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Reno protective role of amlodipine in patients with hypertensive chronic kidney disease

Amlodipine in Chronic Kidney Disease

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Abstract

Chronic Kidney Disease (CKD) and hypertension (HTN) are closely associated with an overlapping and intermingled cause and effect relationship. Decline in renal functions are usually associated with a rise in blood pressure (BP), and prolonged elevations in BP hasten the progression of kidney function decline. Regulation of HTN by normalizing the BP in an individual, thereby slowing the progression of kidney disease and reducing the risk of cardiovascular disease (CVD), can be effectively achieved by the anti-hypertensive use of calcium channel blockers (CCBs). Use of dihydropyridine (DP) CCBs such as amlodipine (ALM) in patients with CKD is an attractive option not only for controlling BP, but also for safely improving patient outcomes. Vast clinical experiences with its use as monotherapy and/or in combination with other anti-hypertensives in varied conditions have demonstrated its superior qualities in effectively managing HTN in patients with CKD with minimal adverse effects. In comparison to other counterparts, ALM displays robust reduction in risk of cardiovascular (CV) endpoints particularly stroke, and in patients with renal impairment, ALM with its longer half-life displays effective BP control over 24-hrs thereby reducing the progression of end-stage-renal disease (ESRD). In conclusion, compared to other classes of CCBs, ALM is an attractive choice for effectively managing HTN in CKD patients and improving the overall quality of life.

Key Words: Amlodipine; CKD; Hypertension; ESRD; monotherapy; combination therapy

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Core Tip: Amlodipine (ALM) is a powerful, well-tolerated, and safe anti-hypertensive agent widely used alone or as a key component of combination therapy for

hypertension in chronic kidney disease (CKD). Its effectiveness in reducing blood pressure (BP) has proven benefits in cardiovascular event reduction and progression of renal disease. Overall, ALM emerges as the drug of choice in comparison to the newer calcium channel blockers in terms of its effectiveness and potency in BP lowering in CKD patients.

INTRODUCTION

Introduction

Hypertension (HTN) – also known as high blood pressure (BP) – is a significant medical illness in which the arterial blood pressure (BP) remains consistently high, with a systolic blood pressure (SBP) of 140 mmHg or higher, or a diastolic blood pressure (DBP) of 90 mmHg or higher [1]. The World Health Organization (WHO) has identified HTN as one of the most important risk factors for morbidity and mortality worldwide, with roughly nine million people dying each year [2]. Even though other risk factors play a role, poor diets, such as excessive salt consumption, a diet high in saturated fat and trans-fats, low intake of fruits and vegetables, physical inactivity, tobacco/alcohol use, and being overweight/obese, appear to be the most common contributing factor to HTN. Non-modifiable risk factors include a family history of hypertension, elderly age, and comorbidities such as diabetes or kidney disease [3]. According to recent analysis and observational research, people in western countries have a higher prevalence of HTN and higher BP levels than those in other parts of the world, and this disparity is narrowing as non-westerners adapt to western culture and lifestyle [4].

HTN continues to be the greatest cause of premature mortality, affecting roughly 1.13 billion people globally and accounting for nearly 45 percent of deaths due to heart disease, 51 percent of deaths due to stroke, and 85 percent to 95 percent of patients with chronic kidney disease (CKD) [5]. The overall prevalence of HTN in India was 29.8% from 1950 to 2014, according to data, and a meta-analysis of prior Indian prevalence studies shows a considerable increase in the incidence of HTN from the 1960s to the mid-1990s. [6]. HTN prevalence studies in urban and rural populations from the mid-

1990s to the present show a growing trend, with a bigger increase in urban (33.8%) than rural (27.6%) populations [6]. Early detection, consistent follow-up, and HTN control methods may be a cost-effective way to lower the worldwide disease burden associated with HTN.

Hypertension and Chronic Kidney Disease

Chronic kidney disease (CKD) is characterised by persistent kidney damage, a decrease in the estimated glomerular filtration rate (eGFR), and the development of albuminuria. It's a long-term disorder that causes kidney function to deteriorate over time, eventually leading to kidney failure or end-stage renal disease (ESRD) [7]. CKD refers to all five stages of kidney damage, from very mild in stage 1 (eGFR ≥ 90 mL/min/1.73 m2) to complete kidney failure in stage 5 (eGFR < 15 mL/min/1.73 m2) [8] (shown in Table 1). In 2017, 12 million people died from CKD worldwide, with a global prevalence of 697.5 million. Women and girls had a greater age-standardized global prevalence of CKD (9.5%) than men and boys (7.3%), and China and India accounted for over one-third of all CKD cases (132.3 million and 115.1 million, respectively) [9]. Since the eGFR estimation equation and the Modification of Diet in Renal Disease formula have not been verified, the incidence of CKD in India is high [10]. The Indian Society of Nephrology established the Indian CKD Registry in 2005 as a comprehensive statewide data collection for examining all aspects of CKD. According to the initial research, diabetic nephropathy has emerged as the leading cause of CKD in India, according to a cross-sectional survey of 52,273 adult patients [11].

