Chapter 2: Lifestyle and pharmacological treatments for lowering blood pressure in CKD ND patients

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INTRODUCTION

This section outlines lifestyle and pharmacological methods to reduce BP in patients with non-dialysis-dependent CKD (CKD ND). Because these strategies were covered in detail in the 2004 *KDOQI Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease* (http://www.kidney.org/professionals/KDOQI/guidelines_bp/index.htm),[1] we concentrate on issues relating to BP control in CKD patients that have arisen since 2004. Additional information that may be of help to the clinician (although not specifically relevant to CKD patients) can be found in the *Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure* (JNC 7) (http://www.nhlbi.nih.gov/guidelines/hypertension/jnc7full.pdf).[9]

GENERAL STRATEGIES

It is generally accepted that a stepwise combination of lifestyle modifications and drug therapy should be used to lower BP in CKD patients, with escalation of efforts depending on factors such as the severity of the BP elevation, the co-morbidities present and the age of the patient.

2.1: Individualize BP targets and agents according to age, co-existent cardiovascular disease and other co-morbidities, risk of progression of CKD, presence or absence of retinopathy (in CKD patients with diabetes) and tolerance of treatment. (*Not Graded*)

RATIONALE

We recognize that individual decision making is required regarding BP targets and agents with the risks and benefit being taken into consideration; however, since there is little evidence from RCTs to guide these decisions, this recommendation has not been graded.

The potential benefits of lower BP include a decreased risk of both CVD and progression of CKD. To assess the likely benefit in a given patient, the clinician needs to consider such issues as the prior rate of CKD progression, the expected course of the specific disease, the level of urinary albumin excretion and the presence or absence of other risks of CVD. Potential adverse effects generic to treatment used to lower BP include decreases in cerebral perfusion (contributing to dizziness, confusion and falls) and acute deterioration in kidney function.

It is widely acknowledged that achievement of a reduction in BP can be difficult in CKD patients, particularly in the elderly, those with co-morbidities, and those with diabetes mellitus.[1,9,30] Increased conduit-artery stiffness, resulting in high pulse pressure (with high systolic and low diastolic pressures) is common in CKD patients, the elderly and patients with diabetes.[31–36] Arterial stiffening is associated with an increased risk of CVD independent of other recognized risk factors.[37–39] With a high pulse pressure, efforts to reduce systolic BP in older patients and those with coronary artery disease (CAD) can result in lowering diastolic BP to levels well below diastolic targets, which may be associated with greater morbidity or mortality.[40,41] A J-shaped relationship between achieved BP and outcome has been observed in the elderly and in patients with vascular disease, possibly suggesting that BP can be reduced too far in these patients.[40,42,43] Discussion of this issue is further elaborated in Chapters 7 and 8. Unfortunately, in CKD patients, the available evidence proved to be insufficient to allow the Work Group to define the lowest BP targets (see Chapter 8).

Similarly, when considering the choice of BP-lowering agents, decision making should be tailored to the individual patient. For instance, ACE-Is and ARBs are potentially harmful in the presence of significant renovascular disease or volume depletion, or when used in combination with nonsteroidal anti-inflammatory drugs (NSAIDs) or cyclooxygenase-2 (COX-2) inhibitors (as outlined later in this chapter). The presence of diabetic retinopathy in a CKD patient may also influence BP target and choice of agent as outlined in Chapter 4.

Based on these considerations, the Work Group concluded that it is good clinical practice to assess the risks and benefits of BP-lowering treatment in an individual patient and to tailor therapy accordingly.

2.2: Inquire about postural dizziness and check for postural hypotension regularly when treating CKD patients with BP-lowering drugs. (*Not Graded*)

RATIONALE

Patients with CKD, particularly the elderly[31] and diabetic patients with autonomic neuropathy, are prone to orthostatic hypotension,[44,45] which may be exacerbated by volume depletion. Many CKD patients will require combinations of drugs to control BP including vasodilators, which can cause or exacerbate postural hypotension. This can lead to postural dizziness, reduced adherence and in extreme cases, syncope

or falls with consequent injury. Accordingly, it is sensible to regularly check for symptoms of postural dizziness and to compare lying, sitting and standing BP in CKD patients, particularly before and after altering the treatment regimen.

LIFESTYLE MODIFICATION

The impact of lifestyle-related factors on BP and the risk of cardiovascular and other diseases have been well documented. A number of observational studies in the general population have linked factors such as salt intake,[46] weight and body mass index (BMI),[47] exercise frequency,[48] and alcohol intake[49] with BP level. RCTs addressing many of these factors have been undertaken, the results of which have led the authors of BP guidelines for the general population[9] (e.g., JNC 7) to make specific recommendations about the management of lifestyle as a key component of BP management.

Individuals with CKD generally have higher[9] BP levels than people with normal kidney function and their BP may be particularly sensitive to some factors related to lifestyle. For example, high salt intake may potentially have a greater impact on BP in patients with CKD than in those without CKD since CKD may reduce the ability to excrete the salt load in the urine. CKD patients may also be more sensitive to harms related to lifestyle interventions; for instance, an individual with tubular disease with salt wasting from the kidney could be at increased risk of hypovolemia if salt intake is restricted. Furthermore, some potential lifestyle interventions, such as increased physical exercise, may be difficult for patients with CKD owing to reduced energy levels.

Lifestyle modification offers the potential to lower BP in a simple, inexpensive, effective fashion while also improving a range of other outcomes (e.g., changes in lipid levels resulting from diet and exercise and liver function through moderation of alcohol intake). Because lifestyle changes are applicable to the general population and are potentially implementable at low expense worldwide, the Work Group felt many were sufficiently important to warrant an evidence grade of level 1, with the strength of the evidence varying in accordance to their potential to do harm in CKD patients.

2.3: Encourage lifestyle modification in patients with CKD to lower BP and improve long-term cardiovascular and other outcomes:

2.3.1: We recommend achieving or maintaining a healthy weight (BMI 20 to 25). *(1D)*

RATIONALE

- Weight reduction lowers BP in the general population.
- Observational studies show that weight-loss strategies reduce BP in CKD patients.
- Weight-reduction strategies may result in other health benefits to CKD patients including reduction in urine albumin or protein levels, improved lipid profile and increased insulin sensitivity.

