Chapter 1: Introduction

Kidney International Supplements (2012) **2,** 343–346; doi:10.1038/kisup.2012.51

There is a strong association between chronic kidney disease (CKD) and an elevated blood pressure (BP) whereby each can cause or aggravate the other. BP control is fundamental to the care of patients with CKD and is relevant at all stages of CKD regardless of the underlying cause. Clinical practice guidelines (CPGs) have been published on this topic by many authoritative bodies over the past decade, the most comprehensive being the National Kidney Foundation's (NKF) *Kidney Disease Outcomes Quality Initiative (KDOQI) Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease*, which was based on evidence collected up to 2001 (http://www.kidney.org/professionals/KDOQI/guidelines_bp/index.htm).[1] The Kidney Disease: Improving Global Outcomes (KDIGO) Board believed that it would be clinically useful to update this CPG to incorporate the evidence gathered since then. KDIGO therefore commissioned an evidence review to include the recent literature and assembled a Work Group with the mandate of writing an updated guideline relevant to an international audience. This KDIGO Guideline, entitled "*Management of Blood Pressure in Chronic Kidney Disease*," is the result of these efforts.

Scope of this guideline

This Guideline has been developed to provide advice on the management of BP in patients with non–dialysis-dependent CKD (CKD ND) (see Reference Keys).

BP. We have avoided using the term 'hypertension' in our title because this implies that there is a BP value above or below which morbidity or mortality changes in a stepwise fashion, hence suggesting that it is possible to set a universal BP target. In reality, it proved difficult to define precise targets appropriate for all CKD subpopulations, consistent with the notion that the 'ideal' BP may differ between patients, once other factors are considered. These factors include specific features of CKD such as the severity of albuminuria or proteinuria, the presence of other risk factors for cardiovascular disease (CVD) and comorbidities. Another reason for our choice of terminology is that agents introduced primarily to treat high BP may have actions that may not be directly linked to BP-lowering (e.g., the anti-albuminuric effects of angiotensin-converting enzyme inhibitors [ACE-Is] and angiotensin-receptor blockers [ARBs]).

Definition of CKD. The Work Group defined CKD according to the standard KDOQI classification system[2] as endorsed by KDIGO.[3]

Populations of interest. The populations covered in this guideline are:

- Adults with CKD ND without diabetes mellitus
- Adults with CKD ND with diabetes mellitus
- Adults with CKD ND who have received a kidney transplant (CKD T)
- Children with CKD ND
- Elderly with CKD ND

The scope of this guideline did not include BP management in patients with dialysis-dependent CKD 5 (CKD 5D) since this has been the topic of a recent KDIGO consensus conference[4] and has been covered by two recent systematic reviews.[5,6] There are other groups of patients with CKD for whom specific recommendations might be welcome, but who are not represented in sufficient numbers in randomized controlled trials (RCTs) to constitute a sufficiently robust evidence base. The evidence review team (ERT) was asked to present the evidence separately for adults with CKD and diabetes, since these individuals constitute the single largest subgroup of CKD patients in the world.

The separation of the evidence base according to diabetes status meant that there were two separate datasets for the Work Group to review. Although the two sets of recommendations had much in common, the Work Group decided that they differed sufficiently in detail to warrant two separate chapters. Adults who received a kidney transplant, children, and the elderly were also thought to deserve dedicated chapters, although the evidence base for each of these subpopulations is rather small.

The Work Group was unable to identify sufficient evidence to make recommendations according to severity (stage) of CKD, although common sense dictates that pharmacological management should differ at least between mild CKD (patients with normal glomerular filtration rate [GFR]) and advanced CKD (patients with low GFR). However, the Work Group did consider the modification of drug dosages and risks related to the various classes of BP-lowering agents in the context of CKD in Chapter 2.

Clearly there are many other populations that could have been considered. CKD patients with glomerulonephritis are the subject of a recent KDIGO Guideline,[7] so they were not considered separately here. Although management of BP in the pregnant CKD patient is an important issue, there is insufficient evidence in this subgroup to allow recommendations to be made.[8] Furthermore, the Work Group did not consider the management of BP in patients with acute kidney injury.

Interventions. Interventions primarily aiming at modifying BP include advice on lifestyle and administration of pharmacological agents that reduce BP. The efficacies of both strategies have been widely studied in the general population with high BP. The pharmacology of anti-hypertensive agents was detailed in the 2004 KDOQI guideline.[1]

Of the available RCTs that met our inclusion criteria, most involved agents interfering with the renin-angiotensin-aldosterone system (RAAS). Accordingly, these agents may be over-represented in this Guideline, and if so, it is because of the availability of the evidence rather than a deliberate focus by the Work Group.