HTN control is important in the care and well-being of CKD patients because it is both a cause and an effect of the disease, and it contributes to its progression [12]. Uncontrolled blood pressure during the day causes a BP "load" in CKD patients, which is linked to eGFR decrease and proteinuria. Masked HTN, nocturnal non-dipping, and 24-hour day/night BP fluctuation are all seen in patients with CKD [12]. As evidenced by studies showing a higher risk of all-cause death, haemorrhagic strokes, and total CV events in people with CKD, BP fluctuation is a powerful predictor of end organ damage [13]. Furthermore, both HTN and CKD are independent risk factors for cardiovascular

disease (CVD), and when both are present, the risk of CVD morbidity and mortality is significantly enhanced. Furthermore, HTN has been recorded in 85 percent to 95 percent of CKD (stages 3-5) patients [14]. The pathophysiology of HTN in CKD is multifaceted and complicated [15]. There is an upregulation of the renin–angiotensin–aldosterone system (RAAS) with a functional drop in eGFR, which increases salt and water retention even more, and this is compounded by an enhanced salt sensitivity of BP [16]. Proteinuria is a critical sign of renal impairment that is related with CKD progression and incident CVD in a gradual and independent manner. Reduced blood pressure lowers proteinuria, which slows eGFR decline and lowers cardiovascular risk. When treating HTN in individuals with CKD, the influence of a medicine on proteinuria is a significant consideration in addition to its antihypertensive effects. Another emerging worry is the prevalence of treatment-resistant HTN in CKD, and include this patient population in large-scale randomized outcome trials may assist to guide future treatments [16].

Blood Pressure Control in CKD

Accurate and effective blood pressure readings are required for optimal HTN therapy. Due to a lack of repeat measurements, diurnal variation in BP, and white-coat HTN, BP obtained in clinic or office BP recordings may provide an erroneous assessment of the clinical condition [17]. [18] Different phenotypes of HTN have been identified and linked to varying degrees of CVD risk and all-cause death. In comparison to clinic measurements, 24-hour ambulatory BP monitoring is more reliable, since it allows assessment of diurnal fluctuation in BP and serves as a stronger predictor of CVD events in people with CKD, according to the 2017 American College of Cardiology guidelines [19]. Home blood pressure monitoring is a less resource-intensive alternative technique, and individuals who acquire data from home readings have better overall blood pressure control than those who do not. HTN and CKD have a cause-and-effect connection that is intertwined. A rise in blood pressure is linked to a reduction in kidney function, and a continuing rise in BP is linked to a faster development of renal function decline. As people get older, the prevalence of HTN rises, making blood

pressure control more challenging [20]. As a result, HTN control is an important part of CKD patient treatment, and medicines that provide 24-hour BP control and thus minimise BP variability should be the preferred therapeutic option for CKD patients.

Use of Anti-Hypertensive Agents in CKD

HTN management in CKD is critical for patients because HTN treatment can improve CV outcomes in patients with ESRD and CKD [20]. The treatment of HTN is crucial in the management of CKD. HTN is common in people with CKD and ESRD because it is both a cause and a consequence of the disease. In addition, HTN therapy is linked to better CV (cardiovascular) outcomes in both CKD and ESRD patients. As a result, both the patient and the practitioner must be vigilant when dealing with HTN in CKD [20]. Dietary salt restriction, maintaining an adequate dry weight, and lifestyle changes are among nonpharmacological therapies for HTN. These techniques, however, are ineffective in treating HTN and must be combined with pharmacological therapies for more efficient blood pressure control in the CKD population [16]. Several anti-hypertensive drug types may be useful in the treatment of CKD with HTN [21]. Most patients with CKD and HTN should start with blood pressure medications that also reduce proteinuria. Proteinuria reduction results with long-term improvements in both CV and renal outcomes, according to data [16]. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs), which target the RAAS, are commonly used as first-line antihypertensive medications [22]. However, it is widely known that RAAS inhibitors cause hyperkalemia, and that when an ACE and an ARB inhibitor are coupled, renal function is worsened, and hypotension occurs [22]. Hyperkalemia was found to be common in patients with CKD who were treated with RAAS inhibitors, and as a result, RAAS inhibitors should be used with caution in patients with underlying CKD and HTN [23]. A preferable first-line therapy in patients without proteinuria has not been firmly established, and drugs such as thiazides may be tried. Patients with CKD and HTN frequently develop fluid retention/fluid overload, necessitating the use of diuretics in their treatment plan [24]. Thiazides are suggested for people with CKD stages 1 to 3 (GFR 30 mL/min) and have been shown to