The prevalence of obesity is very high in Western countries and is increasing rapidly in developed and developing countries around the world. A strong relationship exists between body weight (usually defined as BMI) and BP levels in the general population.[50–52] Compared with a person of normal weight, individuals who are overweight or obese tend to have higher BP levels, abnormalities in a range of other cardiovascular parameters (e.g., dyslipidemia[52]), and an increased risk of cardiovascular events.

Weight and BP. A weight-reducing diet has been clearly demonstrated to lower BP in overweight individuals in the general population. A systematic review[53] published in 2006 identified 14 trials assessing the effects of dietary modification on BP in the general population, all but two of which assessed the effects of weight reduction in overweight persons. Many of the 14 trials also included other modifications to diet (e.g., increased fruit and vegetable intake and salt reduction) and lifestyle (e.g., increased exercise). Trials were 8 to 52 weeks in duration and mostly included participants with elevated BP levels. The quality of the trials was generally suboptimal. Overall, dietary modification reduced systolic BP by 6.0 mm Hg (95% confidence interval [CI] 3.4–8.6) and diastolic BP by 4.8 mm Hg (95% CI 2.7–6.9). High levels of heterogeneity in the trial results were observed.

The available data regarding the effects of weight loss in CKD patients has been systematically reviewed by Navaneethan *et al.*[54] Only two randomized trials were identified but 11 observational studies were also included. A range of surgical and non-surgical weight-loss interventions were assessed. All interventions, when taken together, resulted in significant reduction in weight among CKD patients. This was associated with a reduction in urinary protein excretion (described in two studies) but no overall effect on the GFR, possibly due to the short term nature of the studies. Effects on BP were not reported in the RCTs, whereas the observational studies reported consistently large, significant reductions in BP compared to baseline with both non-surgical weight loss (weighted mean difference in BP 9.0 mm Hg; 95% CI 3.7–14.2 mm Hg; $P<0.0001$) as well as surgical weight loss (weighted mean difference, 22.6 mm Hg; 95% CI 19.1–26.2; $P<0.0001$). Thus, weight loss likely improves BP in patients with CKD, although high-quality RCTs are needed to confirm this finding.

Body weight and outcomes. In the general population, overweight and obesity have been clearly shown to be associated with an increased risk of cardiovascular events and death.[52] A J-curve relationship has been described in many reports, revealing an increased risk in underweight individuals (e.g., those with a BMI <18.5) as well. RCTs have demonstrated that weight loss reduces the incidence of diabetes,[55] but any beneficial effects on cardiovascular outcomes or survival remain to be proven. Indeed, a number of RCTs involving use of pharmacological agents to induce weight loss have been stopped early owing to unintended and unanticipated adverse

effects of the agent being assessed (e.g., rimonabant and sibutramine).[56,57]

The data are less clear for patients with CKD. Obesity has been proposed as a possible potentiator of CKD progression; however, reliable data remain sparse. Many observational studies have suggested that among patients with advanced CKD who are dialysis-dependent, and particularly hemodialysis-dependent, clinical outcomes might actually be better for overweight individuals than for non-overweight individuals.[58,59] Other studies have reported conflicting results.[60] It is possible that these observations are due to reverse causality, with the results driven by underlying malnutrition or inflammation in the lower-weight patients and they may also reflect differences in the proportions of muscle and fat in patients with CKD compared with people without CKD. These data should therefore be interpreted with caution.

For overweight individuals, the method used to reduce body weight may be important within the context of CKD. Popular and widely recommended weight-loss diets are commonly high in potassium and protein and may therefore increase risks of hyperkalemia and CKD progression in patients with CKD. As the potential benefits and harms have not been specifically addressed in the CKD population, the use of these diets is not recommended.

Overall, the available data suggest that achieving or maintaining a body weight in the healthy range will lead to improved BP levels and better long-term CKD outcomes. This is particularly clear for individuals with CKD stages 1–2. Caution should be exercised in patients with more advanced CKD, because malnutrition may be associated with adverse outcomes. Since a high weight may be protective in CKD 5D patients, there could be risks associated with encouraging weight loss in those with advanced CKD. Hence, Recommendation 2.3.1 was graded 1D.

2.3.2: We recommend lowering salt intake to <90 mmol (<2 g) per day of sodium (corresponding to 5 g of sodium chloride), unless contraindicated. *(1C)*

RATIONALE

- Lowering salt intake reduces BP in the general population.
- In CKD patients with reduced GFR, salt retention is associated with an increase in BP.

A relationship between average daily salt intake and BP levels has long been recognized, leading to calls from the World Health Organization (WHO) for salt intake to be restricted to improve BP levels (http://www.who.int/cardiovascular_diseases/guidelines/Full%20text.pdf).[61] Restricting salt intake clearly lowers BP by a moderate amount, as demonstrated in a systematic review of seven trials,[53] most of which assessed the impact of restricting salt intake to 4 to 6 g (70–100 mmol). Overall, BP levels were reduced as compared to baseline levels: systolic BP by 4.7 mm Hg (95% CI 2.2–7.2) and diastolic BP by 2.5 mm Hg (95% CI 1.8–3.3). Moderate heterogeneity was observed in the effects on systolic BP, but this was corrected when one outlier trial was excluded. Other systematic reviews including a different group of trials have suggested similar but somewhat smaller benefits.[62]

Alterations in salt handling are likely to be a significant contributor to elevated BP levels in patients with CKD. Although no large scale long term RCTs of salt restriction in CKD patients were found, there is no reason to believe that BP reductions should not also be observed. Reducing salt intake could have a greater capacity to lower BP in patients with CKD who have salt and water retention and this intervention should be routinely discussed with such individuals. A low-sodium diet has been shown to further reduce BP and urine albumin or protein levels in the short term in patients on ARBs[63–66] and may be a consideration for those with high BP who have a poor response to ACE-Is or ARBs.

Some forms of CKD may be associated with salt wasting from the kidney. Affected individuals may be at higher than usual risk of volume depletion and electrolyte disturbances potentiated by salt restriction. Volume and electrolyte status should thus be carefully monitored in patients with CKD undergoing salt restriction. Recent studies suggesting that low urinary sodium excretion (hence perhaps low dietary sodium intake) associates with higher mortality in diabetes have yet to be confirmed by others or explained.[67,68]

Since salt restriction is an inexpensive and important contributor to lowering BP in the generally population worldwide, this intervention was deemed a level 1 recommendation. But since the evidence base for CKD patients included only small, short-term RCTs involving special circumstances, Recommendation 2.3.2 was graded 1C.