Evidence for interventions

Because CKD is common and BP levels are often elevated in CKD populations, the management of BP in CKD patients could have an enormous global impact. Given that the focus of the Guideline is on management and the comparative effectiveness of various interventions, the preferred and most robust evidence is derived from large-scale RCTs which assessed hard clinical outcomes. The ERT was asked to include RCTs with a minimum of 50 patients in each arm and interventions included pharmacological agents (alone or in combination), lifestyle modifications, and trials assessing various levels of BP control. Outcomes of interest were mortality, cardiovascular events and changes in kidney function including urine albumin or protein excretion.

Reduction in BP, particularly when achieved using agents that interfere with the RAAS, can lead to acute reductions in kidney function and albuminuria; thus the minimal duration of follow-up in RCTs required for their inclusion in the evidence review was set at 1 year for kidney function, cardiovascular outcomes, and mortality and 3 months for urine albumin or protein levels. Because there were so few trials assessing lifestyle modifications, BP reduction was included as an outcome, with the minimum follow-up period set at 6 weeks.

The approach to the evidence review is described in detail in *Methods for Guideline Development*. The ERT conducted a systematic review of RCTs involving individuals with CKD. This was supplemented with published systematic reviews and meta-analyses (which often included smaller RCTs). Work Group members further supplemented this yield with selected RCTs that included individuals at increased risk of CVD but who were not specifically chosen on the basis of having CKD. The Work Group also helped identify RCTs that included CKD subgroups. To a lesser extent, the Work Group made reference to observational evidence from large population studies where evidence from RCTs was perceived to be insufficient.

Not all questions of interest have been the subject of RCTs; some issues do not lend themselves to be studied in this manner. To facilitate further discussion on major issues relevant to management of BP in CKD patients (for which there is some evidence but ongoing controversy remains), the Work Group included a chapter on *Future Directions and Controversies* (Chapter 8). For other issues widely accepted in practice, but not supported by evidence from RCTs, the Work Group wrote ungraded recommendations reflecting the consensus of its members. These ungraded statements are explained in detail in the accompanying narrative.

The Work Group did not wish to provide advice on specific treatment questions for which there was no supporting evidence. By highlighting these gaps in knowledge, we aim to promote further research.

During the preparation of this Guideline, the Work Group was aware that other international organizations were writing new or updating old guidelines that were potentially relevant to the management of BP in CKD patients. The Work Group kept in contact with these other organizations and sought to achieve consistency with their recommendations as much as possible.

Measurement of BP

The Work Group recognized that many reviews on the methodology of BP measurement have been published[9,10] and that this topic was covered in detail in the 2004 KDOQI Guideline.[1] Previous publications have highlighted inconsistencies between conventional office (or clinic) BP measurements and other methods, such as self-measurement of BP at home or ambulatory blood pressure monitoring (ABPM).[11–13] Many recommendations regarding when and how to use ABPM in hypertensive patients not known to have CKD have also been published. Although few studies have assessed the value of ABPM CKD patients, the small, short-term studies that do exist reflect the inconsistency between office BP measurements and other BP measurements and also suggest that ABPM gives a better indication of overall BP and kidney prognosis than office BP measurements.[11–13] Despite this, to date there has only been one large RCT of BP control in CKD patients (all of whom were children) in which ABPM was used as the method for BP assessment.[14] We therefore cannot provide evidence-based recommendations regarding the use of ABPM to evaluate BP in CKD patients but existing evidence is reviewed in Chapter 8.

Since office BP measurements are used in almost all RCTs of interventions that modify BP in CKD, this Guideline can only make recommendations about BP assessed by this method. Because office readings are known to vary from day to day, management decisions should be based on repeated measurements,[15] as emphasized in this guideline by the use of the term 'consistently' (e.g., Recommendation 4.1 … maintain a BP that is consistently $\leq$140 mm Hg systolic …). The term is used simply to imply that the BP has been measured more than once and that there was meaningful agreement between the measurements.

The Work Group also discussed whether to consider pulse pressure and/or pulse wave velocity, measures of arterial compliance that may provide important prognostic information in CKD patients. However, there is a paucity of data from RCTs showing that any particular intervention reliably

alters these measures and subsequently influences mortality or morbidity. Thus the Work Group was not able to make any evidence-based recommendations relating to these measurements. However, these issues are of interest for the future of BP assessment in CKD patients and are discussed in further detail in Chapter 8.

