Chapter 8: Future directions and controversies

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INTRODUCTION

In this chapter, we discuss issues regarding BP management and the use of BP-lowering drugs in CKD patients that are currently the subject of ongoing research or controversy and for which there is insufficient evidence upon which to base a recommendation at this time.

8.1: ASSESSMENT OF BP

The RCTs on which this Guideline is based involved standard office BP measurements, with the exception of the ESCAPE trial in children.[14] In clinical practice BP assessment typically involves measurements made in the clinic or 'office.' In RCTs, the protocols for BP measurement usually require one or more BP readings taken after a period of rest and avoiding prior activities that may have effects on BP. As far as it is possible these protocols should be followed in clinical practice if this evidence is used to guide management. The techniques for office BP measurement and associated problems are well described in the hypertension literature.[10,143,401] There is no reason to believe that office BP measurement should be performed differently in CKD patients than in non-CKD patients, other than a strong emphasis be placed on measuring supine or sitting and standing BP because of the increased likelihood of orthostatic hypotension associated with volume depletion, autonomic neuropathy, older age, and drug effects.[44,45,374,375]

Measuring BP in the general community and in particular, patients with 'essential' hypertension, is becoming increasingly sophisticated. Examples include technologies that assess 'usual' BP as distinct from the BP measured at an office visit and new ways of measuring BP, beyond just systolic and diastolic pressures. Gradually, these advances are being implemented in research and BP management in CKD patients.

Ambulatory BP monitoring and self-monitoring at home. There is a long history of assessing BP by means other than the BP measurement taken at an office visit. The 'gold standard' is automated ABPM, the techniques for which have been well described,[10,143,401] and self-monitoring using automated devices, which is increasingly used. Recommendations and guidelines for the use of ABPM and self-monitoring are accumulating in the hypertension literature (Table 4).

There have been a limited number of studies conducted in CKD patients but data suggest that in CKD, high ABPM systolic pressures, and nocturnal 'non-dipping' (i.e., the absence of a drop in BP during sleep) are associated with increased risks of mortality (as in other populations) and of decline in GFR or kidney failure.[11,77,78] As has been found for non-CKD patients, office BP measurements are commonly overestimates (in the case of white-coat hypertension) or underestimates (in the case of masked hypertension) of 'usual' BP when compared with ambulatory BP assessments.

A recent paper highlights the interest in ABPM in CKD.[79] 436 hypertensive CKD patients were prospectively followed using ABPM and this was shown to be much more accurate in predicting both renal and cardiovascular outcomes than office BP. White coat hypertension was common, and ABPM indicated that non-dipping and reverse dipping of nocturnal BP were particularly predictive of cardiovascular and renal outcomes. Future trials are needed to assess the best means of measuring BP in CKD patients by randomizing patients to ABPM, home BP or office BP directed therapy and to address whether evening dosing to encourage 'dipping' is advantageous as recently demonstrated in non-CKD hypertensive individuals.[80,81]

Given the technical and economic barriers to routine measurement of ambulatory BP, self-BP recording using automated BP devices has been introduced because these give readings that are more in line than with ABPM than those achieved by office BP measurements.[12,402,403]

Self-BP measurement and ABPM are being used increasingly in BP management and the devices for measuring them usually rely on oscillometric assessment of BP at the elbow. Atrial fibrillation and very high pulse pressures can lead to inaccuracies and hence, re-calibration against traditional methods of BP measurement is important.[402] While it is unlikely that self-BP monitoring or ABPM will become part of mainstream CKD montoring in developing countries in the near future, they are likely to become more widely used if further research indicates the value of these techniques in CKD management.

Measurement of pulse pressure and pulse wave velocity. The stiffening of arterial walls that accompanies CKD (as well as aging and chronic high BP) causes a loss of the volume compliance in the large arteries such as the aorta, reducing their ability to effectively buffer the systolic pressure wave generated by the left ventricle and thus resulting in higher systolic BP. In diastole, the loss of elastic recoil leads to a reduced diastolic pressure. These changes together contribute to a higher pulse pressure and faster pulse wave velocity, since the pulse wave travels more rapidly when the larger arteries are less compliant. Measurement of pulse pressure or pulse wave velocity can therefore offer insights into vascular structure and function.[32,373] Studies of pulse pressure or

Table 4 | Existing guidelines on ambulatory BP monitoring (ABPM) and home BP monitoring

