

A European Renal Best Practice (ERBP) position statement on the Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for the Management of Blood Pressure in Non-dialysis-dependent Chronic Kidney Disease: an endorsement with some caveats for real-life application

Francis Verbeke¹, Elisabeth Lindley², Luc Van Bortel³, Raymond Vanholder¹, Gérard London⁴, Pierre Cochat⁵, Andrzej Wiecek⁶, Denis Fouque^{7,8} and Wim Van Biesen^{1,9}

¹Renal Division, Department of Internal Medicine, Ghent University Hospital, Ghent, Belgium, ²Renal Division, Leeds Teaching Hospitals, NHS Trust, Leeds, UK, ³Heymans Institute of Pharmacology, Ghent University, Ghent, Belgium, ⁴Service d'Hémodialyse, Hôpital F.H. Manhès, Fleury-Mérogis, France, ⁵Service de Pédiatrie, Centre de Référence des Maladies Rénales Rares, Hospices Civils de Lyon and Université de Lyon, Lyon, France, ⁶Department of Nephrology, Endocrinology and Metabolic Diseases, Medical University of Silesia, Katowice, Poland, ⁷Department of Nephrology, Hôpital Edouard Herriot, 69003 Lyon, France, ⁸Université Lyon 1, INSERM U 870, Lyon, France and ⁹Methods Support Team ERBP, Renal Division, Ghent University Hospital, Ghent, Belgium

Correspondence and offprint requests to: Wim Van Biesen, Methods Support Team ERBP, Renal Division Ghent University Hospital, De Pintelaan 185, 9000 Ghent; E-mail: guidelines@ERA-EDTA.org

ABSTRACT

Developing guidelines on a subject as broad as hypertension is difficult, especially when the guidance relates to hypertension in the chronic kidney disease (CKD) population. The Kidney Disease: Improving Global Outcomes Guideline Development Group has applied a rigorous methodology in reviewing all available evidence, and their recommendations are consistent with the evidence-based approach. As a result, the European Renal Best Practice endorses most of its recommendations. However, the Work Group feels that some additional advice could help clinicians in daily practice: (i) individualization of treatment should be taken into account, especially (cardiovascular) co-morbidities, age, gender and race; (ii) side-effects, such as postural dizziness should be monitored closely, particularly in elderly, diabetics and patients with arterial stiffness; (iii) the importance of salt restriction should not be neglected; (iv) although angiotensin-converting enzyme inhibitors (ACE-Is) and angiotensin receptor blocker (ARBs)

remain a cornerstone in the management of hypertension, and especially cardiovascular protection, in some particular situations such as in advanced CKD and in patients without proteinuria, their role is less well defined; (v) as most CKD patients need more than one antihypertensive drug to achieve blood pressure control, the specific (renal) (dis)advantages of other classes than ACE-I or ARB should be taken into account.

Keywords: chronic kidney disease, European Renal Best Practice, guideline, hypertension

CHAPTER 1: INTRODUCTION

The 'Kidney Disease: Improving Global Outcomes' (KDIGO) guideline for the management of hypertension in chronic kidney disease (CKD) [1] was published in *Kidney International* in 2012. Developing guidelines on a subject as broad as hypertension is difficult. The task is particularly complex

when the guidance relates to hypertension in the CKD population and is intended to be applicable worldwide. The KDIGO Guideline Development Group (GDG) has applied a rigorous methodology in reviewing all available evidence and delivered an impressive piece of work. The recommendations, which are summarized at the beginning of the document, are consistent with the evidence-based approach. As a result, the European Renal Best Practice (ERBP) Work Group, brought together to review the KDIGO guideline from the European perspective, endorses most of its recommendations. However, the Work Group feels that in some areas the guideline lacks advice that could help clinicians in daily practice. This position statement highlights and expands on certain elements of the rationale following each recommendation. It also includes some comments on the treatment of specific conditions and patients that, whilst not based on randomized controlled trials (RCTs), may still be relevant because of biological plausibility or common sense.

A guideline should never be used as a cookbook. Recommendations, even when based on high-level evidence, should always be considered in terms of their suitability for the individual patient. As the overall evidence level of the recommendations in the KDIGO guideline is low (almost 60% are level D or ungraded), the KDIGO GDG stress that the guideline should be used as 'guidance' in clinical decision-making. It is not intended to define a standard of care applicable for all patients.

As the ERBP Work Group endorses most of the recommendations, they are not repeated in the text but summarized in

Table 1. Acronyms and the characteristics of studies mentioned in the discussion below are listed in Table 2.

CHAPTER 2: LIFESTYLE AND PHARMACOLOGICAL TREATMENTS

General strategies and lifestyle modification

In general, the KDIGO GDG did not rely on evidence from the general hypertension literature, except in a few instances such as in the sections on general strategies and lifestyle modification. The KDIGO GDG points out that checking for postural hypotension, encouraging a healthy lifestyle and individualizing treatment should be part of good medical practice. As these common sense aspects of treatment are too often neglected, it is worth emphasizing them in a separate recommendation. Some very important aspects of 'individualization' need to be highlighted.

