Chapter 14
Interference with Pharmacological Agents to Resistant Hypertension in Chronic Kidney Disease

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Introduction

The accepted definition of resistant hypertension is a seated office systolic blood pressure (SBP) ≥140 mmHg or diastolic blood pressure (DBP) ≥90 mmHg on maximally tolerated doses of three or more antihypertensive agents, one of which must be a diuretic appropriate for the level of kidney function. The National Institute for Health and Care Excellence (NICE) guidelines recommend the use of triple combination therapy that includes a thiazide or a thiazide-like diuretic, a renin-angiotensin system (RAS) blocker including angiotensin converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB), and a calcium channel blocker [1]. White coat hypertension should be excluded using daytime ambulatory blood pressure measurement (ABPM) (readings of SBP ≥135 mmHg or DBP ≥85 mmHg on the same regimen) to confirm resistant hypertension.

True resistant hypertension is a diagnosis of exclusion of pseudo-resistance which refers the situation associated with poor drug adherence, secondary hypertension including endocrine and vascular causes, casual factors, and white coat hypertension. Inadequate blood pressure (BP) control is often related with poor drug adherence. It is very important to deal with barriers for optimum drug therapy including adverse effects of ongoing treatment, insufficient treatment, interfering vasopressor substance or medication, and excessive salt or alcohol intake. Therefore, the first step is to provide appropriate antihypertensive drug combinations with optimal dosage and good patient compliance [2].

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The approach to treatment of resistant hypertension in patients with chronic kidney disease (CKD) should target several factors that contribute to the pathogenesis of hypertension including impaired handling of sodium and volume expansion, increased activity of the renin-angiotensin-aldosterone system, enhanced sympathetic activity, and reduced endothelium-dependent vasodilation [3]. In addition, particular attention should be given to non-dipping BP pattern which leads to increase the risk of target organ damage. In this chapter, we focus on the pharmacological agents to deal with resistant hypertension in CKD.

Treatment Options

Deal with Volume Overload and Salt Retention

Modifying Treatment According to Volume Status

Subclinical volume overload is present in more than one fifth of patients with CKD. It is an important contributor to resistant hypertension. The value of guiding resistant hypertension treatment based on subclinical extracellular fluid excess can be useful to arrange the appropriate type and dose of antihypertensive agents. Thoracic bioimpedance allows to get actual hemodynamic information about alterations in thoracic fluid volume, cardiac output, and systemic vascular resistance by the use of skin electrodes using together with BP measurement. It was tested in an interesting prospected study comparing hemodynamic management using thoracic bioimpedance to hypertension specialist care based on clinical evaluation during 3 months [4]. One hundred and four patients with resistant hypertension were randomized to group of drug selection based on thoracic bioimpedance findings and drug selection by a hypertension specialist. At the end of the study, target of $\leq$140/90 was gained in 56% of patient in hemodynamic measurement group while 33% of patients in specialist group. The number of patients taking diuretics did not differ between groups, but final diuretic dosage was higher in the hemodynamic group. Thus, impedance measurements can provide useful data about actual volume expansion resulting resistant hypertension in CKD patients (particularly in patients with subclinical volume overload) and may guide to determine appropriate diuretic dose.

Dietary Sodium Intake Leads to Resistant to RAS Blockage Agents

Dietary sodium intake is closely related with action of antihypertensive agents particularly those with RAS blockage. Both animal and human studies have indicated that it is closely interacting with RAS, particularly aldosterone, and mediates hypertension, vascular and tissue damage, and kidney disease [3, 5]. Most of patients with CKD are salt sensitive, increasing sodium intake causing BP elevation and failure in action of RAS blockers and diuretics. In a randomized study, 34 patients were