Society or authors	Measurement recommendations
British Hypertension Society[406]	Home BP monitoring: Accuracy of at-home recordings can be improved by calibration of the home instrument with a known standard, but even so, a lower threshold for treatment is recommended (i.e., less than 135/85 mm Hg) because of inaccuracies in home measurements and the tendency for home readings to be lower than office readings. ABPM: Recommended levels of normality for ambulatory BP BP levels (mm Hg) Optimal / Normal / Abnormal Daytime: <130/80 / <135/85 / >140/90 Nighttime: <115/75 / <120/70 / >125/75
Japanese Society of Hypertension Guidelines for self-monitoring of BP at home[407]	Home BP monitoring: 1. Arm-cuff devices based on the cuff-oscillometric method that have been validated officially and the accuracy of which has been confirmed in each individual should be used for home BP measurement. 2. The BP should be measured at the upper arm. Finger-cuff devices and wrist-cuff devices should not be used for home BP measurements. 3. Devices for home BP measurement should be adapted to the American Association for Medical Instrumentation standards and the British Hypertension Society guidelines. In addition, the difference between the BP measured by the auscultatory method and the device should be within 5 mm Hg in each individual. The home measurement device should be validated before use and at regular intervals during use. 4. Home BP should be monitored under the following conditions: The morning measurement should be made within 1 h after waking, after micturition, sitting after 1 to 2 min of rest, before drug ingestion, and before breakfast. The evening measurement should be made just before going to bed, sitting after 1 to 2 min of rest. 5. Home BP should be measured at least once in the morning and once in the evening. 6. All home BP measurements should be documented without selection, together with the date, time, and pulse rate. Use of devices with a printer or an integrated circuit memory is useful to avoid selection bias. 7. The home BP in the morning and evening should be averaged separately for a certain period. The first measurement on each occasion should be used for totaling. 8. Home BP values averaged for a certain period ≥135/80 mm Hg indicate hypertension and ≥135/85 mm Hg, definite hypertension. Normotension is defined as less an average BP <125/80 mm Hg and definite normotension as <125/75 mm Hg.
American Society of Hypertension[408]	ABPM: Ambulatory BP monitors measure BP by means of auscultatory or oscillometric methods. Auscultatory monitors use a microphone on the bladder cuff to detect the Korotkoff sounds. The advantage of this technique is that arm movement does not interfere with the recording; however, these monitors are sensitive to background noise. Oscillometric monitors sense arterial pressure vibrations and calculate systolic and diastolic values using an algorithmic approach. They are unaffected by background noise, but arm movement can cause errant readings. Both types of monitors are validated by the British Hypertension Society and the Association for the Advancement of Medical Instrumentation. Patients wear the monitor for a 24-hour period, usually a workday. The monitor is preprogrammed to record BP, usually every 15 to 20 minutes during daytime hours and every 20 to 30 minutes during night-time hours. Patients are instructed to keep an activity log throughout the testing period for evaluation of stress- and activity-related BP changes.
Pickering *et al.*[409]	ABPM: Currently available ambulatory monitors are fully automatic and can record BP for 24 hours or longer while patients go about their normal daily activities. Most monitors use the oscillometric technique. They can be worn on a belt or in a pouch and are connected to a sphygmomanometer cuff on the upper arm by a plastic tube. Subjects are asked to keep their arm still while the cuff is inflating and to avoid excessive physical exertion during monitoring. The monitors are programmed to take a reading every 15 to 30 minutes throughout the day and night. At the end of the recording period, the readings are downloaded into a computer. Standard protocols are used to evaluate the accuracy of the monitors, and approved devices are usually accurate to within 5 mm Hg of readings taken with a mercury sphygmomanometer. The daytime level of ambulatory BP that is usually considered the upper limit of the normal range is 135/85 mm Hg.
The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure[143]	ABPM is warranted for evaluation of white-coat hypertension in the absence of target-organ injury. It is also helpful in patients with apparent drug resistance, hypotensive symptoms with antihypertensive medications, episodic hypertension, or autonomic dysfunction. Ambulatory BP values are usually lower than office readings. Individuals with hypertension have an average BP of >135/85 mm Hg when awake and >120/75 mm Hg during sleep. The level of BP measurement by using ABPM correlates better than office measurements in patients with target organ injury. ABPM also provides data on the percentage of BP readings that are elevated, the overall BP load, and the extent of BP reduction during sleep. In most individuals, BP decreases by 10 to 20% during the night; those in whom such reductions are not present are at increased risk for cardiovascular events. Home BP monitoring: Home measurement devices should be checked regularly for accuracy.
European Society of Hypertension[337,401,403]	1. Refers to http://www.dableducational.org/ for UK available ABPM and home measuring devices. 2. Details proper equipment and technique. 3. Outlines accepted and potential clinical indications for ABPM.
NICE Guideline[117]	Out-of-office BP measurements are now recommended as part of the proper diagnosis of hypertension. ABPM should be offered to confirm the diagnosis of hypertension if two BP measurements during an office consultation are ≥140/90 mm Hg. If ABPM is used, at least two measurements per hour must be taken during waking hours (08:00 to 22:00). The average value at least 14 measurements taken during the waking hours is needed to confirm the diagnosis of hypertension. Home BP monitoring is a suitable alternative to ABPM and requires two consecutive BP measurements a minute apart in the seated position, taken twice daily (usually morning and evening) for at least 4 days (but ideally 7). The first day's measurements are discarded and the average of the remaining measurements are used to confirm a diagnosis of hypertension. Stage 1 hypertension is diagnosed if average BP from ABPM or home monitoring is ≥135/85 mm Hg. When using ABPM or home BP monitoring to assess response to treatment, the target average BP during waking hours should be <135/85 mm Hg for people aged under 80 years and <145/85 mm Hg for people aged ≥80 years.