2.3.3: We recommend undertaking an exercise program compatible with cardiovascular health and tolerance, aiming for at least 30 minutes 5 times per week. *(1D)*

RATIONALE

Increased physical exercise has been linked to a broad range of positive health outcomes through a wide variety of mechanisms. A clear inverse relationship between exercise and average daily BP has been demonstrated by a large volume of previous epidemiological data in the general population, although exercise may lead to modest and acute physiological increases in BP during the time of the activity.

The effects of exercise on BP in the context of RCTs have been systematically reviewed in the general population.[53] Most of the 21 RCTs included in the review examined the efficacy of 3 to 5 weekly sessions of aerobic exercise lasting 30 to 60 minutes. Overall, the exercise group had an average reduction in systolic BP of 6.1 mm Hg from baseline (95% CI 2.1–10.1) and in diastolic BP of 3.0 mm Hg (95% CI 1.1–4.9). The effects were slightly reduced when one outlier trial was excluded from the analysis (to average reductions of 4.6 and 2.6 mm Hg, respectively), but moderate heterogeneity among the results remained.

No RCTs in the CKD population were found. A *post hoc* observational analysis[69] of the Modification of Diet in Renal Disease (MDRD) study population did not identify a clear relationship between level of physical activity at baseline and the subsequent risk of death, although trends toward better outcomes for active individuals were observed. Two larger studies from the US Renal Data System found that CKD 5D patients who are sedentary have a higher risk of death than those who are active.[70,71] All of these studies are observational and more data are required.

The benefits of exercise on BP and on general health appear likely to be similar in the CKD and the general population, with no strong rationale for different recommendations. On this basis, Recommendation 2.3.3 was graded 1D.

2.3.4: We suggest limiting alcohol intake to no more than two standard drinks per day for men and no more than one standard drink per day for women. *(2D)*

RATIONALE

Alcohol has been shown to produce both acute and chronic increases in BP, suggesting that restricting alcohol intake would lower BP. In a systematic review of four trials,[53] restricting alcohol intake in the general population resulted in a 3.8 mm Hg reduction (95% CI 1.4–6.1) in systolic BP and a 3.2 mm Hg reduction (95% CI 1.4–5.0) in diastolic BP, with no evidence of heterogeneity among the results. No data specific to CKD patients were found, but the effects are expected to be similar.

Most data suggest that up to two standard drinks per day for a man and 1 standard drink per day for a woman are likely to be safe. The definition of a standard drink varies from 8 to 19.7 g of alcohol in different countries (see http://whqlibdoc.who.int/hq/2000/who_msd_msb_00.4.pdf).[72] 10 g of alcohol is equivalent to 30 ml of spirits, 100 ml of wine, 285 ml of full-strength beer, and 425 ml of light beer. The benefits of alcohol moderation on BP and on general health appear likely to be similar in the CKD and the general population, with no strong rationale for different recommendations. On this basis, Recommendation 2.3.4 was graded 2D.

OTHER INTERVENTIONS

Cigarette smoking. Cigarette smoking and exposure to environmental tobacco smoke are clearly among the most potent modifiable risk factors for CVD in the general population and in patients with CKD. Although it does not have a clear, direct impact on long-term BP, the avoidance of exposure to cigarette smoke is a critical aspect of cardiovascular risk reduction but as yet there are no RCTs in the CKD population.

Dietary supplementation. The effects of potassium supplementation on BP have been assessed in a number of studies.[53] These have produced conflicting results, with some but not all indicating a benefit. CKD patients often have reduced capacity for potassium excretion, particularly as the GFR falls, such that the risk of hyperkalemia may be increased. In the absence of specific studies demonstrating a benefit in CKD patients, we cannot recommend potassium supplementation to reduce BP in patients with CKD.

The evidence base for magnesium supplementation is similar, with some but not all studies suggesting a benefit with respect to BP.[53,73] Although hypermagnesemia is not a common problem in CKD patients, magnesium supplementation cannot be recommended without specific data demonstrating its safety and efficacy.

Fish-oil supplementation has been shown to produce small but significant reductions in BP in a number of RCTs and systematic reviews.[53,74] The mechanisms of these effects remain uncertain, however and the safety of fish oil has not been clearly demonstrated in CKD patients. Although some data supporting the use of fish oil exists for patients with IgA nephropathy,[75] it is premature to recommend this treatment for BP lowering in the CKD population.

BP-LOWERING AGENTS

RCTs involving both CKD and non-CKD populations in which a target BP has been set at the levels recommended in this Guideline clearly show that most patients will require two or more antihypertensive agents to achieve these targets. Surveys of BP control in CKD patients indicate that three or more agents are frequently needed. With the exception of ARBs or ACE-Is in CKD patients with high levels of urinary albumin or protein excretion, there is no strong evidence to support the preferential use of any particular agent(s) in controlling BP in CKD; nor are there data to guide the clinician in the choice of second- and third-line medications. Since the 2004 KDOQI Guideline[1] was published, there has been an increasing trend towards tailoring antihypertensive therapy to the individual patient, taking into account issues such as the presence or absence of high urine albumin excretion, co-morbidities, concomitant medications, adverse effects, and availability of the agents. Ultimately, the choice of agents is less important than the actual reduction in BP achieved, since BP reduction is the major measurable outcome in the individual patient.

