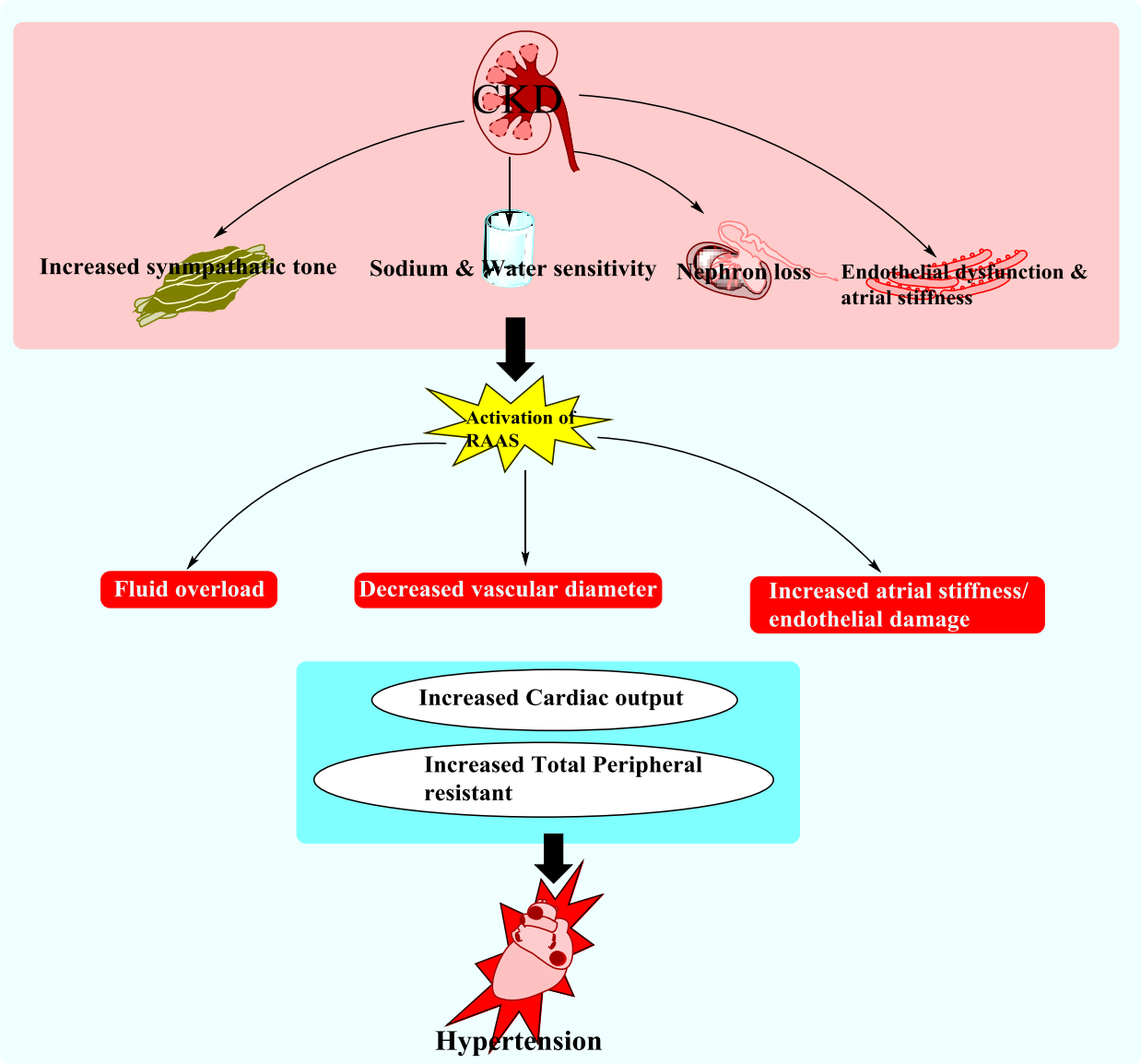

Figure 01: Underlying mechanisms of developing HTN in CKD Patients.

Current approaches to managing HTN in CKD

All HTN guidelines recommendlifestyle modifications, which are regarded as the first step in lowering BP, even in CKD patients.Hence, all CKD patients should be advised to quit smoking, manage their weight, drink less alcohol and exercise (30, 31).Despite lifestyle modifications, pharmacological treatment is also required. Hence, the most chosenantihypertensive agents for the managementof HTN in CKD are angiotensin receptor blockers (ARBs) and ACE inhibitors since of theircombined effects on proteinuriaand

reduced renal sympathetic activity, subsequently slowing the CKD progression (32-34).However, several other antihypertensive drugs are also prescribed to getting a successful reduction in declined GFR and anti-proteinuric effects in individuals with CKD (35).

Moreover, metoprolol and Carvedilol has shown to have anti-proteinuric effects. Direct adrenergic activation of the renal sympathetic nervous system may be as significant in the development of CKD as the other theorized causes that ACE inhibition targets (36).Similarly, calcium channel blockers (CCBs) may be renoprotective because they lower systemic blood pressure, prevent or reduce renal hypertrophy, reduce pressure-induced calcium entry, and reduce free radical generation (37). Therefore, hypertension guidelines show the effective use of these hypertension medicines in CKD patients as shown in (Fig 02). According to New hypertension guidelines, if albuminuria exceeds 300 mg/g, an ACE inhibitor or, in the case of ACE inhibitor intolerance, an ARB should be used (38, 39).

