Initiating Early Combination Therapy in Patients with Hypertension and Associated Chronic Kidney Disease: A Narrative Review

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Abstract

Hypertension and chronic kidney disease (CKD) are inter-related. Hypertension is both a cause and the consequence of CKD and both these conditions are independent risk factors for cardiovascular disease (CVD). Blood pressure control remains suboptimal in patients with CKD. This needs to be addressed on an urgent basis in order to prevent kidney damage. Combination anti-hypertensive treatment is the need of the hour in CKD patients with hypertension. Hence, the present narrative review was carried out to explore the significance of early combination therapy in the management of patients with hypertension and CKD. A PubMed search was conducted with the search terms 'hypertension', 'chronic kidney disease' and 'combination therapy' for randomized controlled trials, reviews and systematic reviews, published between 2010 and 2020. Abstracts were screened and relevant articles were selected. A search was then conducted on Google Scholar with the same search terms and relevant articles were selected. In a backward chronological search, the reference lists of all the selected articles were checked and more articles relevant to the topic were selected. The selected papers were used to evaluate the role of early combination therapy in patients with hypertension and CKD. Data suggest that combination therapy is needed to manage hypertensive patients with CKD and is indicated in patients with SBP ≥ 20 mmHg or DBP ≥ 10 mmHg above the goal. Initial combination therapy can therefore be considered for patients with hypertension and CKD.

Keywords: Blood pressure, hypertension, CKD, antihypertensive, combination therapy

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Introduction

Hypertension and chronic kidney disease (CKD) are linked with each other in a 'vicious cycle.[1] Hypertension is both a cause and the consequence of CKD and is also involved in CKD progression. A fall in estimated Glomerular Filtration Rate (eGFR), on the other hand, heightens the incidence and severity of hypertension.[2] Additionally, both hypertension and CKD act as independent risk factors for cardiovascular disease (CVD).[3]

Hypertension is seen in nearly 80–85% of the patients with CKD, while in hypertensive patients, CKD is evident in about 15.8%.[3] The simultaneous presence of hypertension and CKD make it difficult to control the blood pressure to the target levels.[3]

In patients with CKD, the control of hypertension remains inadequate,[3] and needs to be addressed seriously in order to prevent further damage to the kidneys. It is well known that patients with CKD need treatment with a combination anti-hypertensive regimen in order to bring down the BP to goal levels.[4]

This narrative review aims to explore the significance of combination therapy, particularly early combination therapy, in the management of patients with hypertension and CKD.

Methodology

A PubMed search was conducted with the search terms 'hypertension', 'chronic kidney disease' and 'combination therapy' for randomized controlled trials, reviews and systematic reviews, published between 2010 and 2020 and 329 results were returned. Abstracts were screened and five articles were selected. A search was then conducted on Google Scholar with the same search terms and the abstracts of the searched articles were scanned and final articles were then identified and selected. In a backward chronological search, the reference lists of all the selected articles were checked for citations that could not be detected in the primary search and relevant articles were selected.

Information from the selected articles was extracted and an analysis of the selected articles was then conducted by the investigators. Data were extracted after reading the articles. A narrative review was developed based on themes identified in the analysis of the selected articles.

Results and Discussion

A total of 33 articles were used to prepare the review. The themes that emerged after the analysis of selected literature included the significance of early combination therapy in hypertension, combination therapy in hypertension with CKD, early combination therapies available for hypertension with CKD, pharmacoeconomics of early combination therapy in hypertension with CKD, and guideline recommendations for combination therapy in hypertension with CKD.

Significance of Early Combination Therapy in Hypertension

Despite the fact that there are several anti-hypertensive agents known to be effective and safe in the management of hypertension, the proportion of patients who attain the recommended therapeutic goals remains low.