ABPM, ambulatory blood pressure monitoring; BP, blood pressure.

pulse wave velocity have been widely performed in the general, hypertensive, and diabetic populations as well as to a limited extent, in hemodialysis patients, in whom the correlation of pulse wave velocity with mortality has been well documented.[32,35]

Pulse wave velocity may be increased in early CKD[34,404,405] but it is unclear what this means in terms of CVD risk and kidney-disease prognosis. It is also unclear whether treatment of BP will alter pulse wave velocity in the longer term for CKD 1-5 patients and if so, whether this might influence the prognosis. While sophisticated studies such as pulse wave velocity are unlikely to become widespread in the global CKD community, especially in less economically advanced communities, further research is likely to lead to better use of this tool for assessment of BP related changes in the cardiovascular system in CKD patients and possibly to treatment changes based on pulse wave velocity indices.

8.2: IS THERE AN EVIDENCE-BASED LOWER LIMIT FOR BP REDUCTION?

The Work Group discussed whether it would be preferable to recommend a target range (lowest to highest) for BP rather than just a single target for highest acceptable BP. Although the benefits of lowering BP in CKD have been demonstrated, allowing us to recommend that we should aim for BP consistently $\leq$140/90 mm Hg when albumin excretion is $<$30 mg per 24 hours and $\leq$130/80 mm Hg if albumin excretion is $\geq$30 mg per 24 hours in both non-diabetic (Chapter 3) and diabetic (Chapter 4) adults with CKD ND, we were unable to give any recommendations for a lower BP target level due to a lack of evidence.

There are observational data that support the intuitive notion that excessive BP reduction might be harmful, at least in trials that have not specifically recruited CKD patients. In a cohort of 4071 very elderly ($\geq$80 years) ambulatory American veterans (hence 96.6% males) with hypertension on 1.7 ± 1.2 (mean $\pm$ SD) antihypertensive medication classes, a J-shaped survival curve was noted when the relationship between both systolic and diastolic pressure and survival was examined. The optimum survival was associated with the ranges of diastolic BP between 70–79 mm Hg and systolic BP between 130-139 mm Hg.[43] In another smaller study ($n = 331$) of mortality with 2 year follow-up in elderly hospitalized subjects $>$70 years with vascular disease or hypertension, the longest survival was observed when diastolic BP was in the range 71–80 mm Hg, with a pronounced increase in risk with diastolic BP $\leq$60 mm Hg.[410]