prospectively enrolled to compare high and low-sodium diet according to antihypertensive and antiproteinuric effects of ARB and thiazide-type diuretic [6]. At the end of the study, investigators found that sodium restriction provides similar effects with diuretic in reducing proteinuria and BP when added to ARB. And, strongest effects on proteinuria and BP were obtained with combining of ARB, diuretic, and low sodium, together. They mentioned that sodium status is an effective method to maximize the antiproteinuric and antihypertensive efficacy of RAS blockade. Thus, approaches to reduce salt intake can be beneficial because of synergism with the actions of thiazides, ACEi, or ARB, resulting in improved BP control and less proteinuria. The Kidney Disease: Improving Global Outcomes (KDIGO) guideline on hypertension in patients with CKD recommends limiting sodium intake to 2–4 g per day in patients not on dialysis [7]. However, most of no added salt diets contain nearly 4 g sodium which already overdoes the limit that the kidney can excrete without diuretic administration in CKD patients. It should be noted that selection of low-sodium foods contributes to improving effectiveness of antihypertensive agents.

Appropriate Diuretic Therapy

Most commonly accepted hypothesis for resistant hypertension is excessive sodium retention due to impaired sodium excretion during the day. Usage of diuretics sufficiently to deal with sodium retention is one of the most effective treatments to achieve BP target. But diuretics remain underutilized and underdosed in many patients. Particularly, CKD patients are more predisposed to sodium retention and volume overload because of impaired renal function. Thus, the use of appropriate diuretics is principal therapy in patients with CKD and resistant hypertension.

Switching Thiazide-Like Diuretic to a More Potent Diuretic

Hydrochlorothiazide (HCTZ) is the most commonly prescribed antihypertensive drug worldwide. More than 97% of all HCTZ prescriptions are for 12.5–25 mg per day. But, in a meta-analysis of 14 studies of HCTZ dose 12.5–25 mg with 1234 patients and 5 studies of HCTZ dose 50 mg with 229 patients, it was reported that decrease in ABPM with HCTZ dose 12.5–25 mg (SBP:6.5 mmHg and DBP:4.5 mmHg) was inferior compared to the ABPM reduction of ACEi (mean BP reduction 12.9/7.7), ARB (mean BP reduction 13.3/7.8 mmHg), beta-blockers (mean BP reduction 11.2/8.5 mmHg), and calcium antagonists (mean BP reduction 11.0/8.1 mmHg) [8]. Another remarkable result was that there was no significant difference in both SBP and DBP in ABPM reduction between HCTZ 12.5 mg and HCTZ 25 mg, but HCTZ 50 mg provided significant higher reduction in ABPM which was comparable to that of other agents. Thus, first step using should be using HCTZ in appropriate dose before switching to other diuretics.

Chlorthalidone is approximately twice as potent as HCTZ with a much longer duration of action (8–15 h for HCTZ compared with >40 h for chlorthalidone) [9]. In a randomized study, investigators compared the effect of chlorthalidone 12.5 mg/day

(force-titrated to 25 mg/day) and HCTZ 25 mg/day (force-titrated to 50 mg/day) on ABPM in untreated hypertensive patients after 8 weeks [10]. As compared to HCTZ, chlorthalidone indicated a greater reduction in SBP primarily due to its effect on reducing nighttime mean SBP (−13.5 ± 1.9 mmHg versus −6.4 ± 1.8 mmHg). Therefore, strong consideration should be given to using chlorthalidone over HCTZ, especially in patients with CKD. Thiazide diuretics are most effective in patients with an eGFR >50 mL/min/1.73 m^2, although chlorthalidone can be effective to a GFR of 30–40 mL/min/1.73 m^2 in the absence of severe hypoalbuminemia. Consequently, BP control can also be improved by increasing diuretic dosage or by switching to a more potent, thiazide-like diuretic with a longer duration of action than the existing drug such as chlorthalidone and indapamide instead of hydrochlorothiazide when GFR is 30 mL/min or over.