Uncontrolled hypertension can heighten the relative risk of coronary disease, stroke, heart failure, peripheral arterial disease, renal insufficiency, a trial fibrillation as well as dementia/cognitive impairment by 2- to 4-fold. Poorly controlled hypertension is linked to an increased risk for cardiovascular complications.[5]

The need to attain adequate control of blood pressure (BP) in patients with uncontrolled BP prompts an increase in the dose of monotherapy or the use of drug combinations. Increasing the dose of monotherapy is; however, associated with an increased risk of side effects.[5]

Furthermore, there are diverse mechanisms associated with a rise in BP in a patient.[5,6]

Figure 1 summarizes the systems that play a role in the development of hypertension.[7]

Monotherapy can act on one or two of the mechanisms. Combination therapy, on the contrary, acts on

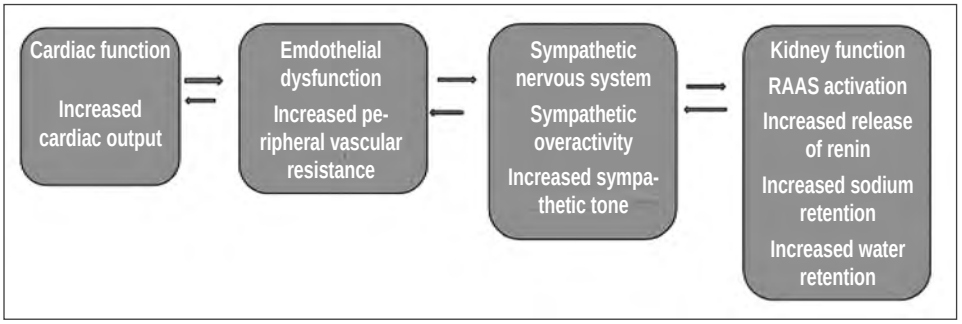

Figure 1: Involvement of different systems in the development of hypertension

several different mechanisms. Administering a combination of two drugs with different mechanisms of action can yield an anti-hypertensive effect which is two to five times greater than that observed with monotherapy.[5,6]

Combination therapy with lower doses of each anti-hypertensive agent should be able to decrease the BP equivalent to or more than monotherapy since two or more agents in the combination target different hypertensive mechanisms. This prevents counter-regulatory responses.[8]

Reducing the dose of anti-hypertensive agents to half the standard dose can considerably reduce the prevalence of adverse effects while the BP-lowering effect is decreased by a mere 20%.[9] It, therefore, seems wise to use combination therapy as the first-line treatment for hypertension.

Combination therapy seems to provide better target organ protection than increasing the dose of monotherapy.[5]

Initiation of hypertension management with a dual combination is linked with a faster and greater anti-hypertensive effect as well as persistent BP control at one-year follow-up. It is possible to attain adequate BP control during the first year of treatment in patients who are initially started on single-pill combination therapy compared to those who receive free combinations or monotherapy. It has been reported that the additional BP reduction obtained from combining drugs from 2 different classes is nearly 5-fold than that obtained from doubling the dose of one drug.[10,11]

Reduction in the time to control BP is the priority in high-risk patients. There are lesser cardiovascular events after one year in hypertensive patients given combination treatment compared to monotherapy.[12]

Initial treatment with a combination of agents is tied to earlier and more effective anti-hypertensive control, as well as sustained results in terms of CV prevention. Therefore, combination therapy should be the first-line choice, more so in high or very-high risk patients.[10]

Table 1 summarizes the benefits of using combination therapy in hypertension management.[5]

Table 1: Benefits of combination anti-hypertensive therapy

A combination of anti-hypertensive agents is associated with the following advantages:

- Increased reductions in blood pressure levels in comparison with monotherapy
- Reduced likelihood of adverse effects
- Inhibition of several different pathophysiological mechanisms of increased blood pressure
- Better protection to target organs
- Rapid control of blood pressure
- Some effects independent of the agents' anti-hypertensive action, such as anti-inflammatory and metabolic effects

Combination Therapy in Hypertension with CKD

Chronic kidney disease (CKD) and hypertension are closely associated with each other in what is called a 'vicious cycle.[1] Hypertension acts both as a cause and is the effect of CKD and has a role in CKD progression. Additionally, there is an increase in the incidence and severity of hypertension with a decline in eGFR. Furthermore, hypertension and CKD both act as independent risk factors for cardiovascular disease (CVD).[2]

Adequate control of the BP is therefore essential for patients with CKD, with the aim being inhibition of the progression of CKD, delaying the worsening of the disease to end-stage kidney disease and inhibition of the occurrence of cardiovascular events.[1]

A large number of patients with hypertension need two or more anti-hypertensive drugs to achieve the BP target of <130/80mmHg. In addition, patients with CKD often may not respond to treatment and need concomitant use of two or more anti-hypertensive agents.[1] Monotherapy is seldom able to achieve the BP levels required to delay the decline in GFR.[4] Combination anti-hypertensive therapy is, therefore, the answer.