Further evidence to discourage aggressive reduction in BP in high risk groups comes from secondary analyses of outcomes associated with achieved BPs in the context of large RCTs. Such analyses are retrospective in nature and the trials themselves have not specifically recruited (and often excluded) patients with reduced GFR, so they cannot be used to formulate a guideline for a lower BP target in the context of CKD. One example of such a study is a retrospective analysis of the active treatment group of the SHEP trial. In this study, 4736 subjects aged $\geq$60 years with a systolic BP $>$160 mm Hg and diastolic $<$90 mm Hg were randomized to placebo or BP reduction with chlorthalidone with or without atenolol to reduce systolic BP. Perhaps surprisingly, a low diastolic BP on treatment was associated with an increased risk of stroke, coronary heart disease and CVD.[41] Likewise in INVEST, a multi-national RCT comparing verapamil sustained-release and atenolol-based treatment in 22,576 patients with hypertension and CAD, BP control and outcomes were equivalent between the groups, but the risk of the primary outcome (all-cause death, non-fatal myocardial infarction and non-fatal stroke) progressively increased with a BP lower than 119/84 mm Hg, although taken alone, stroke risk did not increase with lower BP. After adjustment for multiple variables the relationship between low diastolic BP and primary outcome persisted.[40] Further analysis of the above association including only the 2699 patients with peripheral artery disease also showed a J-shaped relationship, such that the primary outcome occurred least frequently at a systolic BP of 135-145 mm Hg and a diastolic BP of 60-90 mm Hg, with the effect most strongly related to systolic BP.[411] Stratifying patients into those aged $<$60, 60 to $<$70, 70 to $<$80 and $\geq$80 years and plotting survival versus diastolic BP produced a pronounced J-curve effect with a HR nadir at 75 mm Hg up to 80 years, then 70 mm Hg for subjects $>$80 years. For systolic BP the HR nadir increased with increasing age: 115 mm Hg up to 70 years, 135 mm Hg for 70 to $<$80 years, and 140 mm Hg for $\geq$80 years.[42]

In ONTARGET involving 25,588 patients with atherosclerotic disease or diabetes with organ damage, a J-shaped relationship between on-treatment systolic BP (nadir around 130 mm Hg) and all outcomes except stroke was observed in a retrospective analysis.[412] Data from IDNT showed that a systolic BP below 120 mm Hg was associated with an increased risk of cardiovascular deaths and congestive heart failure, but not myocardial infarction in hypertensive type 2 diabetics.[228]

Finally, in the ACCORD study, while targeting a systolic BP of $<$120 mm Hg rather than $<$140 mm Hg did not reduce cardiovascular outcomes, serious adverse events occurred in 3.3% of the lower BP group compared with 1.3% ($p < 0.001$) in the higher BP target group indicating the potential penalty paid for aggressive BP reduction.[159]

In CKD ND patients, there is observational evidence from two community-based longitudinal studies including 1549 subjects with CKD 3-4. In one study, a J-shaped relationship between stroke and systolic BP was observed, with lowest stroke risk in the range of systolic BP between 120 and 129 mm Hg, and higher risk above and below this.[158] A cohort study of 860 US veterans (comprising mainly men) with CKD (GFR $<$60 and a subset with GFR $<$30 ml/min/1.73 m^2) showed greater mortality when systolic BP was $<$133 mm Hg or diastolic BP $<$65 mm Hg, although it appeared that the association might not be causal but instead related to atherosclerotic CVD as a co-morbidity.[413]

In summary, with respect to a lowest BP target, most of the relevant evidence is observational, derived from retrospective analyses, and nearly all involves non-CKD populations. No studies to date have specifically tested a strategy of

reducing blood-pressure-lowering drug treatment if the BP falls below a certain limit. We anticipate that there would be major practical difficulties in implementing such a practice, particularly in patients with reduced conduit artery compliance and consequent increased pulse pressure (in whom a lower limit for diastolic BP might entail accepting an systolic BP much higher than the current targets). Although the available evidence is enough to support our guideline statements advising caution in those with co-morbidity, we do not consider it is robust enough to allow us to specify a lower limit for either systolic BP or diastolic BP, even though other organizations have done so.[396] Although inferences can be drawn when treatment-related BP is too low, especially in patients with diabetes, the elderly and those with CVD, we are left without a lowest BP target.

The NIH funded SPRINT trial currently recruiting patients in the US may clarify this issue. It will randomize over 7500 patients with systolic BP to targets of <140 mm Hg or <120 mm Hg, deliberately including approximately 1750 patients over 75, and followed for cardiovascular, cognitive and kidney end points over a period of 9 years, commencing 2010.[171,172]

8.3: SHOULD A REDUCTION IN ALBUMINURIA BE A TARGET FOR TREATMENT WITH AGENTS THAT MODIFY BP?