be beneficial in lowering blood pressure and reducing the risk of cardiovascular disease. In addition, loop diuretics are favored in patients with CKD stage 4 or 5 (GFR 30 mL/min) because they have been found to be more successful in lowering extracellular fluid volume in individuals with significantly reduced GFR [12, 20]. Beta-blockers have a limited effect on CKD progression and proteinuria, thus they're only used as a second- or third-line treatment if the patient has a compelling reason to take one, such as coronary artery disease (CAD) or chronic heart failure (CHF) [25]. When first- and second-line therapy fails to reach BP targets, aldosterone receptor antagonists such as spironolactone and eplerenone may be used in CKD treatment [21]. When used with an ACE inhibitor or an ARB, these drugs reduce proteinuria. Aliskiren, a renin inhibitor, is the only drug approved for the treatment of HTN as a monotherapy or in combination with valsartan [26]. Because of the increased risk of renal impairment, hypotension, and hyperkalemia, the ALTITUDE trial has led to the contraindication of its usage with ACE/ARB inhibitors in patients with diabetes or renal impairment [27]. If a patient is unable to take an ACE inhibitor or an ARB, Aliskiren may be tried; however, it is not indicated for individuals with stage 4 or 5 renal failure.

Calcium channel blockers (CCBs) are drugs that relax blood arteries and enhance blood and oxygen supply to the heart while lowering the strain of the heart [28]. Based on electrophysiological and pharmacological features, CCBs are classified as L-, N-, P-, Q-, R-, and T-type [29]. L-type voltage-gated CCBs are potent vasodilators that are commonly utilized as first- or second-line treatments for HTN. In the treatment of HTN in patients with CKD, they are considered second- or third-line therapy [30]. Dihydropyridines (DP) and non-dihydropyridines (NDP) are two types of CCBs that have been demonstrated to be effective in the treatment of HTN in patients with CKD [31]. In non-proteinuric CKD, DP CCBs (such as amlodipine, cilnidipine, felodipine, nifedipine, and others) can be utilised as first-line therapy alone or in combination, but their impact in proteinuric CKD is inferior to RAAS inhibition [32]. Adding DP CCB to proteinuric patients with RAAS inhibition improves BP control without worsening proteinuria, according to ESC/ESH guidelines, which recommend combination therapy

with an ACE inhibitor and CCB as first-line therapy in proteinuric circumstances [33]. In conclusion, the decision to use one medication over another is based on patient-specific considerations such as probable adverse effects, cost, and other underlying comorbidities.

Emergent Role of CCBs in Patients with HTN and CKD

The most potent and common situation presently is the use of CCBs and RAAS inhibitors (ACE/ARB) as anti-hypertensive medicines for mild to moderate HTN. Although there is no consensus on which antihypertensive drugs should be given as first-line therapy in patients with CKD, a systematic review and meta-analysis of 21 randomised controlled trials (RCTs) involving 9,492 patients found that CCBs and RAAS inhibitors had similar BP-lowering effects in HTN patients with CKD and ESRD [34]. In the test population, there were no significant changes in long-term blood pressure maintenance, mortality, heart failure, stroke, cerebrovascular episodes, or renal function. Overall, this study demonstrated that CCBs are comparable to RAAS inhibitors and can protect the kidneys in CKD patients with HTN. This was in line with a prior study (ALLHAT) that found CCBs to be particularly beneficial for long-term GFR maintenance when compared to diuretics and ACE inhibitors [35]. Furthermore, the INSIGHT study randomised 6,321 HTN patients with one or more related risk factors to the DP CCB, nifedipine gastrointestinal therapeutic system, or the diuretic combination hydrochlorothiazide/amilozide for the treatment of HTN. The major composite end point of CV mortality, non-fatal myocardial infarction, stroke, and heart failure had no statistically significant difference in both groups throughout the trial [36]. The ACCOMPLISH (Avoiding CV Events via Combination Therapy in Patients Living with Systolic Hypertension) trial compared the effectiveness of amlodipine (ALM)/ACE inhibitor against hydrochlorothiazide/ACE inhibitor combination therapy in adults with HTN and CKD in lowering CVD mortality [37]. The superior efficacy of ALM plus ACE inhibitor on CVD mortality was revealed in this multicenter, double-blind, randomised experiment. Notably, the ALM group had a considerably decreased probability of CKD progression, which was independent of BP values obtained. In the