There is no indication that using an ACE inhibitor or an ARB is extra efficacious than new antihypertensive first-line medicines in CKD patients without albuminuria.While,several evidences have shown that RAAS blockers have a significant advantage in delaying CKD development in patients with an eGFR lower than 50 mL/min/1.73 m2, even then these medications are routinely kept away by most clinicians in these patients (40, 41).

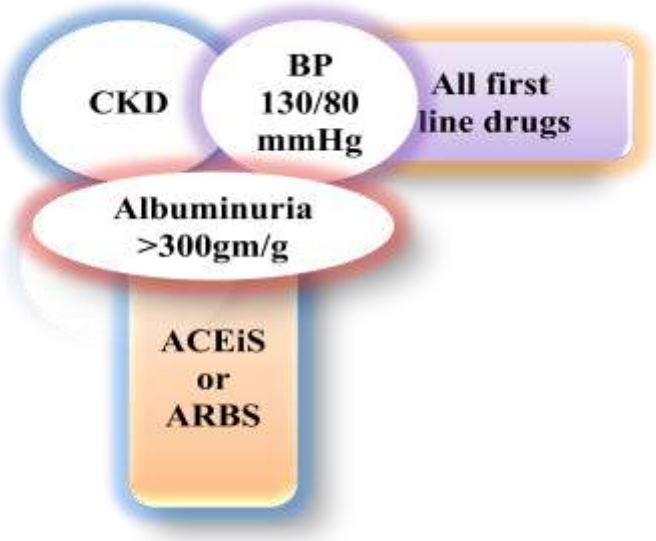

Figure 02: Illustrating treatment strategies by using antihypertensive medicines in CKD Patients with or without Albuminuria.

Abbreviations: CKD, Chronic Kidney Disease; BP, Blood Pressure; ACEiS, Angiotensin converting enzyme inhibitors; ARBS, Angiotensin receptor blockers.

New Strategies to manage HTN with CKD

In the last five years, a large quantity of novel pharmacological alternatives has emerged to lower thepossibility of cardiac disease and succession to ESKD in CKD patients (42, 43).Glucagon-like peptide-1 receptor agonists(GLP-1-RA) and inhibitors are the main components of these novel alternatives for individuals with diabetic nephropathy and type 2 diabetes (44, 45).According to the latest meta-analysis, SGLT2i causes a typical decrease in systolic/diastolic BP of 3.6/1.7 mm of Hg using 24-hour ambulatory BP monitoring (46, 47).Similarly, a DAPA-CKD trail was done on 4304 CKD (diabetic or non-diabetic)patients where the results have intensified that in addition to RASi, dapagliflozin decreased the key combined outcome (sustained > 50% eGFR decline, renal, ESRD, and CV mortality) by 39% and the secondary products (CV death) by 29% and 31% (48-50).
Due to the SGLT2i's shown advantages in postponing CKD progression and showing cardiac advantages, its usage is currently advised in CKD patients despite the existence of diabetes (51).

Future Perspective

As people live longer lives, the worldwide burden of CKD along with HTN is predicted to grow and management is crucial since decreased blood pressure lowers the risk of renal and cardiovascular problems.Therefore, managing HTN in an individual with CKD is an area of major importance. Moreover, several studies demonstrated that treating HTN in CKD individuals will reduce the risk of heart failure and other cardiovascular measures, even though, evidence on the risk of HTN with CKD in higher populations is still lacking.Therefore, future research should attempt to improve our perception of optimal BP goals in older individuals with CKD for both cardioprotection and renoprotection.

Conclusion

The prevalence of HTN rises with time as kidney functions decline. Therefore, an intense BP aim of less than 130/80 mmHg has been suggested for individuals with CKD. The 24-h-ABPM and HBPM may reveal whitecoat hypertension, concealed hypertension, and BP fluctuation that accurately predict CV events. Therefore, several classes of medicines are designed to provide varying degrees of risk reduction depending on the patient’scharacteristics.ACE inhibitors must be the medicines of Primeselection in patients with CKD with albuminuria more than 300 mg/g, whereas ARBs should be administered if the ACE inhibitor were not well suited. In addition to using a RAAS blocker, a CCB should be considered. Similarly, Beta-blockers should be the drug of choice in CKD individuals with a prevalent risk of heart failure and ischemic heart disease.

Conflicts of interest: Each author certifies that they have no financial relationships (such as consulting contracts, stock ownership, equity stakes, patent or licencing agreements, etc.) that could create a conflict of interest in connection to the submitted paper.

Author Contributions Statement: Zubia, Mayank and Dr Gaurav has been the main in the conception and systematic review design creation. DrShilpi Agarwal has made the critical analysis and final reviewing of the manuscript. Dr Rajiv made it procession, and formed the manuscript. All of the authors have read and approved the final variant of the manuscript.

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