For patients with CKD and/or diabetes with albuminuria, guidelines recommend a BP goal of < 130/80 mmHg. A level above that in CKD patients calls for lifestyle modifications and multiple anti-hypertensive medications. The first-line treatment for such patients is angiotensin-converting enzyme (ACE) inhibitors. However, if not tolerated, they can be replaced with angiotensin II receptor blockers (ARBs).[3] The KDIGO 2020 guidelines also recommend the initiation of an ACE inhibitor or an ARB in patients with diabetes, hypertension, and albuminuria.[13]

Treatment with an ACE inhibitor or ARB in proteinuric kidney disease often requires the addition of adiuretic or a calcium channel blocker (CCB).[4,14] Combination therapy with ACE inhibitors, ARBs, or direct renin inhibitors tends to decrease BP and al-

buminuria to a greater level than monotherapy with these agents.[13]

The addition of a dihydropyridine CCB to proteinuric patients with established Renin Angiotensin Aldosterone System (RAAS) blockade tends to improve BP control without worsening proteinuria. A study by Brenner *et al*,[15] noted that losartan (50 to 100 mg once daily), taken in addition to conventional antihypertensive treatment (calcium-channel antagonists, diuretics, alpha-blockers, beta-blockers, and centrally acting agents) was associated with significant renal benefits in patients with type 2 diabetes and nephropathy, and was generally well tolerated.

A study by Mori *et al*,[16] noted that a combination of doxazosin, an alpha1-antagonist, and diuretics, in hypertensive patients with chronic renal failure, led to a decline in BP and was associated with an increase in glomerular filtration and a reduction in plasma Blood Urea Nitrogen (BUN) and creatinine levels.

A meta-analysis compared the efficacy and safety of olmesartan combination therapy with that of olmesartan monotherapy in adults with hypertension and the evaluation was done in the following subgroups of patients with hypertension: elderly, nonelderly, CKD, and non-CKD. At week 8, seated BP was lower (137.5/86.1 mmHg vs 144.4/89.9 mmHg), and the mean change from baseline in BP and BP goal achievement (<140/90 mm Hg) were greater (−22.7/−15.0 mmHg vs −16.0/−11.3 mmHg and 51.2% vs 34.7%, respectively) for combination therapy vs monotherapy. In comparison with monotherapy, mean seated blood pressure (SeBP) changes, compared to the baseline, were found to be greater in those who received combination therapy.[17]

Early Combination Therapies Available for Hypertension with CKD

Management of hypertension in CKD aims to reduce BP, with a reduction in protein excretion.[18]

Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial, a hypertension trial, evaluated single-tablet combination therapy for initial treatment of high-risk hypertension. In the trials, Mean (+SD) BP declined from 145+18/80+11 mmHg at randomization to 132+16/74+10 mmHg at 6 months. The 6-month BP control rate was 73% in the overall trial, 43% in diabetics and 40% in patients with renal disease. Among the uncontrolled patients, 61% were not receiving maximal medications.[19]

The ACCOMPLISH (Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension) trial looked into the role of combination therapy with amlodipine plus ACE inhibitor compared to hydrochlorothiazide plus ACE inhibitor in reducing CVD mortality in those with hypertension and at high risk of CVD (characterized by the presence of diabetes, left ventricular hypertrophy, peripheral arterial disease, CKD or history of CVD). The amlodipine combination was found to be superior to the hydrochlorothiazide combination in reducing cardiovascular events in patients with hypertension at high risk for such events. There was a significantly lower risk of CKD progression in the amlodipine group. The addition of amlodipine to ACE inhibitor therapy, therefore, seems to have an additional renoprotective effect over the addition of a thiazide diuretic.[2,20]

Egan *et al*,[21] evaluated the effectiveness of initial anti-hypertensive monotherapy, free combinations, and single-pill combinations for the control of untreated, uncontrolled hypertensives during their first treatment year. Control was characterized by the first follow-up visit with blood pressure <140/<90 mmHg for patients without diabetes mellitus or chronic kidney disease and <130/<80 mmHg for patients with either or both conditions. Initial treatment with single-pill combinations led to better control of hypertension in the first year (HR, 1.53 [95% CI, 1.47–1.58]), in comparison with free combinations (HR, 1.34; [95% CI, 1.31–1.37]) ormonotherapy. The study concluded that increased use of single-pill combinations as initial therapy could help enhance the control of hypertension and cardiovascular outcomes in the first year of treatment.