Albuminuria and proteinuria

Some BP-lowering agents are particular effective at reducing albuminuria or proteinuria, suggesting that BP management should differ depending on the amount of albumin or protein in the urine.[16–19] Accordingly, as in the KDOQI 2004 Guidelines and the majority of other CPGs addressing BP control in patients with CKD or diabetes, the Work Group has attempted to stratify treatment effects according to urinary albumin excretion. Based on a recent KDIGO Controversies Conference and data from the CKD Prognosis Consortium, the Work Group used three categories (levels) of albuminuria.[20] Wherever possible, the Work Group modified its recommendations to fit these categories, although since not all RCTs use this classification system, consistency was not achievable. The three categories of urinary albumin excretion are as follows: >300 mg per 24 h (or 'macroalbuminuria'), 30 to 300 mg per 24 h (or 'microalbuminuria'), and <30 mg per 24 h (Table 1). When other measures (such as assessment of proteinuria, ratios of urinary albumin or urinary protein to urine creatinine, or protein reagent strip readings) were used in RCTs, these measures were translated to albumin excretion rates (AERs) per 24 h, recognizing that these converted values are approximations at best. Recommendations and suggestions for interventions based on albumin levels expressed in milligrams per 24 h can also be converted (Table 1).

Table 1 | Relationship among categories for albuminuria and proteinuria[a]

	Categories		
Measure	Normal to mildly increased	Moderately increased	Severely increased
AER (mg/24 h)	<30	30–300	>300
PER (mg/24 h)	<150	150–500	>500
ACR			
(mg/mmol)	<3	3–30	>30
(mg/g)	<30	30–300	>300
PCR			
(mg/mmol)	<15	15–50	>50
(mg/g)	<150	150–500	>500
Protein reagent strip	Negative to trace	Trace to +	+ or greater

ACR, albumin/creatinine ratio; AER, albumin excretion rate; PCR, protein/creatinine ratio, PER, protein excretion rate.

Albuminuria and proteinuria can be measured using excretion rates in timed urine collections, ratio of concentrations to creatinine concentration in spot urine samples, and using reagent strips in spot urine samples. Relationships among measurement methods within a category are not exact.

The relationships between AER and ACR and between PER and PCR are based on the assumption that average creatinine excretion rate is approximately 1.0 g/24 h or 10 mmol/24 h. The conversions are rounded for pragmatic reasons. (For an exact conversion from mg/g of creatinine to mg/mmol of creatinine, multiply by 0.113.) Creatinine excretion varies with age, sex, race and diet; therefore the relationship among these categories is approximate only. ACR <10 mg/g (<1 mg/mmol) is considered normal; ACR 10–29 mg/g (1.0–2.9 mg/mmol) is considered 'high normal.'

The relationship between urine reagent strip results and other measures depends on urine concentration.

[a]Tentatively adopted by KDIGO CKD Work Group.

BP thresholds and targets

Perhaps the most important questions for health care professionals are first, at what BP level should BP-lowering strategies be introduced in CKD patients (i.e., what is the BP treatment threshold?), and second, what BP levels should be aimed for (i.e., what is the BP treatment target?). Although the evidence base for the BP treatment threshold differs from the evidence base for the BP target, we could not find a robust justification to recommend different BP levels for these two parameters. Doing so might also lead to confusion, since we would be recommending two different BP levels possibly with two evidence ratings and would not be able to provide coherent advice for managing patients between the recommended threshold and target BPs.

Studies that have not specifically targeted CKD patients demonstrate that BP is a continuous risk factor for CVD outcomes.[21] BP targets could differ depending on the presence of other CVD risk factors in each patient. This approach contrasts with the 'one size fits all' philosophy that has previously been endorsed. There are far less data in CKD patients to inform the best approach. In RCTs involving CKD patients who are randomized to different BP targets, the achieved differences between groups are usually less than the targeted differences. Intention-to-treat analyses allow conclusions to be drawn based on target BP levels rather than achieved BP levels. The Work Group generally followed this convention and based recommendations on target levels BP levels rather than those achieved in the RCTs. It also considered the evidence derived from RCTs in which patients were not randomized to BP targets but achieved BPs were reported. The logic for using target BP levels in RCTs rather than the achieved BP levels observed as the basis for setting guideline targets has been questioned;[22] this concern is one reason for our conservative approach to BP target setting in this Guideline.