HTN/CKD group, the addition of ALM to ACE inhibitor therapy appears to provide an additional Reno protective benefit compared to the addition of a thiazide diuretic. In summary, the anti-hypertensive use of CCBs in patients with CKD is an attractive option for reducing BP variability with minimal side effects.

In certain countries, dihydropyridine (DHP) CCBs are a common class of antihypertensive medicines. Amlodipine and barnidipine, for example, are third generation DHPs that are more lipophilic and have stable pharmacokinetics with long-term effects. They are well tolerated in people with heart failure and advantageous for those with chronic kidney disease since they are less cardio-selective. [31].

Amlodipine –The Unique CCB

DP CCBs are a class of potent, well-tolerated, and safe medicines that are widely used to treat high blood pressure as a monotherapy or as a crucial component of HTN treatment [38]. ALM was first released in the early 1990s and has a number of distinguishing characteristics that set it distinct from other agents in this category. ALM is a longer-acting DP CCB that has been proven in trials to block all channels as well as the N-type channel more effectively than cilnidipine [39]. The elimination half-life of 40-60 h confers various pharmacokinetic properties not found with other calcium-antagonist medications due to its low clearance. It has a high oral bioavailability (60-80%) and a steady-state accumulation with once-daily dosage over a period of 1-1½ weeks. Furthermore, the pharmacodynamic profile is consistent with the drug's disposition, with BP steadily decreasing over 4-8 hours following a single dose and returning to baseline over 24-72 hours. Furthermore, stopping ALM therapy causes a delayed restoration of blood pressure to baseline over 7-10 days, with no indication of a'rebound' impact.

It has great selectivity for vascular smooth muscle, has limited impact on heart rate, no negative inotropic effects/electrophysiological disturbances, and milder side events [40]. It is a well-studied classic medication with a wide range of capabilities, including blood pressure regulation and anti-anginal and anti-atherosclerotic effects [41]. Studies documenting ALM's gradual and protracted drop in BP due to a long elimination half-

life and delayed receptor dissociation kinetics [42, 43] demonstrate its function in delaying the onset of CKD. ALM also has a long duration of action of at least 24 hours and good anti-hypertensive effects with high safety in clinical trials with HTN patients at doses of 2.5 - 5 mg once a day [44]. Furthermore, 35 HTN patients with renal dysfunction were given ALM at 2.5-5.0 mg/day for 8 weeks to examine its clinical efficacy and safety in HTN patients with renal dysfunction. With moderate side effects, target BP reduction was reached in 28 of the 35 patients (80%), and ALM was deemed clinically helpful in 27 of the 35 patients (77.1%) [45]. In a clinical trial, individuals treated with telmisartan and ALM combined therapy had a 70% lower urine albumin-to-creatinine ratio (UACR) than those treated with ALM alone [46]. In a similar vein, compared to high dose monotherapy of either medication alone, a low dose telmisartan–ALM combination showed considerably higher BP reductions for both SBP and DBP [47]. ALM safely lowers SBP in hypertensive haemodialysis patients and has a favourable influence on CV outcomes [48]. The link between ALM and contrast-induced acute kidney injury (CI-AKI) is uncertain, although a retrospective, matched cohort investigation in a large Chinese hypertension population found that ALM medication prior to contrast exposure protected hypertensive patients from CI-AKI and increased survival [49]. Results from several trials proving the superiority of ALM in decreasing hypertensive CKD are shown below and summarized in Table 3.