A secondary analysis of the ACCOMPLISH trial revealed superior efficacy of benazepril plus amlodipine compared with benazepril plus hydrochlorothiazide. There were 2.0% events of chronic kidney disease progression in the benazepril plus amlodipine group compared to 3.7% in the benazepril plus hydrochlorothiazide group. Initial anti-hypertensive treatment with benazepril and amlodipine should therefore be preferred over benazepril and hydrochlorothiazide as it has the potential to slow down the progression of nephropathy to a greater extent.[22]

The choice of an agent in hypertension with CKD depends on the presence of proteinuria. Among patients with proteinuria, the first-line agents include an ACEI or ARB and often need a diuretic or a CCB to be added. Among patients without proteinuria, diuret-

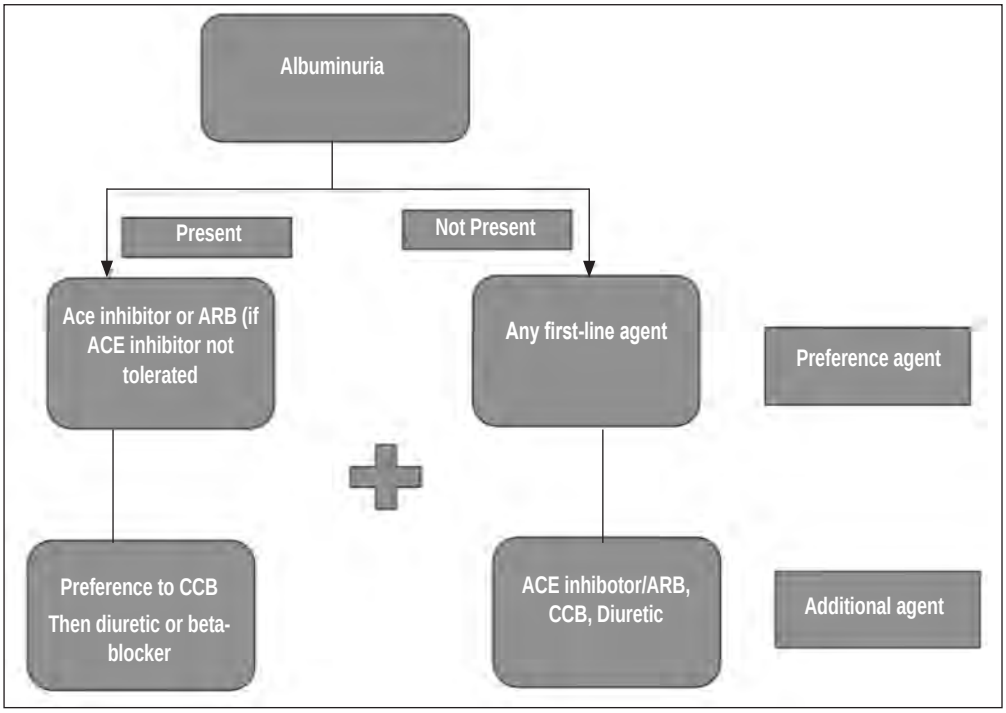

Figure 2: Accepted combinations in the management of hypertension in CKD
(ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blocker; CCB: calcium channel blocker)

ics are a potential alternative or an addition to RAAS blockade. Thiazide diuretics can be used if the glomerular filtration rate (GFR) is > 40 mL per minute per 1.73m^2 (body surface area), while loop diuretics may be used if GFR < 40 to 50 mL per minute per 1.73 m^2.[18]

Figure 2 summarizes the available anti-hypertensive combinations for hypertension in CKD.[3]

Guidelines recommend a combination of a RAS blocker with a CCB or a diuretic as initial therapy in CKD patients.[23]