Other information of value in deciding on the optimal BP lowering regimen include data on drug half-life and dose adjustments in CKD stage 5D, which may be of help in guiding the use of BP lowering drugs in advanced CKD ND.[4,76]

The optimal timing of administration of medication has not been studied in CKD patients. CKD patients who do not have the normal decrease in BP during sleep (non-dippers and reverse dippers) have worse cardiovascular and kidney outcomes when compared to dippers.[11,12,77–79] Whether the recently reported strategy of evening dosing to produce nocturnal dipping will improve outcomes in CKD patients, as has been described in individuals with essential hypertension, remains to be established.[80–82]

The ERT was not asked to search for evidence of the effectiveness of established anti-hypertensive agents in lowering BP in patients with CKD, since it is generally believed that all such drugs are effective, although the sensitivity in individual patients may vary, as may be the side

effects. Instead, the ERT focused on two issues. Firstly, studies that compared different BP targets were identified. In these studies, only the BP targets were randomized; the protocols varied with respect to the sequence of drugs and escalation of dose. Secondly the ERT searched for studies that included a comparison of different combinations of anti-hypertensive agents. In these studies, only the choice of first-line drug was randomized, with study protocols varying with respect to drug dose, use of concomitant agents and BP thresholds for drug titration (Table 5, see Methods for Guideline Development).

The *KDOQI Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease* (http://www.kidney.org/professionals/KDOQI/guidelines_bp/index.htm)[1] contains details of clinical pharmacology and practical guidance on the use of the various agents to lower BP in CKD patients. Information on CKD- and CVD-related indications, side effects, dosages and contraindications relevant to all commonly used anti-hypertensive agents as well as strategies to improve adherence and warnings regarding the hazards of certain combinations are also noted therein. The Work Group believed that there was insufficient new evidence to warrant rewriting the clear guidance provided in the KDOQI Guideline. However, at the request of the KDIGO Board, the Work Group summarize specific aspects of the use of antihypertensive agents in CKD patients. We outline the information that can be drawn from the known pharmacology of agents or observations in non-CKD patients, emphasizing the difficulty in extrapolating to CKD patients, especially those with advanced CKD.

Given that the prescribed drug regimen commonly involves many medications, it is reasonable to use strategies that might maximize the likelihood of adherence, including the use of cheaper drugs, convenient frequency of dosing and reduction in pill numbers. This can be achieved by prescribing once-daily medication and combination pills (which are simpler to take and in some circumstances may be less expensive than the individual agents) when possible.[83]

Renin–angiotensin–aldosterone system blockers

Because of its pivotal role in regulation of BP, the RAAS system is an obvious target for BP-lowering medications. Although other agents, particularly beta-blockers, interfere with the RAAS pathway, the main RAAS inhibitors are ACE-Is, ARBs, aldosterone antagonists, and DRIs.

ACE-Is and ARBs. ACE-Is block the conversion of angiotensin I to angiotensin II and the degradation of bradykinin. It seems likely that the accumulation of bradykinin leads to persistent dry cough, a recognized side effect which occurs in 5 to 20% of patients on ACE-Is. Angioneurotic edema can occur with both ACE-Is and ARBs, although the relative frequencies and the mechanism are not clear. ARBs act by competitively antagonizing the interaction between angiotensin II and angiotensin receptors and were first introduced as an alternative to ACE-Is in patients who had an ACE-I induced cough.

ACE-Is and ARBs are valuable BP-reducing agents in CKD patients, are indicated if urinary albumin excretion is elevated and are safe to combine with most other BP-reducing agents. Clinically significant hyperkalemia and reductions in GFR can occur in patients receiving ACE-Is or ARBs, particularly in those who have renal-artery stenosis or reduced intravascular volume, or when these agents are used together with NSAIDs, COX-2 inhibitors, or potassium-sparing diuretics. The use of these drugs in women of child-bearing age should be balanced with the risk of pregnancy since they are potentially teratogenic (see Chapter 6).[84,85]

The sequential marketing of ACE-Is first (captopril in 1977) and ARBs later (losartan in 1995) has influenced the design of RCTs involving these drug classes. The first large-scale RCT of RAAS blockade in diabetes involved patients with type 1 disease given captopril. By the time ARBs were introduced, the benefits of ACE-Is (in CKD patients with type 1 diabetes) were well established. Thus RCTs involving ARBs generally targeted individuals with type 2 diabetes. This has led to some bias in the evidence base underpinning recommendations for using ACE-Is or ARBs in the treatment of BP. There is no substantive evidence to suggest that ACE-Is and ARBs differ in their ability to reduce BP in patients with essential hypertension.[86] In most health care settings, ACE-Is are less expensive than ARBs, which may influence the choice between an ACE-I or ARB.

The most prominent BP-related effects of the blockade of angiotensin II by ACE-Is or ARBs are as follows:

- Generalized arterial vasodilatation, resulting in lower BP.
- Vasodilatation of the efferent and afferent glomerular arterioles, particularly the efferent, resulting in decreased intra-glomerular pressure and hence reduction in both GFR and urine albumin excretion. This is believed to result in some degree of long-term renoprotection, at least in patients with albuminuria.[87] On initiation of therapy a reversible reduction in GFR of up to 30% (accordingly a 30% increase in SCr concentration) has been regarded as reasonably attributable to this physiological mechanism. Greater reductions may indicate underlying renal artery stenosis.[1,88] It has been suggested that in advanced CKD, cessation of RAAS blockade may allow an increase in GFR of sufficient magnitude to delay end-stage kidney failure.[23] This concept is further discussed in Chapter 8.
- Reduction in adrenal secretion of aldosterone. In about 50% of subjects prescribed ACE-Is or ARBs, aldosterone production is restored to at least pre-treatment levels over a period of months (a phenomenon termed aldosterone breakthrough).[89] This may explain the efficacy of aldosterone antagonists in patients already taking an ACE-I or ARB.

ACE-Is and ARBs may have other effects, including inhibition of fibrosis and enhancement of vascular and cardiac remodelling. Discussion of these effects, which may

be of relevance to renoprotection, is beyond the scope of this Guideline.

Dose considerations in CKD patients. Most available ACE-Is have active moieties that are largely excreted in the urine. Fosinopril and trandolapril are partially (in general, approximately 50%) excreted by the liver, such that the blood levels are less influenced by kidney failure than levels of other ACE-Is which are predominantly excreted by the kidneys. Since ACE-Is are generally titrated to achieve optimal clinical effect, the mode of excretion is not regarded as a major factor in dosing.[76] If hyperkalemia occurs in CKD patients taking a renal excreted ACE-I, possible interventions include dietary advice, reducing the dose, switching to fosinopril or trandolapril, or adding a potassium-losing diuretic.