The Use of Loop Diuretics

A loop diuretic is preferred for patients with advanced CKD. It has suggested that loop diuretics should be prescribed when eGFR is less than 30 mL/min [11]. It is indicated in the presence of edema or volume overload due to nephrotic syndrome or heart failure. Furosemide and bumetanide should be administered twice daily (preferentially concurrent with sodium ingestion) because of their short duration of action, whereas longer-acting torasemide can be administered once daily. Higher loop diuretic doses might be needed in patients with severe chronic kidney disease with or without albuminuria. However, counter-regulatory rebound sodium retention could abolish the efficacy of loop diuretics in patients with chronic kidney disease in both the short and long term. To overcome this phenomenon, the diuretic dose or dosing frequency could be increased, or sequential nephron blockade using a combination of loop diuretics and thiazides might be needed for patients with resistant hypertension, especially in the presence of edema or heart failure [12]. But, careful monitoring of renal function, serum electrolytes, and fluid status is needed to detect dehydration, hypokalemia, hyponatremia, hypovolemia, or progressive renal dysfunction.

Aldosterone Blockage

Mineralocorticoid Receptor Antagonists as a Fourth-Line Therapy

The suggested fourth-line therapy is to add mineralocorticoid receptor antagonists (MRA, 12.5–25 mg per day spironolactone or 25–50 mg per day eplerenone, to be adapted according to eGFR level) in patients with GFR of 30 mL/min or over and plasma potassium concentrations 4.5 mmol/L or lower or in patients with other indications, such as heart failure with left ventricular dysfunction [13]. MRA reduces BP and left ventricular hypertrophy in patients with resistant hypertension

and an eGFR 50–60 mL/min, but it doubles the risk of hyperkalemia when added to ACEi or ARB in patients with moderate chronic kidney disease (eGFR 30–90 mL/min per 1.73 m^2) [14]. The long-term effects of MRA on renal and cardiovascular outcomes, mortality, and safety in patients with CKD still remain to be established. ESH guidelines do not recommend the routine use of MRA in patients with CKD, especially in combination with RAS blockers, because of the risk of further renal impairment and hyperkalemia [13].

Spironolactone Versus α-Blocker and/or Beta-Blocker

As mentioned previously, most commonly accepted hypothesis for resistant hypertension is excessive sodium retention due to impaired sodium excretion during the day. Usage of diuretics sufficiently to deal with sodium retention is also one of the most effective additional treatments. Thus, spironolactone would be superior to non-diuretic add-on drugs at lowering BP in resistant hypertension.

In this perspective, in PATHWAY study, investigators compared the effectiveness of spironolactone (25–50 mg) as add-on drugs to bisoprolol (5–10 mg), doxazosin modified release (4–8 mg), and placebo according to BP control during 12 months [15]. They enrolled 314 patients with resistant hypertension who were receiving at least three antihypertensive agents, including a diuretic, at full or maximum tolerated doses in the study. The primary endpoints consisted of the difference in home SBP between spironolactone versus placebo, average of doxazosin and bisoprolol, and each of doxazosin and bisoprolol. The average reduction in home SBP by spironolactone was superior to placebo (−8.70 mmHg), superior to the mean of the other two active treatments (doxazosin and bisoprolol; −4.26 mmHg), and superior when compared with the individual treatments, versus doxazosin (−4.03 mmHg) and versus bisoprolol (−4.48 mmHg). Spironolactone was the most effective treatment for almost 60% of all patients, and they concluded that it was at least three times the proportion in whom doxazosin or bisoprolol was the most effective. Spironolactone was well tolerated and did not increase drug discontinuation owing to renal impairment, hyperkalemia, or gynecomastia compared with placebo and the other active treatments. Serum potassium exceeded 6.0 mmol/L in only six of the 285 patients, who received spironolactone. Consequently, they suggested that spironolactone was the most effective add-on drug for the treatment of resistant hypertension. As indicated above, ESH guideline does not recommend the routine use of MRA in patients with CKD, especially in combination with RAS blockers, but 12.5–25 mg per day spironolactone can be given safely to patients as add-on drugs with eGFR of 30 mL/min or over and plasma potassium concentrations 4.5 mmol/L or lower, and close monitoring should be done when using higher dose of spironolactone.