As outlined elsewhere in this Guideline, RAAS intervention is effective in not only lowering BP but also protecting individual patients with CKD from further decline in kidney function. Although the BP-lowering effect of RAAS inhibition contributes to renoprotection, a component of the protective effect may be independent of the effect on BP. Thus, to achieve maximum renoprotection using a RAAS inhibitor, the clinician might consider monitoring the reduction in urine albumin excretion (an 'off target' effect). This is particularly important in macroalbuminuric and microalbuminuric hypertensive subjects with type 2 diabetes, in whom the BP response to RAAS inhibitors may be discordant with the anti-albuminuric response.[414,415] Studies in such patients indicate that those in whom urine albumin was lowered without significant lowering of BP gained some renoprotection, whereas patients who did not have urine albumin lowered in spite of BP-lowering did not have renoprotection.[414] Thus, albuminuria may be an independent factor in renoprotection. In a prospective study supporting this concept, Hou *et al.*[416] detected nearly 50% additional renoprotection with a dose of a RAAS inhibitor titrated to maximally reduce urine albumin levels as compared to a standard dose used for the BP lowering effect.

There have been no RCTs assessing hard renal or cardiovascular outcomes, in which patients have been randomized to different targets of urinary albumin excretion irrespective of BP.

8.4: SHOULD RAAS INHIBITION BE MAXIMIZED IN CKD PATIENTS?

Accepting that RAAS inhibitors may be used to both lower BP and urine albumin excretion, options are available to optimize the albuminuria lowering effect of these agents. For example, it is well recognized that co-administration of a low-sodium diet[417,418] or the addition of a diuretic[63,66,419] enhances the effect of both ACE-Is and ARBs on lowering urine albumin excretion. Such therapeutic combinations make good sense and are unlikely to be associated with harmful side effects.

Whether more aggressive blockade of the RAAS using supramaximal doses of ACE-Is or ARBs is beneficial is less certain. Recently, Burgess et al.[420] showed that increasing the dose of candesartan well beyond the guideline-recommended dose for BP-lowering resulted in further reduction of the urine albumin levels.

The substantial evidence suggesting that RAAS inhibition using ACE-Is or ARBs has renoprotective effects when these agents are used individually has led to the hypothesis that combining the two classes of agents, or adding an aldosterone antagonist or a DRI, may provide additional benefit. Interest in this approach has been increased by the evidence that individuals treated with ACE-Is may have 'aldosterone breakthrough'[89] with angiotensin I to angiotensin II conversion occurring via other pathways[421] and by the fact that there may be other active receptors for angiotensin II[422] that may have a range of roles.

A number of moderate-sized studies, mostly in patients with diabetes, have demonstrated that proteinuria levels may be further lowered by combining ACE-Is and ARBs than by using each agent alone.[423] Aldosterone antagonists may substantially lower proteinuria when used on top of ACE-Is or ARBs.[424] Similarly when the DRI, aliskiren, was added to an ARB,[112] proteinuria was reduced.

The optimism generated by these findings has recently been seriously dampened. The ONTARGET trial did not demonstrate any cardiovascular benefit for dual RAAS blockade (with the ACE-I ramipril and the ARB telmisartan), in a population at high risk of CVD, but did suggest an increased risk of major renal outcomes with dual RAAS blockade.[281] This finding has been questioned for a range of reasons, and it has been suggested that the result may have been different if the population included a greater number of patients with CKD.[425]

The ALTITUDE trial randomized type 2 diabetic participants to receive either aliskiren or matching placebo on top of an ACE-I or ARB[113] and included a large number of diabetic individuals with CKD.[426] Although the results have not been published at the time of writing this Guideline, the trial was recently stopped early due to a low likelihood of ever demonstrating benefit and a suggestion of an increased risk of some adverse outcomes, including non-fatal stroke, renal complications, hyperkalemia and hypotension,[427] resulting in the US FDA counselling against this practice.[114]

As a result, any benefits of combined blockade of the RAAS for clinically important renal outcomes currently remain unproven, and the safety issues should be taken into account prior to using this therapeutic approach.

8.5: SHOULD ACE-IS AND ARBS BE DISCONTINUED IN CKD 5 BECAUSE THEY COMPROMISE RESIDUAL KIDNEY FUNCTION?