All ARBs are substantially excreted by the liver, with the proportion of drug elimination ranging from 40% (in the case of candesartan) to >95% (in the case of irbesartan and telmisartan). As with ACE-Is, the dose in ARBs is usually adjusted according to clinical effect rather than kidney function.[76]

ACE-Is and ARBs should be used with caution or even avoided in certain CKD subgroups, particularly in patients with bilateral renal-artery stenosis or with intravascular fluid depletion, because of the risk of a large reduction in GFR. The normal capacity of the kidney to auto-regulate GFR in the face of fluctuations in BP is impaired in CKD and further compromised by the use of ACE-Is or ARBs. Hypotension (e.g., as a result of hypovolemia or sepsis) may cause an acute decline in GFR in patients with CKD taking ACE-Is or ARBs.[90] Several case series have reported a high risk of acute kidney injury in diabetic patients on an ACE-I or ARB during sepsis[91–93] and when they are used in combination with NSAIDs[94] or diuretics.[95] Reducing the dose or holding off on using ACE-Is or ARBs until recovery is sensible in patients who develop inter-current illnesses that lead to dehydration as a result of diarrhea, vomiting, or high fever.

Indications for ACE-Is and ARBs. In this guideline, ACE-Is and ARBs are recommended for specific groups of CKD patients with increased urinary albumin excretion in which context use of these agents may be associated with better kidney[96] and cardiovascular outcomes.[97] In non-CKD patients, these drugs are indicated for the treatment of heart failure and for use soon after myocardial infarction, stroke, and in patients with high cardiovascular risk.[98–100]

The Oregon Health Resources Commission reported in 2005 on the use of ACE-Is in essential hypertension. No differences were found among various ACE-Is in terms of the BP-lowering effect and serious complications which were independent of gender, age, or African-American heritage.[99] In 2006, the Commission reviewed the evidence for the use of ARBs.[100] It reported that there were no data to suggest that any particular ARB was superior to another in the context of a variety of clinical scenarios, including essential hypertension and high cardiovascular risk; nor was there evidence of any ARB being associated with a higher risk of serious complications or differences in efficacy or side effects regardless of age, race, or gender. In reviewing studies specifically involving patients with CKD, no important differences in the effect of ARBs on BP or side effects were found.

Accordingly, ACE-Is or ARBs might be considered for use in patients with CKD who have heart failure, recent myocardial infarction, a history of stroke, or a high cardiovascular risk. However, it is not possible to make any recommendations for CKD patients in particular, since the data are largely from studies of non-CKD patients. In addition, because CKD patients are at higher risk of side effects, particularly hyperkalemia and reduction in GFR, the use of ACE-Is or ARBs may not have the same risk-to-benefit ratio in CKD patients as in non-CKD populations.

Drug combinations. The antihypertensive and anti-albuminuric effects of ACE-Is and ARBs are complemented by dietary sodium restriction or administration of diuretics.[63,65,66] ACE-Is and ARBs are therefore valuable adjuncts to diuretics for the treatment of high BP and vice versa. Co-administration of beta-blockers and calcium-channel blockers with ACE-Is or ARBs is also acceptable. One recent *post hoc* analysis of a large trial involving hypertensive individuals demonstrated that a combination of an ACE-I (benazepril) and calcium antagonist (amlodipine) was superior to the same ACE-I used with a diuretic (hydrochlorothiazide) in slowing CKD progression.[101]

Patients given NSAIDs, COX-2 antagonists or potassium-sparing diuretics can develop hyperkalemia if these drugs are used in combination with ACE-Is or ARBs. The combination of ACE-Is and/or ARBs with aldosterone-blocking antagonists is an area of current controversy that is covered in more detail below and in Chapter 8.

Aldosterone antagonists. The aldosterone antagonist spironolactone has been in use as a BP-lowering agent since the late 1950s. Prescribed as a diuretic in the treatment of edema and resistant hypertension, it fell into disuse with the advent of more powerful diuretics and antihypertensives. With the high doses initially used (up to 300 mg/day), spironolactone use was associated with side effects, particularly those due to its estrogen-like activity (gynecomastia and menstrual disturbances). Recognition that BP-lowering could be achieved with much lower doses of spironolactone (12.5–50 mg/day) has led to renewed interest in aldosterone antagonists over the past decade.[102–105] As a result, eplerenone, a mineralocorticoid-receptor blocker without estrogen-like effects, has been developed. In CKD, the major emphasis has been on using aldosterone antagonists to reduce urine albumin levels and as an adjunct to other antihypertensive agents in treating resistant hypertension. Aldosterone antagonists are of proven benefit in non-CKD patients with heart failure, including heart failure after myocardial infarction. Because of the risk of hyperkalemia and reduction in GFR, they should be used with caution in CKD patients.

Dose considerations in CKD patients. Impaired renal excretion of native drug or active metabolites of spironolactone and eplerenone and an increased risk of hyperkalemia

may limit their use in patients with CKD. Plasma potassium levels and kidney function should be monitored closely during the introduction of aldosterone antagonists and during intercurrent illnesses, particularly those associated with a risk of GFR reduction, as occurs with dehydration.

Indications for aldosterone antagonists. In patients without CKD, aldosterone antagonists are recommended for the treatment of severe cardiac failure that is resistant to other therapies and for use after acute myocardial infarction complicated by cardiac failure. These agents also have a place in the management of essential hypertension that is resistant to other therapies. It is unclear whether this information can be extrapolated to CKD patients, particularly those with advanced CKD in whom the risks associated with the use of aldosterone antagonists, particularly of hyperkalemia, may be increased.