Deal with Enhanced Sympathetic Activation: Beta-Blockers

The sympathetic nervous system is activated in CKD which acts an important role in the progression of renal dysfunction and contributes to the onset and progression of cardiovascular disease including resistant hypertension. It has demonstrated that patients treated with metoprolol had similar clinical composite outcomes (renal function decline, onset of end-stage renal disease, and/or death) with patients treated with amlodipine [16]. β-blockers are the drug of choice and can be used at any stage in CKD, especially in patients with coexisting coronary artery disease, heart failure, or arrhythmias. If BP remains uncontrolled, a β-blocker (preferably with a hepatic elimination route including metoprolol, carvedilol, nebivolol, and propranolol to avoid drug accumulation which could lead to an increased risk of bradyarrhythmias) could be appropriate agent to deal with resistant hypertension [2].

A New Approach: Endothelin Receptor Antagonists

Endothelin is a potent vasoconstrictor peptide derived from the endothelium. Increased circulating endothelin concentrations are determined in patients with hypertension indicating the potential therapeutic value of the endothelin receptor blockade. Especially, it might meet a significant need in patients with resistant hypertension. Because none of the standard antihypertensive therapies including renin-angiotensin system blockers, diuretics, and calcium-channel blockers do not inhibit vasoconstrictor effects of endothelin type A receptor, effectively. To date, several clinical studies have investigated whether endothelin receptor antagonists (ERAs), both selective and nonselective, might be a promising treatment option in hypertensive patients.

Bosentan is a nonselective, sulfonamide-type ERA which is often used in pulmonary hypertension. Its antihypertensive effect was studied in 93 patients with mild-to-moderate essential hypertension [17]. Patients were randomly assigned to receive one of four oral doses of bosentan (100, 500, or 1000 mg once daily or 1000 mg twice daily), placebo, or the enalapril (20 mg once daily) for 4 weeks. As compared with placebo, bosentan provided further decline in both DPB and SBP with a daily dose of 500 or 2000 mg (an absolute reduction of 5.7 mmHg at each dose in DBP) which was similar to the reduction with enalapril (5.8 mmHg) without activation of the sympathetic nervous system. In addition, the reductions in mean 24-h, daytime, and nighttime DP in the bosentan groups (greatest with 2000 mg) were significantly larger than those in the placebo group.

Darusentan is a selective, propionic acid-based ERA with higher affinity for the type A receptor. In a multicenter randomized, dose-response study, 392 patients with stage 1 or 2 hypertension were randomized to darusentan (10 mg, 30 mg, and 100 mg) and placebo [18]. As compared with placebo, darusentan at a dose of 100 mg once daily significantly decreased both DBP (8.3 mmHg) and SBP

(11.3 mmHg) after 6 weeks of treatment. Later studies have focused on the impact of ERAs in the setting of resistant hypertension. In a randomized trial, 379 patients (96 of them were CKD patients) with resistant hypertension who were receiving at least three antihypertensive agent, including a diuretic, at full or maximum tolerated doses were randomly assigned to 14 weeks treatment with placebo or darusentan 50 mg, 100 mg, or 300 mg taken once daily [19]. The primary endpoints were changes in office SBP and DBP. As compared to placebo, darusentan provided further reduction in both SBP (9 mmHg) and DBP (5 mmHg) in patients with resistant hypertension who already receiving standard antihypertensive treatment. In addition, darusentan produced sustained BP reductions across the 24-h dosing interval and obtained significant reduction in ABPM. Moreover, in subgroup analysis, similar decreases in SBP and DBP with darusentan were achieved in CKD patients with resistant hypertension. Generally, darusentan was well tolerated, the main adverse effects being related to fluid retention.

Despite clear evidence of a key role for the endothelin system in BP control and hypertension, the clinical use of ERAs to treat hypertension has not yet been approved. A major disadvantage has been the relatively high incidence of side effects, notably hepatotoxicity with the sulfonamide drugs bosentan, and fluid retention with all ERAs. Fluid retention fortunately seems amenable to management with diuretics, and to some degree, these side effects appear dose related, and certain studies have been criticized for excessive dosing. Probably ERAs will not have been destined to become first-line therapy for treating essential hypertension, but ERAs have excellent potential for providing benefit to select subgroups of patients especially with resistant hypertension accompanied by fluid management with effective diuretic therapy.