No distinction is made regarding ethnicity or gender. It is well-known that calcium channel blockers lower blood pressure more effectively than most other antihypertensive drugs in black patients [2], and there seems to be no reason to assume that this would not be the case in black CKD patients. However, angiotensin-converting enzyme inhibitor (ACE-I) may still be advocated in this population to decrease overall cardiovascular risk or when there is proteinuria.

Many patients with advanced CKD have vascular calcification, and are at risk of low diastolic blood pressure when aiming at 'normal' systolic blood pressure. For these patients,

Table 1. Summary of KDIGO recommendation statements

Chapter	Number	Intervention (threshold)	Target	Grading	
(2) Lifestyle and pharmacological treatments					
General strategies	2.1	Individualize of targets and agents according to age, CVD, comorbidities, risk of CKD progression, retinopathy (DM) and tolerance of treatment		Not graded	
	2.2	Inquire about postural dizziness	Check for postural hypotension regularly	Not graded	
Lifestyle modification	2.3.1	Achieve/maintain healthy weight	BMI 20–25 kg/m ²	1D	
	2.3.2	Lower salt intake	<90 mmol/day (<2 g/day) of sodium	1C	
	2.3.3	Exercise Programme	≥30', 5×/week	1D	
	2.3.4	Limit alcohol intake	≤2 drinks/day (male); ≤1 drink/day (female)	2D	
(3/4) CKD patients without/with diabetes (DM–/DM+)					
	DM–/DM+	Ualb (Uprot) ^a	BP threshold ^b	BP target ^c	DM–/DM+
	3.1/4.1	<30 (<150)	>140/90	≤140/90	1B/1B
		Agent: no recommendation			
	3.2; 3.3/4.2	≥30 (≥150)	>130/80	≤130/80	2D; 2C/2D
	3.4; 3.5/4.3; 4.4	Agent: ACE-I or ARB			2D; 1B/2D; 1B
(5) Kidney transplants					
	5.1	Any	>130/80	≤130/80	2D
	5.2	Agent: time after transplantation, use of calcineurin inhibitors, albuminuria, comorbidities			Not graded
(6) Children					
	6.1/6.2	Any	>90th percentile ^d	≤50th percentile ^d	1C/2D
	6.3	Agent: ACE-I or ARB			2D
(7) Elderly					
	7.1	<ul style="list-style-type: none"> • Tailor, age, co-morbidities, other therapies • Gradual escalation • Close attention to adverse events: electrolyte disorders, acute deterioration in kidney function, orthostatic hypotension and drug side effects 			Not graded

^aUlb, albuminuria; Uprot, proteinuria; in g/24 h or g/g urinary creatinine.

^bBP, blood pressure (mmHg); should be consistently above the systolic or diastolic threshold.

^cBP, blood pressure (mmHg); should be consistently at or below the systolic and diastolic goal.

^dThresholds and targets for mean arterial pressure, percentiles for height, age and sex.

Table 2. Study acronyms and characteristics (to convert creatinine from mg/dl to $\mu\text{mol/l}$, please multiply by 88.4)

Study	Disease and inclusion criteria	Renal function	Age (years)	Intervention	n	FU (years)	Primary end point
RENAAL	Diabetic nephropathy (type 2 diabetes); UACR ≥ 300	Screat 1.3–3.0 mg/dL	31–70	Losartan versus placebo	1513	3.4	Doubling Screat, ESRD or death
ALLHAT	Stage 1 or 2 hypertension + ≥ 1 other CV risk factor	Screat < 2.0 mg/dL	≥ 55	Chlorthalidone, amlodipine, lisinopril or doxazosin	33 357	4.9	Fatal coronary heart disease or non-fatal MI
ESCAPE	CKD + 24-h MAP > 95 th percentile or antihypertensive medication	CKD II–IV	3–18	Intensified versus conventional BP control (fixed dose ramipril + other antihypertensives)	468	5.0	Time to 50% \downarrow GFR or ESRD
HYVET	Hypertension (systolic BP ≥ 160 mmHg)	Screat ≤ 1.7 mg/dL	≥ 80	Indapamide versus placebo + perindopril versus placebo to target BP 150/80 mmHg	3845	2.1	Fatal or non-fatal stroke

n, number of patients; FU, follow-up; UACR, urinary albumin-to-creatinine ratio; Screat, serum creatinine; ESRD, end-stage renal disease; CV, cardiovascular; MI, myocardial infarction; MAP, mean arterial pressure; GFR, glomerular filtration rate; BP, blood pressure; RENAAAL, reduction of end points in NIDDM with the angiotensin II antagonist losartan; ALLHAT, Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial; ESCAPE, Effect of Strict Blood Pressure Control and ACE Inhibition on the Progression of CRF in Pediatric Patients; HYVET, Hypertension in the Very Elderly Trial.

it is particularly important to look for signs of organ hypoperfusion such as postural dizziness or chest pain due to coronary hypoperfusion.