Outcomes

The major outcomes relevant to BP control in CKD patients are kidney disease progression and cardiovascular events (including stroke).

Kidney outcomes. Although it is possible for a diagnosis of CKD to be made in an individual with a normal GFR and AER and even a normal BP (for example on the basis of an imaging study, as in early adult polycystic kidney disease), most patients recruited into RCTs addressing BP and its management in CKD have a reduced GFR or persistently elevated albumin excretion. Entry criteria for RCTs involving

CKD patients are usually based on these parameters, changes in which may form the basis for kidney end points.

Kidney function. Changes in kidney function are important outcomes in clinical trials assessing the effects of various BP-management regimens in CKD patients. Although the most important events are the requirement for renal replacement therapy or death due to kidney failure, many studies have used surrogates such as changes in GFR or the percentage of patients in whom the serum creatinine (SCr) level doubles. Such numerical end points may be particularly relevant in trials that include patients with early-stage CKD, among whom kidney failure and death are uncommon events. One problem with the assessment of such surrogates is that the therapeutic agent used to modify BP may also directly alter kidney function. For example, ACE-Is are known to reduce GFR through a vasodilator effect on the efferent arteriole. This effect may be beneficial in the early stages of CKD when a reduced intra-glomerular pressure is protective, but might be detrimental at a later stage when kidney function is severely compromised and dialysis may be imminent, at which time GFR may increase if ACE-Is are withdrawn.[23] Thus, a drug may modify GFR via a mechanism that does not directly involve changes in systemic BP and the impact of this effect on the patient may vary according to CKD stage. The Work Group bore such considerations in mind when assessing the evidence and viewed consistency in the change of GFR outcomes across various CKD stages as a strong indicator of the benefits of a particular agent on kidney function.

Albuminuria. The level of albuminuria in CKD predicts not only the prognosis with respect to kidney function but also morbidity and mortality from CVD events including stroke.[16–19] Urinary albumin excretion is influenced by BP and by many of the agents used to reduce BP, particularly ACE-Is and ARBs.

The concept of using albuminuria as a surrogate marker for CKD progression and CVD outcomes is widely accepted, with the reduction of urine albumin levels often being regarded as a target for therapy. This would mean that treatment would be escalated to reduce albuminuria to a preferred level, regardless of BP. Treating to an albumin target usually involves an escalation of RAAS blockade, which can be achieved by restricting dietary salt intake, increasing doses of an ACE-I or an ARB, combining the two classes of medication, or by adding a thiazide diuretic, an aldosterone-receptor blocker or a direct renin inhibitor (DRI).

While a strong case has been made for targeting a reduction of albuminuria, particularly with agents that interfere with the RAAS, there have been no large studies in CKD patients reporting long term differences in GFR or CVD outcomes where reduction in urinary albumin levels (regardless of BP) was the primary objective. There is also uncertainty as to whether the dose of a particular agent that is required to achieve BP control is necessarily the same as the dose required for albuminuria reduction.[24] The Work Group thus decided that it was premature to recommend an albuminuria reduction target strategy for all cases of CKD but felt this deserved further discussion in Chapter 8.

Cardiovascular outcomes. Recognition that premature CVD is a major cause of death in CKD has led to CVD risk management becoming a recognized component of the care of the CKD patient. In planning appropriate interventions, one strategy is simply to extrapolate data from CVD outcomes trials in the general population. This approach has been challenged because the benefits of interventions predicted in observational studies[25] are not always observed in RCTs involving CKD patients.[26,27] In CKD-ND patients,[28] unlike CKD patients on dialysis (CKD 5D),[29] a higher BP is generally associated with a higher CVD risk, making BP-lowering an attractive goal in an effort to reduce cardiovascular morbidity and mortality.

Although no RCTs assessing BP lowering agents have been specifically designed or powered to assess cardiovascular event rates as the primary outcome in any group of CKD patients, several studies assessing cardiovascular outcomes have included CKD patients and this information was considered in making the recommendations.

Intended Users of this Guideline

This Guideline is primarily aimed at health care professionals caring for individuals with CKD, including nephrologists, nurses, and pharmacists, as well as at physicians involved in the care of patients with diabetes and primary care providers. The Guideline is not aimed at health care administrators, policy makers, or regulators, although the explanatory text might be of value to these groups and assist in enhancing implementation and adherence to BP-lowering strategies. The Guideline is also not designed to be used in the development of clinical performance measures. Some of the difficulties in implementation and in auditing BP target achievement are discussed in Chapter 8.

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