In patients with CKD, aldosterone antagonists have been shown to decrease urine albumin excretion when added to ACE-I or ARB therapy. In the largest relevant RCT available involving CKD patients with elevated urine albumin levels and type 2 diabetes, 177 patients received eplerenone (either 50 or 100 mg daily) and 91 patients received placebo.[106] The addition of eplerenone to enalapril (20 mg/day) resulted in a reduction in AERs of 40 to 50% by 12 weeks in the eplerenone groups, but by $<10\%$ in the placebo group. The greater reduction in AER in the CKD patients receiving an aldosterone antagonist in addition to an ACE-I or ARB is consistent with the findings of many smaller trials.[103,107,108] Small reductions in GFR and systolic BP have also been reported. Hyperkalemia is a risk, but may have been mitigated by the concurrent use of a thiazide diuretic according to the smaller studies. Thiazide diuretics, however, were not used in the larger RCT cited above and the risk of hyperkalemia was similar among participants receiving enalapril alone and those receiving the combination of eplerenone and enalapril in that trial.[106] It is premature to draw a definite conclusion as to whether aldosterone antagonists—through their anti-albuminuric, anti-hypertensive, or anti-fibrotic effects—reduce the rate of decline in kidney function in the long term. This is an area for future research.[109,110]

Drug combinations. Aldosterone antagonists are potassium-sparing diuretics and thus may be combined with thiazide or loop diuretics that enhance potassium loss in the urine. Great care should be exercised when aldosterone antagonists are combined with ACE-Is, ARBs, or other potassium-sparing diuretics. There is little information regarding the combination of aldosterone antagonists with NSAIDs or COX-2 inhibitors, but as with ACE-Is and ARBs, caution is warranted. Both spironolactone and eplerenone interact with cytochrome P-450, but definitive information regarding any effect on calcineurin inhibitors (CNIs) is not available. Caution is also advised when aldosterone antagonists are combined with other cytochrome P-450–metabolized agents such as verapamil.

Direct renin inhibitors. The first clinically available DRI, aliskiren, was approved by the US Food and Drug Administration (FDA) in 2007. It binds to renin, preventing the conversion of angiotensin I to angiotensin II. Data relevant to DRIs were not available at the time of publication of the *KDOQI Clinical Practice Guidelines on Hypertension and Antihypertensives Agents in Chronic Kidney Disease* in 2004.[1]

Dose considerations in CKD patients. The usual dose of aliskiren is 150 to 300 mg given once daily. The dose is not modified according to kidney function. It has been reported that cyclosporine administration increases the half-life of aliskiren in healthy subjects.[111]

Indications for DRIs. Although approved by the US FDA only for the treatment of hypertension, it is uncertain whether the indications for DRIs will eventually be similar to those of ACE-Is and ARBs.

There has been one large study of aliskiren in CKD patients, in which the drug was used in combination with the ARB losartan in patients who also had type 2 diabetes with nephropathy.[112] A total of 599 patients were randomized to losartan, 100 mg daily, either alone (control group) or plus aliskiren—150 mg daily for 3 months and then 300 mg daily for 3 months. The addition of the 300 mg dose of aliskiren reduced the urinary albumin/creatinine ratio (ACR) by 20% as compared with the use of losartan alone. There were only small differences in BP between the two groups, and no differences between the rates of adverse or serious adverse events. Given the limited data available, the place of DRIs in the management of BP in CKD has yet to be determined. Indeed another trial involving the use of DRI combined with losartan in patients with diabetes and CKD has recently been terminated early due to an increased risk of adverse events and no evidence of benefit in the combination therapy group. Early termination of the Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints (ALTITUDE) trial casts doubt on the future use of DRIs in combination with ACE-Is or ARBs,[113] and very recently the US FDA has counselled against this combination.[114]

Diuretics

Salt and water retention are major factors contributing to high BP in CKD patients and to morbidity and mortality through systemic or pulmonary edema. Thus, diuretics potentially have an important role in the control of hypertension in this clinical setting. The pharmacology of diuretics and indications for their use have recently been reviewed.[115] Given that most CKD patients will require multiple drugs to control elevated BP, thiazides have a role, especially since their only major drawback is a propensity to induce or aggravate hyperglycemia and other features of the metabolic syndrome.[116]

Thiazides. Of the currently available antihypertensive agents, thiazides and thiazide-like diuretics are most often used and have been assessed in many RCTs involving CKD patients, either as the primary investigational agent or as an add-on therapy. Their side-effect profile is well known and their pharmacology has recently been extensively reviewed,[115]

as has their role in treating hypertension.[115,117,118] Although salt and water excretion may initially account for their antihypertensive effect, why they lower BP over the long term is less well understood and may involve direct or indirect vasodilator actions.[115,119] The metabolic side effects (hyperglycemia, hyperuricemia, visceral adiposity) are also not completely understood[119] but should be considered in patients at risk of metabolic syndrome.

There are 2 broad groups of thiazide-type diuretics: thiazides whose names end in 'thiazide,' and thiazide-like agents such as chlorthalidone and indapamide. In recent years, the thiazide diuretics have been used in low doses in treatment of hypertension (hydrochlororthizide 12.5 to 25 mg, bendroflumethiazide 2.5 mg daily). The valid comparison is thus of low dose thiazide versus thiazide-like diuretic. These regimens have been compared in the recent UK National Institute for Health and Clinical Excellence (NICE) guidelines on primary hypertension.[117] There was limited evidence of any differences in BP control, clinical outcomes or cost-effectiveness. NICE recommended that in newly treated primary hypertensives, the thiazide-like diuretics were preferable to the thiazides, based on the larger volume of evidence for efficacy. The relevance of these observations to CKD patients is unclear.

Dose considerations in CKD patients. Although thiazides are excreted by the kidney, no dose adjustment is recommended in patients with reduced GFR. As the GFR falls below about 30–50 ml/min/1.73 m^2, the ability of thiazides to overcome fluid retention is diminished, although their antihypertensive benefit may be preserved, at least according to small, short-term studies in humans.[120] Most clinicians switch to a loop diuretic in patients with CKD 4, particularly if the BP is becoming resistant to therapy or edema becomes a problem.

Drug combinations. Thiazides are often one of the first 2 or 3 drugs used for BP lowering in CKD, particularly if there is edema or if ACE-Is or ARBs have already been prescribed. Thiazides are known to potentiate the effect of other antihypertensive agents, particularly ACE-Is and ARBs[63,66] and may also reduce the risk of hyperkalemia. The inclusion of thiazides in fixed-dose combinations with other antihypertensives is convenient for patients and may improve compliance.[83]

Loop diuretics. Furosemide (also called frusemide), bumetanide, torsemide and ethacrynic acid are the most commonly used loop diuretics, with wide dose ranges and differing pharmacodynamics. In primary hypertension they are effective in the short term[121] but less so than thiazides in the long term.[115] Loop diuretics are particularly useful when treating edema and high BP in CKD 4–5 patients in addition or as an alternative to thiazide diuretics.