Combination therapy with an ACE inhibitor and a CCB may have synergistic renoprotective effects besides BP control. A combination of these two agents may yield better control of the BP, and may even be better tolerated than either monotherapy. The combination may also exert a greater renoprotective effect in patients at risk for renal failure than either of the agents alone.[24]

ACE inhibitors and ARBs have cardioprotective as well as renoprotective properties and have particular significance in patients with CKD. RAAS blockade can potentially decrease the systolic BP by ~20 mmHg in patients with hypertension and CKD. Combination therapy with an ACE inhibitor and ARB could result in increased adverse events without a significant reduction in the primary end point of progression of CKD, End Stage Renal Disease (ESRD) or death. Combination therapy with an ACE inhibitor and ARB is thus not advised in patients with CKD.[2]

Volume overload affects nearly half of the CKD population and is an independent risk factor for CVD. Diuretics reduce volume expansion and constitute a part of combination therapy in CKD while extending anti-hypertensive and cardioprotective effects.[2]

Dihydropyridine CCBs can be used in the first-line treatment of non-proteinuric CKD, both alone or in combination. However, in proteinuric CKD, they appear to be inferior to RAAS blockade. Adding a dihydropyridine CCB to proteinuric patients with established RAAS blockade tends to improve BP control without worsening proteinuria. β-blockers can also be added in the setting of established RAAS blockade, especially when there is overt CVD.[2]

Hypertension is a common occurrence in patients after renal transplantation and poses a unique challenge. A vast majority of kidney transplant patients receiving a calcineurin inhibitor (CNI)-based immunosuppression are hypertensive after transplant. Additionally, there are greater odds of the BP being uncontrolled in this patient population. Close to 50% of such patients do not achieve a systolic BP <140 mmHg at 1 year. This is associated with worse outcomes.[2]

A retrospective study assessed hypertension management and adherence to BP targets in renal transplant recipients (RTRs). The most commonly used anti-hypertensive drugs were beta-blockers (BB), followed by CCBs. The average number of anti-hypertensive agents used per patient was shown to rise significantly from 2.24±1.03 in 2001 to 2.55±1.25 in 2014 ($p < 0.05$). The combination therapy used most often included two or three anti-hypertensive drugs and the most frequently used two-drug combination included BB and CCB followed by BB and ACE inhibitors.[25]

Pharmacoeconomics of Early Combination Therapy in Hypertension with CKD

The complexity of drug treatment schemes, poor tolerability and drug substitutions often lead to poor adherence. This results in insufficient BP control, a greater likelihood of cardiovascular events and increased global health costs.[26]

It is well known that combination therapy as the initial management strategy helps achieve target blood pressure with fewer adverse effects, as lower doses of each agent may be used. However, early use of combination therapy is also linked with potential economic benefits such as a limited need to switch medications and better long-term outcomes owing to improved BP control. Switching therapy can increase the cost to a considerable extent.[4,27]

Saito *et al*,[28] assessed the cost-effectiveness of lifetime anti-hypertensive therapy with ARB monotherapy, CCB monotherapy, or ARB+CCB combination therapy in Japan. The combination therapy was found to be a more cost-effective lifetime anti-hypertensive strategy than monotherapy with either agent alone.

A Swedish retrospective cost-effectiveness analysis of felodipine-metoprolol and enalapril noted that the costs per mmHg reduction and per patient reaching target DBP after 8 weeks were 40 and 34% lower in the felodipine-metoprolol group, respectively. Combination therapy was thus cost-effective in the treatment of hypertension.[29]

In a study from India, pharmacoeconomic analysis of monotherapy revealed that CCBs were the most cost-effective anti-hypertensive drugs in CKD patients when associated with additional anti-hypertensive drugs. A cost-effective analysis of two-drug combination therapy found CCB+α agonist to be the most cost-effective therapy.[30]

Additionally, if a large number of patients can attain BP control with a combination, there will be a lesser need for switching medication, thus minimizing a major source of expense. Furthermore, low dose combinations may help improve tolerability, compliance and positively impact quality-of-life measures. Even small improvements in quality of life can offer a huge impact on cost-utility measures.[27]

Patients with CKD often require polypharmacy, thus increasing the burden of cost.[30] Therefore, early combination treatment in hypertension with CKD seems to be a cost-effective approach.