Dual ACE/ARB Inhibition

Proteinuria can be lowered by dual RAS blockade with ACEi and ARBs or with direct renin inhibitors to a greater extent than either RAS blocker alone. However, this combination has not been shown to improve BP control or improve cardiovascular outcomes compared with single RAS blockade in patients with resistant hypertension, although it might preserve renal function in patients with diabetes and chronic kidney disease to some extent, according to a recent network meta-analysis [20]. Additionally, this combination increases the risk of hyperkalemia, hypotension, and acute renal failure. Dual RAS blockade is discouraged by the guidelines [13]. Replacement of ACEi and ARB with other antihypertensive drugs in patients with advanced chronic kidney disease (stages 4–5) should be considered when there are no contraindications, such as heart failure or when discontinuation of the drug is expected to relieve side effects such as hyperkalemia, acute kidney injury, or symptomatic hypotension [2].

Deal with Non-dipping Status: Chronotherapy

The non-dipping pattern refers the situation of impaired circadian BP rhythm, and it is defined as decrement in SDP and/or DBP less than 10% during the night. Non-dipper has particular importance, and the prevalence of abnormally high sleep BP is very often in CKD patients. It was shown that the capacity of excreting sodium during daytime is a significant determinant of nocturnal BP and dipping pattern as reduced capacity leads to higher nocturnal BP and non-dipping pattern [21]. Non-dipping BP is associated with target organ damage including left ventricular hypertrophy, higher prevalence of proteinuria and higher risk of CKD progression, and poorer cardiovascular outcomes. In patients with true resistant hypertension, non-dipping pattern is associated with nearly twofold increased risk of cardiovascular morbidity and mortality. Thus, therapeutic restoration of normal physiologic BP reduction during nighttime sleep (dipping status) is the most significant independent predictor of decreased risk and the basis for the chronotherapy. Chronotherapy is a therapeutic strategy of taking at least one dose of antihypertensive medications at bedtime, instead of all in the morning time to provide dipping status (normal circadial variation) and ABMP control.

Chronotherapy Against to Non-dipping Pattern

Several studies have investigated the effect of chronotherapy on the ABPM control and the non-dipping pattern. The Monitorización Ambulatoria para Predicción de Eventos Cardiovasculares (MAPEC) is a prospective randomized study which examines the effect of chronotherapy on ABPM and clinical outcomes (primary endpoint including composite of all-cause mortality and cardiovascular events) in 2156 patients with untreated or resistant hypertension [22]. Study population divided into two groups consisting of control group, took all antihypertensive medications in the morning and the treatment group and took one or more antihypertensive at bedtime. Patients were followed during median of 5.6 years with a primary composite endpoint of all-cause mortality and total cardiovascular events. 48-h ABPM was performed to patients at least annually. Patients randomized to the treatment arm (bedtime administration) demonstrated lower sleep-time BP, a higher rate of controlled ABPM (62% vs. 53%, $p < 0.001$), and a much lower incidence of the non-dipper status (34% versus 62%, $p < 0.001$). As a clinical outcome, those in the bedtime administration group had a reduction in the primary endpoint of 11.95 versus 27.8 events per 1000 patient-years, NNT = 63 over 1 year. All-cause mortality alone was also reduced (2.11 versus 4.16 events per 1000 patient-years, NNT 488 over 1 year). It has been concluded that switching at least one medication to bedtime administration is cost-effective, simple intervention that contributes to improve BP control and reduce cardiovascular events. In another interesting study, 27 consecutive patients with resistant hypertension and non-dipper BP pattern on ABPM were enrolled to investigate whether shifting all non-diuretic antihypertensive drugs from

morning to evening (maintaining the same drugs at the same doses) improves ABPM control after 6 weeks. At the end of the study, they determined significant decrement in ABPM (SBP: 140.5 ± 10.4 to 135.7 ± 12.5 mmHg and DBP: 80.5 ± 9.6 to 73.8 ± 9.3 mmHg), and 15% of the patients restored dipping pattern (normal circadian rhythm) after the drug shift, while no changes were observed in the control group [23]. Consequently, chronotherapy suggests a prospect to recover nocturnal BP control and the non-dipper pattern without changing the total number of medications.