Potassium-sparing diuretics. Triamterene and amiloride are usually avoided in patients with CKD because of the risk of hyperkalemia. They are less effective in reducing extracellular fluid volume than thiazides or loop diuretics. Aldosterone antagonists such as spironolactone and eplerenone are discussed separately, above.

Beta-blockers

Beta-blockers are one of the most extensively investigated class of agents, having been used to treat hypertension and CVD for over 40 years. Although all beta-blockers are effective at reducing BP, other issues may influence whether they are appropriate in a given patient and which specific drug is chosen, since beta-blockers vary widely in their pharmacology.[122–124] Specific attention should be paid to beta-blocker accumulation in patients with advanced CKD and to ensuring that the beta-blocker usage is appropriate in targeting a patient's co-morbidities.

Dose considerations in CKD patients. In patients with CKD, the accumulation of beta-blockers or active metabolites could exacerbate concentration-dependent side effects such as bradycardic arrhythmias.[123] Such accumulation occurs with atenolol and bisoprolol, but not carvedilol, propranolol, or metoprolol.[123]

Indications for beta-blockers. A consensus report based on evidence reviewed by the Pharmaceutical Subcommittee of the Oregon Health Resources Commission in 2008 gave an update of the indications for use of beta-blockers in non-CKD patients.[125] The subcommittee concluded that although no particular beta-blocker had been shown to be more effective in reducing BP or alleviating angina than another, in cases of mild-to-moderate heart failure, bisoprolol, carvedilol, and metoprolol succinate reduced mortality and in cases of severe heart failure, carvedilol and metoprolol succinate reduced mortality. After a recent myocardial infarction, acebutolol, carvedilol, metoprolol tartrate, propranolol and timolol all reduced mortality. A recent systematic review and meta-analysis of beta-blockers in CKD[126] endorsed the use of beta-blockers in CKD patients with heart failure but did not provide any definitive specific advice on the their efficacy in preventing mortality, cardiovascular outcomes or renal disease progression in CKD patients without heart failure.

Drug combinations. Beta-blockers have often been combined with diuretics in RCTs and clinical practice.[124,127] There are no theoretical reasons why beta-blockers should not be combined with ACE-Is or ARBs.[128] The combination of atenolol or bisoprolol (which accumulate in CKD patients) with bradycardia-inducing drugs such as non-dihydropyridine calcium-channel blockers is not recommended. The combination of lipophilic beta-blockers (which cross the blood–brain barrier) with other centrally acting drugs such as clonidine may lead to drowsiness or confusion, particularly in the elderly. Again, the relevance of these data to patients with CKD remains uncertain.

Calcium-channel blockers

Calcium-channel blockers are valuable BP-lowering agents in CKD patients, but this class of drugs is very heterogeneous in several respects and the choice of the type of agent used should take into account these differences as well as co-morbidities and other medications the patient is taking.

The major subclasses are the dihydropyridines (e.g., amlodipine, nifedipine and lercanidipine), the non-dihydropyridine benzothiazepines (e.g., diltiazem) and the phenylalkylamines (e.g., verapamil).[129] Dihydropyridines tend to be more selective for vascular smooth muscle (vasodilatation) with less action on the myocardium. Accordingly, the side effects may include fluid retention and ankle edema, which can be problematic in patients with CKD. Dizziness, headache and redness in the face are also common side effects. Non-dihydropyridines have direct effects on the myocardium, including the sinoatrial and atrioventricular nodes and reduce the heart rate and cardiac-muscle contraction.

Calcium-channel blockers also vary in their effects on glomerular arterioles, reflecting differential blockage of T-channel receptors (on the afferent and efferent arteriole) versus L-channel receptors (predominantly on the afferent arteriole). T-channel blockade leads to a reduction in intraglomerular pressure, and accordingly a fall in urine albumin levels, while an increase in the urine albumin level can occur with blockade of L-channel receptors. In general, dihydropyridine calcium-channel blockers act on L-channel receptors, hence have the effect of increasing urine albumin excretion, whereas non-dihydropyridines tend not be associated with this side effect.[130] Later generation dihydropyridines (e.g., manipine, cilnidipine) are less prone to increasing albumin excretion and may even reduce it.

Dose considerations in CKD patients. Most calcium-channel blockers do not accumulate in patients with impaired kidney function, with the exception of nicardipine and nimodipine. Accumulation of these agents may also be due to reduced blood flow to the liver in the elderly.[129] Caution is thus advised when using these two agents in elderly patients with CKD.

Indications for calcium-channel blockers. Calcium-channel blockers are widely used in the treatment of hypertension, angina, and supra-ventricular tachycardia. The Oregon Health Resources Commission report on calcium-channel blockers in 2005 concluded that there was no clear evidence to differentiate the antihypertensive effects of one calcium-channel blocker from another (inadequate evidence for felodipine).[131] Whether these observations can be translated to the CKD population is uncertain.

It is wise to avoid dihydropyridine calcium channel blockers in CKD patients with already increased urinary albumin excretion, particularly if there is not concomitant use of an ACE-I or ARB.[132]

Drug combinations. Fluid retention, seen particularly with dihydropyridines, can be problematic in patients with CKD, such that avoiding other vasodilators may be sensible. The combination of non-dihydropyridines such as verapamil and diltiazem with beta-blockers can lead to severe bradycardia, particularly in patients with advanced CKD if drugs such as atenolol and bisoprolol, (that accumulate in CKD) are used.

Calcium-channel blockers, particularly non-dihydropyridines, interfere with the metabolism and excretion of the CNIs, cyclosporine and tacrolimus, as well as the mammalian target of rapamycin (mTOR) inhibitors, sirolimus and everolimus[76] (Table 2). This is relevant to the treatment of high BP in kidney-transplant recipients, but also in patients with immune-mediated CKD requiring immunosuppression. When such patients are prescribed non-dihydropyridine calcium-channel blockers, careful monitoring of CNIs and mTOR inhibitors blood levels is required if drugs or dosages are changed. Some clinicians use non-dihydropyridine calcium-channel blockers to increase CNI or mTOR inhibitor blood levels and thus reduce cost, particularly in kidney-transplant patients.