When is Early Combination Therapy Advised: Guideline Recommendations in Hypertension with CKD?

It is known that most patients with hypertension require combination anti-hypertensive therapy to attain target blood pressure. Combination therapy improves BP control and lesser time is needed to achieve the target BP with a combination regimen, with equivalent or better tolerability, compared to higher-dose monotherapy.[4]

It has been confirmed time and again that initial treatment with single-pill combinations tend to achieve more rapid BP control during the first 3 to 6 months in comparison with initial monotherapy with add-on medications. Adherence is also better with single-pill combinations.[20]

In particular, patients with co-morbidities may obtain benefits from the effects of different anti-hypertensive agents as a combination.[4] The key indications for combination anti-hypertensive therapy include:[4]

- Blood pressure not at target level with a single agent
- Adverse effects of a single agent that may be improved by the addition of a second agent– adding an ACE inhibitor to a CCB to reduce peripheral edema.
- SBP ≥ 20 mmHg or DBP ≥ 10 mmHg above the goal
- Compelling indications that may be benefitted by different mechanisms of action of several anti-hypertensives.

The positive association between BP and the risk of kidney failure and kidney disease mortality is seen even in the so-called normal BP range. BP-lowering interventions with the combination of anti-hypertensive agents can slow the decline in GFR. Patients with high BP and reduced kidney function less often attain the goal BP compared to those without kidney disease.[31] Monotherapy is seldom able to attain the goal BP level required to slow the decline in GFR.[4]

Hence, it seems reasonable to conclude that initial combination therapy is needed to achieve the low therapeutic goal BP levels in patients with kidney disease.

The latest guidelines also recommend initial combination therapy for hypertension with CKD. The recommendations from some of the updated guidelines are summarized below.

ESC/ESH Guidelines for the management of arterial hypertension-2018[23]

- RAAS blockers are more effective for reducing al-

buminuria compared to other anti-hypertensives and should be used as part of the treatment regime in hypertensives in the presence of microalbuminuria or proteinuria.

- A combination of RAAS blocker with CCB or diuretic is recommended as starting treatment.
- A combination of two RAAS blockers is not recommended.

2020 ISH Guidelines[32]

- Core medication-treatment strategy - Step 1: Dual low-dose combination (ACE inhibitor or ARB + CCB); Step 2: Dual full-dose combination (ACE inhibitor or ARB + CCB); Step 3: Triple combination (ACE inhibitor or ARB + CCB + Thiazide-like diuretic); Step 4: Triple combination + spironolactone or other drug.
- RAAS-inhibitors are the first-line medications in hypertension and CKD as they reduce albuminuria in addition to BP control.
- CCBs and diuretics (loop-diuretics if eGFR <30 ml/min/1.73m^2) can be added.

2017 ACC/AHA Guidelines[33]

- Starting of anti-hypertensive medication treatment with 2 first-line agents of different classes, either as separate agents or as a fixed-dose combination, is recommended for adult patients with stage 2 hypertension and average BP > 20/10 mmHg above their BP target.
- In adult patients with hypertension and CKD (stage 3 or above or stage 1 or 2 with albuminuria [≥300 mg/d, or ≥300 mg/g albumin-to-creatinine ratio or the equivalent in the first-morning void]), ACE inhibitor therapy is reasonable to slow kidney disease progression.
- In adults with hypertension and CKD (stage 3 or higher or stage 1 or 2 with albuminuria [≥300 mg/d, or ≥300 mg/g albumin-to-creatinine ratio in the first-morning void]). If an ACE inhibitor is not tolerated in the patient, ARBs are a good alternative choice.

Considering the available data and the guideline recommendations, combination treatment appears to be the choice of initial treatment in patients with hypertension and CKD.

Conclusion

There is ample evidence to suggest that early combination therapy is the way forward in the management of hypertensive patients with CKD. Combination therapy is clearly indicated in the case of SBP ≥ 20 mmHg or DBP ≥ 10 mmHg above the goal.

Also, it is known for a fact that the BP goal required to delay GFR deterioration can seldom be achieved with monotherapy. Hence, it seems prudent to consider initial combination therapy for patients with hypertension and CKD, in line with the recommendations from leading international guidelines.

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