Chronotherapy: A Promising Approach in Hypertensive Patients with CKD

Several studies suggest that chronotherapy is a promising approach in hypertensive patients with CKD. In one of them, 32 patients with CKD (eGFR of 46 ± 12 mL/min/1.73m^2) and night-day ratio of mean ABPM greater than 0.9 indicating non-dipper status but with normal daytime ABPM (<135/85 mmHg) were enrolled in the study [24]. They were treated with 2.4 ± 1.4 of antihypertensive drugs consisted of ACEi, ARB, thiazide diuretic, calcium channel blockers, and beta-blockers. It was investigated whether shifting 1 antihypertensive drug from morning to evening (except diuretics to avoid patient discomfort caused by nocturnal diuresis) after 8 weeks provides changing in the percentage of patients with night-day ratio of mean ABPM from greater than 0.9–0.9 or less. After the drug shift, normal circadian rhythm is restored in 87.5% of patients independently from number and class of shifted drug. In addition, significant decrement in office blood pressure in the morning (from SBP: 136 ± 16 to131 ± 13, DBP: 77 ± 10 to 75 ± 8 mmHg) and in proteinuria (especially in patients with >300 mg proteinuria) were obtained at the end of the study. It was concluded that changing the timing of antihypertensive therapy decreased nocturnal blood pressure and proteinuria in non-dipper patients with CKD with limitation of the absence of a control group and patients with severe proteinuria or uncontrolled daytime ABPM. Consequently, it has shown that time of ingestion of hypertension medications can affect circadian patterns of BP in this study, but whether this translates into an effect on clinical outcomes has been investigated in another prospective, randomized study. They enrolled 661 patients with CKD (eGFR <60 mL/min/1.73m^2 and/or albuminuria defined as albumin excretion ≥30 mg/24-h urine) to compare the effects of taking at least one of prescribed hypertension medications at bedtime to taking them all upon awakening according to cardiovascular outcomes (a composite of death, myocardial infarction, angina pectoris, revascularization, heart failure, arterial occlusion of lower extremities, occlusion of the retinal artery, and stroke) [25]. After a median follow-up period of 5.4 years, it was reported that patients who took at least one antihypertensive medication at bedtime had nearly one third risk of patients who took all medications upon awakening for total cardiovascular events. In addition, patients on bedtime treatment had a significantly lower mean sleep-time BP and a greater proportion demonstrated control of their ABPM (56% versus 45%, $P = 0.003$). Each 5-mmHg

decrease in mean sleep-time systolic BP was related with a 14% reduction in the risk for cardiovascular events during follow-up. They concluded that patients with CKD and hypertension, taking at least one antihypertensive medication at bedtime, improve control of BP and reduce the risk for cardiovascular events. Therefore, changing at least one antihypertensive medication to bedtime dosing should be considered in CKD patients with resistant and/or non-dipping hypertension.

Other Drugs

If BP remains uncontrolled, an α-blocker or a centrally acting α-agonists, which preferably do not require dose adjustments (methyldopa or clonidine), could be used. Direct vasodilators such as hydralazine or minoxidil are sometimes used but could induce severe fluid retention and tachycardia, especially minoxidil which has other side effects (hirsutism, pericardial effusion).

Conclusion

Resistant hypertension is failure to achieve target blood pressure despite the use of three or more appropriately dosed antihypertensive drugs including a diuretic. It is still a common clinical problem, especially in patients with chronic kidney disease. First approach should be dealing with barriers for optimum drug therapy including adverse effects of ongoing treatment, insufficient treatment, interfering vasopressor substance or medication, and excessive salt or alcohol intake. Subsequently, next approach should target factors that contribute to the resistant hypertension including impaired handling of sodium and volume expansion, increased activity of the renin-angiotensin-aldosterone system, enhanced sympathetic activity, and reduced endothelium-dependent vasodilation. Pharmacological interferences should be applied including appropriate diuretic therapy, aldosterone blockage, beta-blocker, and chronotherapy to deal with resistant hypertension in chronic kidney disease. An algorithm for resistant hypertension treatment in CKD is shown in Fig. 14.1.