Table 2 | Selected calcium-channel blockers

	Class	Accumulate in renal failure	Increase CNI levels	Increase sirolimus levels
Amlodipine	D	N	Y	—
Diltiazem	B	N	Y	Y
Felodipine	D	N	—	—
Isradipine	D	N	—	—
Lercanidipine	D	N	—	—
Nicardipine	D	Y	Y	Y
Nifedipine	D	N	N	—
Nimodipine	—	Y	—	—
Nisoldipine	D	N	—	—
Verapamil	P	N	Y	Y

B, non-dihydropyridine benzothiazepine; CNI, calcineurin inhibitor; D, Dihydropyridine; N, No; P, phenylalkylamine; Y, Yes; —, no data.

Centrally acting alpha-adrenergic agonists

Centrally acting alpha-agonists cause vasodilatation by reducing sympathetic outflow from the brain.[133,134] The main agents in use are methyldopa, clonidine, and moxonidine. Moxonidine was not widely available in 2004 and thus was not reviewed for the *KDOQI Clinical Practice Guidelines on Hypertension and Antihypertensives Agents in Chronic Kidney Disease*.[1] The use of this drug in essential hypertension was extensively reviewed by Fenton at al. in 2006.[133] Dosing of centrally acting alpha-antagonists is limited by side effects, but since they interact minimally with other antihypertensives or immunosuppressants, they are valuable as adjunct therapy for resistant hypertension in CKD patients.

Dose considerations in CKD patients. Doses of methyldopa or clonidine are not generally reduced in patients with impaired kidney function. Moxonidine is extensively excreted by the kidney and accordingly it has been recommended that the dosage (usually 200 to 400 mg daily) should be reduced in the presence of a low GFR.[134] On the other hand, an RCT of moxonidine, 300 mg daily, or the calcium-channel blocker nitrendipine, 20 mg daily, added to an ACE-I or ARB plus loop diuretic in 177 hypertensive CKD patients (GFR by the Cockcroft–Gault equation, <30 ml/min/1.73 m^2) indicated that adverse events occurred in similar proportions of patients treated with moxonidine (50 of 89 [56.2%]) and nitrendipine (46 of 82, [56.1%]), as did those adverse events possibly due to the study drug (moxonidine 28%, nitrendipine 32%), suggesting that although side effects are common, moxonidine can be used in advanced CKD.[135] Common

severe adverse events associated with moxonidine in this RCT were gastrointestinal symptoms, dizziness, headache and tiredness; all of which occurred in between 10 to 15% of the patients receiving moxonidine.

Indications for centrally acting alpha-agonists. Since alpha-agonists do not interact with other commonly used antihypertensive agents, they are valuable as adjunctive therapy for high BP in CKD patients already taking other antihypertensive medications. Because of the side-effect profile, however, caution is advised when using alpha-agonists in the elderly, in patients with advanced CKD and in those taking sedating drugs.

In one large study of non-CKD patients with advanced heart failure, high-dose moxonidine use was associated with increased mortality.[136] How this relates to patients with CKD is unclear. Avoidance is probably wise if overt heart failure is present. Since clonidine can slow pulse rate, this drug should be avoided if bradycardia or heart block is present.

Drug combinations. Combination of alpha-agonists with thiazides is probably advantageous to reduce vasodilatation-induced fluid retention. Combination with other antihypertensive drugs is usually trouble-free, but caution is advised if the agents have similar side effects. Interactions are not common between alpha-agonists and CNIs or mTOR inhibitors.

Alpha-blockers

Alpha-adrenergic blockers selectively act to reduce BP by causing peripheral vasodilatation. Prazosin, doxazosin, and terazosin are the alpha-blockers most commonly used in treatment of hypertension. Alpha-blockers are an adjunctive treatment for elevated BP in CKD patients in whom ACE-Is, ARBs, diuretics, calcium-channel blockers, and beta-blockers have failed or are not tolerated. Alpha-blockers may also be advantageous if symptoms of prostatic hypertrophy are present.

Dose considerations in CKD patients. Alpha-blockers do not require dose modification in cases of kidney failure, since they are excreted via the liver.[4]

Indications for alpha-blockers. Alpha-blockers reduce the symptoms of benign prostatic hyperplasia, which may be a co-morbidity to consider in older men with CKD. In general, alpha-blockers are not considered a first-line choice because of the common side effects of postural hypotension, tachycardia and headache. They should be commenced at a low dosage to avoid a first-dose hypotensive reaction.

Drug combinations. There are few data available about alpha-blocker combinations with other BP lowering drugs. Vasodilatation can lead to peripheral edema, so diuretics are commonly combined with alpha-blockers, although the efficacy of this maneuver has not been studied. Alternatively, a non-selective beta-blocker can be used.

Direct vasodilators

Hydralazine and minoxidil both act by directly causing vascular smooth-muscle relaxation and hence vasodilatation. There have been no important changes to our understanding of these drugs since the publication of the *KDOQI Clinical Practice Guidelines on Hypertension and Antihypertensives Agents in Chronic Kidney Disease* in 2004.[1]

Dose considerations in CKD patients. Hydralazine and minoxidil do not require dose adjustment in patients with impaired kidney function.[4]

Indications for direct vasodilators. Hydralazine has little value in the management of chronically elevated BP in CKD, although it is sometimes used as a parenteral hypotensive agent. Minoxidil is generally used in patients with very resistant hypertension and thus may be helpful in patients with CKD. However, its side effects (e.g., severe fluid retention, headache, tachycardia, hirsutism, and pericardial effusion) limit its use to the most resistant cases.

Drug combinations. Because of the side effects of fluid retention and tachycardia, direct vasodilators (especially minoxidil) are usually combined with a beta-blocker and loop diuretic.

RESEARCH RECOMMENDATIONS

- Salt restriction appears to be a very promising method of reducing BP and the risk of progressive kidney disease and cardiovascular events. Therefore, large scale RCTs assessing the impact of this intervention on these patient-level outcomes are required. Patients with CKD should be included in these trials, given the potential for differences in the risks and benefits of reduced salt intake in these individuals.
- RCTs should be undertaken to evaluate the benefit of weight loss at different stages of CKD.
- RCTs should be undertaken in CKD with and without elevated albumin excretion levels comparing various combinations of RAAS blocking drugs.

DISCLAIMER