It has long been recognized that commencing ACE-Is and ARBs can lead to an acute reduction in GFR that may be

reversed if the dose is reduced or if the drug is discontinued. This phenomenon has been observed in the context of RCTs such as the RENAAL trial. In a *post hoc* analysis of this study, an initial fall in GFR was found to predict better long-term renoprotection.[87] Such acute changes in GFR are likely to reflect the hemodynamic changes that accompany initiation of RAAS blockade.[88,428] However, since a reduction in GFR is not usually considered beneficial, observers have recently questioned the value of commencing or continuing BP-lowering regimens based on an ACE-I or ARB in elderly patients with advanced CKD and have specifically suggested that use of such agents in CKD 4–5 patients may compromise residual kidney function or even accelerate its rate of decline in both diabetic[429] and non-diabetic patients.[430]

This opinion is based on uncontrolled observations and is contrary to the observations made from the RENAAL RCT in patients approaching renal replacement therapy.[431] For example in one such observational study, discontinuation of ACE-Is and ARBs in 52 patients with CKD 4–5 was followed by a greater than 25% increase in the GFR in 61.5% of patients, and a greater than 50% increase in 36.5% of patients.[23] An RCT that specifically randomized patients with advanced CKD to benzapril or placebo did not support this.[192] The study reported that 112 predominantly CKD 4 patients with a mean GFR of 26 ml/min/1.73 m^2 receiving benzapril had a lower risk of doubling of SCr, kidney failure, or death compared with the same number of patients receiving placebo. A small study of 60 peritoneal dialysis patients showed better preservation of residual kidney function among patients randomized to ramipril as compared to no treatment.[432]

Thus, the current evidence does not support the discontinuing ACE-Is and ARBs in patients with advanced CKD in an effort to preserve residual kidney function, although hyperkalemia or hypotension may be a specific reason for discontinuation in some patients.

8.6: ETHNICITY, RACE, AND GENES

In this Guideline, the individualization of BP control is emphasized, yet specific advice to tailor therapy according to ethnicity, race, or genetic influences is not available. In lieu of such advice, we have drawn on RCTs specific to various racial and ethnic populations: African-American, Chinese, Japanese, Pakistani, and European whites (sometimes from a single country). We have generalized the observations derived from these ethnicity- or race-specific RCTs to management advice applicable to all ethnic and racial groups. However, there is good reason—but not good evidence—to believe that ethnicity, race, and genotype influence elevated BP and CKD, with familial aggregation and ethnic–racial disparities in both conditions. Currently, it is difficult to disentangle ethnic–racial disparities from social, economic, and environmental disparities.

The evidence for ethnic or racial influence on CKD is mainly epidemiological. The incidence of kidney failure requiring dialysis is higher in a wide variety of non-white groups (African-American, Asian, Native American, Native Australian, and Pacific Islander) than in white groups of European heritage in North America, Europe, and the Asia–Pacific region.[366,433–435] Hypertension is also more common, develops earlier in life, and manifests with a higher average BP among African-Americans than whites in the United States.[436]

Although profound environmental and socioeconomic issues are clearly involved, information is gradually being gathered that enlightens us about some of the links among genetics, high BP and kidney disease in the African-American population.[437] Genetic variance in the non-muscle myosin heavy chain 9 gene (*MYH9*) was reported to be partly responsible for progressive kidney disease in hypertensive African-Americans.[438] This might provide a rationale for lower BP targets in hypertensive African-Americans than other racial groups,[439] especially in African-Americans with genetic variation in the *MYH9* gene. More recently, polymorphisms in the apolipoprotein L-1 gene (*APOL1*), which is located immediately upstream to *MYH9*, has been implicated in this process, with the *APOLI* G1 and G2 alleles associating with focal segmental glomerulosclerosis in African-Americans.[440] Intriguingly, these variants seem to confer resistance to *Trypanosoma brucei rhodesiense*, which may explain the persistence of this seemingly otherwise disadvantageous gene in West Africans, but this hypothesis does not clarify the association between *APOL1* and focal segmental glomerulosclerosis.

Epidemiological evidence is suggestive of many other ethnic–racial differences among individuals with CKD. In addition to the differences in the prevalence of types of kidney diseases in different groups, there appear to be differences in the rates of CKD progression, in the effects of BP control on CKD progression, in BP responses to various antihypertensive regimens, and in cardiovascular risk associated with a particular BP level. Outlining this evidence is beyond the scope of this Guideline, but clearly the scientific community is currently only scratching the surface of the links among BP, CKD, race, ethnicity, genes, and epigenetics. In the future evidence may become available regarding how to modify BP control in CKD according to an individual's genetic profile, or ethnic or racial background. In the meantime, we must pay greater attention to socioeconomic and environmental issues related to ethnicity or race, which are more immediately amenable to modification.