ACCOMPLISH trial: his double-blinded, randomised trial with 11,506 patients randomised benazepril (20 mg) and ALM (5 mg; n = 5,744) or benazepril (20 mg) plus hydrochlorothiazide (12.5 mg; n = 5,762), orally once day, as previously stated in Section 4. In comparison to the hydrochlorothiazide plus benazepril, ALM plus benazepril group demonstrated a 48% reduction in the progression of CKD and 49% reduction in doubling of serum creatinine. Initiating antihypertensive treatment in CKD with with benazepril plus amlodipine preference to benazepril plus hydrochlorothiazide should be preferred as it slows progression of nephropathy to a greater extent [37].

SAKURA trial: The Study of Assessment for Kidney Function by Urinary Microalbumin in Randomized (SAKURA) experiment was conducted to examine the anti-albuminuric effects of L-/N-type and L-type CCBs in HTN patients with diabetes and microalbuminuria. The anti-albuminuric effects of cilnidipine and ALM were investigated in RAAS inhibitor-treated patients with HTN (BP: 130-180/80-110 mmHg), type 2 diabetes, and microalbuminuria (UACR: 30-300 mg/g) in this prospective, multicenter, open-labeled, randomised investigation. Despite the fact that cilnidipine and ALM both reduced blood pressure and showed similar effects on UACR, ALM provided greater renoprotection in RAS inhibitor-treated hypertensive patients with type 2 diabetes and microalbuminuria. Clinidipine provided no more renoprotection than amlodipine in RAS inhibitor-treated hypertensive patients with type 2 diabetes and microalbuminuria.

ASCOT-BPLA trial: The Anglo-Scandinavian Cardiac Outcomes Trial: Blood Pressure-Lowering Arm trial found that an ALM-based regimen outperformed an atenolol-based regimen in terms of lowering BP variability and preventing major CV events in patients with HTN [51].

Treatment-resistant HTN is emerging as an increasingly recognized problem and is markedly over-represented in patients with CKD [52]. Uncontrolled blood pressure despite maximally effective dosing of three drugs from different classes, one of which should be a diuretic. Recent evidence has highlighted the heightened risk for both adverse renal and CV outcomes associated with resistant HTN, even when BP control is attained [52]. In a study involving 157 resistant HTN patients (over 60 years old) who were randomised to 8 weeks of treatment and received double-blinded treatment with placebo, ALM (10 mg/day), olmesartan medoxomil (40 mg/day), and ALM (10 mg/day) + olmesartan medoxomil (40 mg/day), the research findings suggested that ALM and OM combination therapy had superior efficacy to ALM or OM monotherapie Furthermore, patients who received combination therapy met their BP goals more often than those who received placebo, ALM, or OM monotherapies. The long-term CV effects of ALM were compared to other classes of anti-hypertensive medicines in high-

risk HTN patient subgroups with diabetes and/or renal failure in another investigation [53]. Thirty-eight RCTs comparing ALM/CCBs to diuretics, -blockers, ACE/ARB inhibitors, and -blockers with a 6-month follow-up were enrolled, with BP and CV events examined. ALM was found to be successful in lowering SBP and DBP, making it a promising treatment alternative for the long-term management of HTN in diabetic and renal failure patients. In terms of preventing major cardiovascular events and causing less diabetes, an amlodipine-based regimen was found to be superior than an atenolol-based regimen [54].

CONCLUSION

CCBs are a good choice of anti-hypertensive medications in HTN patients with CKD. ALM is a well-known medication having a wide range of effects, including blood pressure regulation and anti-anginal and anti-atherosclerotic characteristics. ALM is a longer-acting DP CCB that controls blood pressure for up to 24 hours and minimises BP variability. Several pharmacokinetic properties can be linked to it, including limited clearance and a longer rate of elimination (elimination half-life of 40-60 hours). It also has a high oral bioavailability and a steady-state accumulation with once-daily treatment. In the absence of albuminuria and with a preserved GFR (> 60 mL/min), it can be used as a first-step therapy since it can block all calcium channels and the N-type channel more effectively than cilnidipine. It is a strong, well-tolerated, and safe antihypertensive drug that is commonly used for HTN in CKD, either alone or as part of a combination therapy. Its effectiveness in lowering blood pressure has been linked to a reduction in cardiovascular events, as evidenced by large RCTs. ALM in combination with other medicines that elicit RAAS blockage (ACE/ARB) has demonstrated to be an effective blood pressure-lowering strategy in reducing CV risk and slowing the progression of renal impairment. AML substantially lowers blood pressure in patients with hypertension and renal impairment while causing minimal or little worsening of renal dysfunction. In terms of effectiveness and potency in

decreasing BP in CKD patients, ALM emerges as the medicine of choice when compared to the newer CCBs.

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