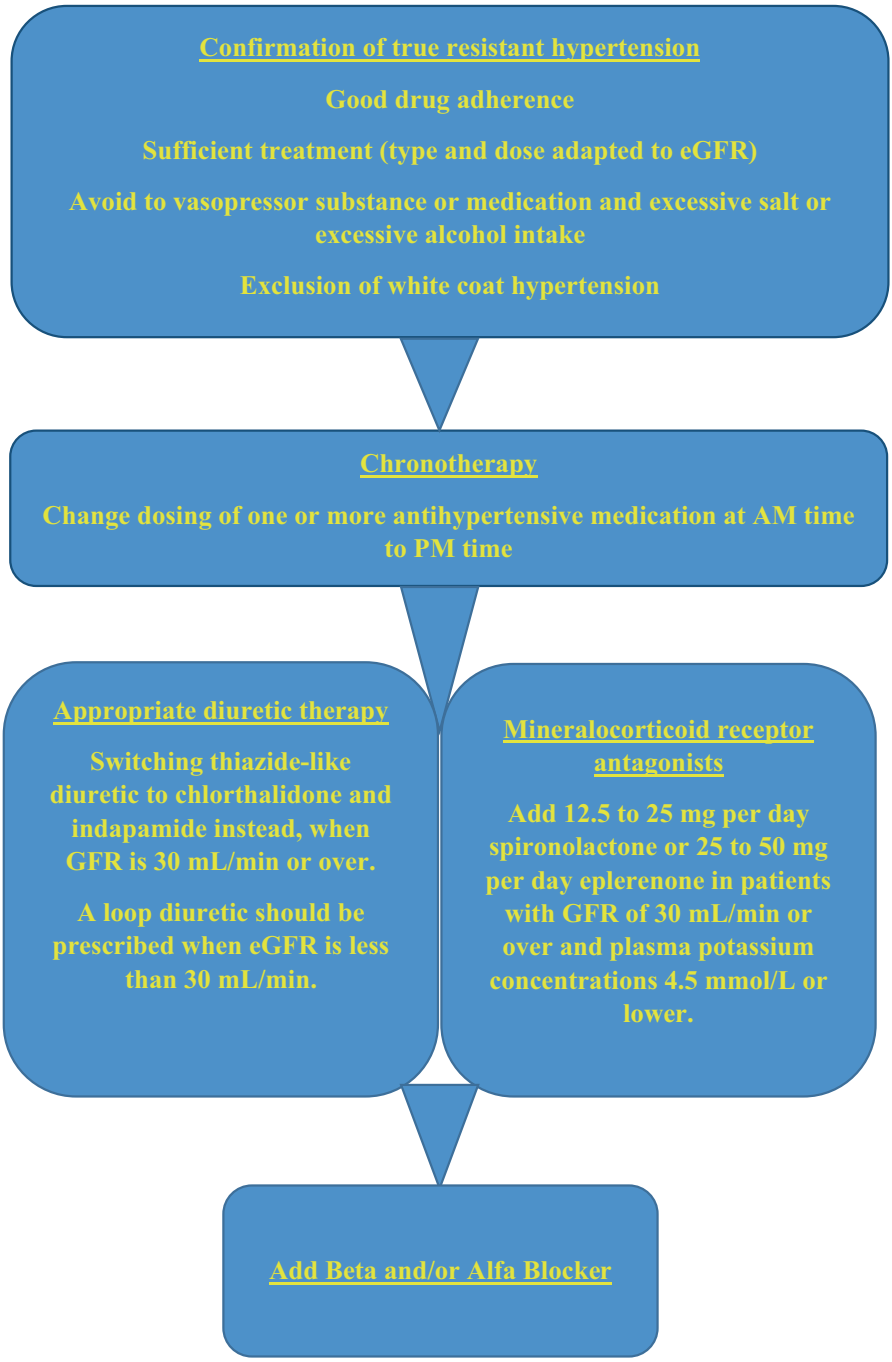

Fig. 14.1 An algorithm for resistant hypertension treatment in chronic kidney disease

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