8.7: BARRIERS TO IMPLEMENTATION

Although several guidelines on BP management in CKD have been published, BP management in CKD patients is often suboptimal and audit studies suggest that the target readings are not achieved in many patients.[441] The reasons why it is challenging to implement recommendations and to achieve target BP in CKD (and other) patient populations are multiple and complex, but are likely to include the issues listed below. Because of these uncertainties we cannot suggest that the recommended BP targets in this Guideline should be

used as performance measures in the management of CKD patients.

The credibility of the guideline is questioned. Not all clinicians agree with the currently recommended BP targets, at least not for all of their patients. The evidence supporting current BP targets in CKD has been challenged, reinforcing clinicians' concerns.[22] However, surveys have shown that less stringent BP targets, such as 160/90 mm Hg, are also not regularly achieved.[441] The BP targets recommended in this guideline are higher than those in some previous publications and it remains to be seen whether this will result in a higher proportion of CKD patients achieving them.

The trial data are not directly relevant to a real world setting. There are few systematically collected data to support the notion that BP control cannot be achieved in most patients. However several important issues need to be considered when extrapolating from clinical trials to a 'real world' setting. Firstly, patients recruited into RCTs are selected for characteristics that increase the likelihood of BP control. These include a lack of co-morbidities, an absence of previous adverse reactions to the BP-modifying agents used in the trial, good BP control during a run-in or washout period and high motivation, reflected by the patients' willingness to enroll. Secondly, patients participating in trials are often micro-managed in specialized clinics, where frequent reinforcement and pill-counting increases the likelihood of adherence to the drug regimen. Thirdly, patients who drop out because of drug-related side effects or non-adherence are usually accounted for in intention-to-treat analyses and the overall proportion of dropouts is not often reported (although may be 10% or more of the recruited population). Finally, although the mean achieved BP is often close to the intended target, the SD of the reported BP measurements is often large, suggesting that the recorded values in many patients are well above the mean and hence well above the target.[22] Only rarely is the actual number of patients not achieving the target BP reported. Taken together, these factors indicate that the proportion of patients with CKD in whom BP cannot be controlled to a specified target may be much higher than indicated by the data derived from RCTs.

Patients do not adhere to the treatment. The reasons why patients do or do not adhere to medical advice are believed to depend in part on cost–benefit analysis by the patients themselves. This is particularly relevant to the use of BP-modifying drugs that do not provide immediately perceivable improvement in quality of life or relief of symptoms, yet have immediately observable negative effects in terms of expense and inconvenience, even if there are no adverse side effects. The literature contains many reports of poor adherence to BP-modifying drug regimens and suboptimal BP control in CKD patients is known to be associated with poor adherence to medication.[442]

BP fluctuates. In a usual clinical setting, if a BP target is set, a clinician will gradually increase the number of drugs prescribed to a given patient until this target is achieved. The regimen will not then be altered again unless several BP readings are above (sometimes well above) that target. Because BP fluctuates, there is a good chance that a proportion of the subsequent BP readings will inevitably be above a previously achieved target. One way to circumvent this problem is to set a threshold level for treatment that is lower than the desired target. This strategy has been used in several health care recommendations, including the WHO nutrition goals and the 1997 NKF–Dialysis Outcomes Quality Initiative Hemodialysis Adequacy guideline. As previously stated and in line with several previous guidelines on BP management in CKD, we have set the same values for the threshold for treatment and desired target systolic and diastolic levels. We emphasize the value of checking for consistency by using repeated BP measurements to direct therapy and believe that this strategy will improve target attainment.

BP is measured infrequently. Traditionally, BP control is audited by measuring the BP in a patient or a group of patients on just one occasion. In an individual patient, the BP can be better assessed by means of repeated clinical measurements over a period of time or by more sophisticated techniques such as home self-measurement of BP or ABPM. Evaluating guideline implementation in a group of patients is difficult, as repeated or more sophisticated measurements are not possible in everyone. We have insufficient knowledge of what proportion of patients at any one time will have a BP level above the target value, even when guidelines have been closely followed and adherence has been high. In a *post hoc* analysis of a large RCT of essential hypertension, a single elevated office BP reading in a patient with previously well controlled BP was unlikely to indicate a persistent loss of BP control, but rather reflect day-to-day variation.[443]