Black patients have a higher muscle mass than those of other races and men usually have more muscle than women, therefore defining a healthy weight only with BMI at 20–25 kg/m^2 may not be justified. A measure of abdominal fat mass, such as waist circumference, might be more useful [3]. The observed reverse epidemiology, where higher BMI is associated with lower mortality in patients with advanced CKD and are on haemodialysis, makes it unclear whether advocating a BMI $< 25 \text{ kg/m}^2$ is warranted in these patients.

Finally, the recommendation on lowering salt intake to < 90 mmol per day deserves particular attention, as hypertension in CKD should be considered predominantly secondary to a reduced capability of the kidney to handle salt loading.

Blood pressure measurement and targets

Methodological issues of blood pressure measurement in CKD are comparable to those in the general population and therefore were not covered in detail in the KDIGO guideline. Nevertheless, one should bear in mind some important aspects of how blood pressure should be measured when interpreting the recommendations. As almost all RCTs evaluated treatment effects using ‘office’ blood pressure readings, which have been demonstrated to have substantial spontaneous variability over time, the word ‘consistently’ in the guideline statements (see Table 1) is of great importance. Blood pressure should be measured more than once during the same visit, with an interval of at least 1–2 min. Where possible, measurements should be made on more than one occasion and for both arms when the patient is seen for the first time.

Ensuring that blood pressure is consistently high when diagnosing hypertension will help avoid treatment of patients with occasional hypertension (e.g. due to the white coat effect). Home or ambulatory blood pressure monitoring may be more representative of ‘real-life blood pressure’. The UK’s National Institute of Health and Clinical Excellence (NICE) recommends confirming true hypertension with ambulatory or home monitoring before starting or increasing anti-hypertensive agents [4]. However, RCTs using these methods for

blood pressure assessment are still scarce. Target blood pressure values are also significantly (at least 5–10 mmHg) lower for these approaches, a point that should also be communicated clearly to patients who monitor their blood pressure at home.

The term ‘consistently’ also appears in the recommendation statements for achieving a given blood pressure target with treatment. The ERBP Work Group is uncertain whether this is appropriate, as it implies that patients should have a blood pressure below the indicated target at all times and in all situations. This is probably not what is intended as it negates the existence of a Gaussian distribution of blood pressure readings in an individual patient. This conflicts with the recommended approach to diagnosis, where it is acknowledged that some variation is expected. The ERBP Work Group suggests that treatment should aim ‘to achieve a blood pressure that is below a target in resting conditions most of the time’.

Another often-neglected aspect of blood pressure management is the time factor. Hypertension is a chronic condition and the longer hypertension exists, the longer it should take to obtain the desired target. Rapid correction of blood pressure should be avoided as the arterial system adapts to a higher pressure by remodelling. The autoregulation curve shifts towards a higher pressure load, making patients more vulnerable to the side effects of low blood pressure. This is especially important in CKD where, as stated earlier, vascular stiffness is frequent.

Finally, one should be aware that oscillometric blood pressure measurements may be erroneous in patients with advanced arteriosclerosis and arterial stiffness [5].

Choice of blood pressure lowering agents

ACE-Is and ARBs. As in many other guidelines, ACE-Is and ARBs receive a prominent position in the KDIGO recommendations on the management of hypertension in CKD, particularly in patients with proteinuria. There is a predominance of available evidence for this drug class, induced by a wide industry interest, and, as a consequence, provision of funding for RCTs. However, uncertainty still remains on whether the superiority of ACE-Is and ARBs is not simply a reflection of better blood pressure control rather than a class effect.

There remains substantial controversy on whether or not ACE-Is and ARBs can or should be combined. The KDIGO GDG does not provide specific advice on this issue, but does recommend that this topic should be further explored in future studies. The NICE guideline on hypertension [4] explicitly states that ACE-Is and ARBs should not be combined. The ERBP Work Group considers the NICE guidance to be reasonable, as some large trials point to increased risk of harm (hyperkalaemia) when blocking the renin–angiotensin–aldosterone axis at different levels [6, 7] and studies proving any benefit from this strategy are lacking. For the same reason, also the combination of direct renin inhibitors with ACE-Is or ARBs cannot be recommended. Of note in the European context is that the European Medicine Agency started a review of the risks of combining inhibitors of the rennin–angiotensin system in May 2013 (EMA/291202/2013).

Another interesting area of controversy is the benefit versus the potential harm to the residual renal function of initiating or continuing ACE-Is and ARBs in patients with CKD stages 4–5. In Chapter 8 (Section 8.5), the KDIGO GDG argues that current evidence does not support discontinuation of these agents. This is based on a *post hoc* analysis of the RENAAL study [8] (Table 2) and an RCT in Chinese non-diabetic CKD 4 patients [9], which showed a favourable effect on renal outcome and mortality when treating these patients with an ARB and ACE-I, respectively. However, one has to question the generalizability of these studies taking into account the more careful selection and closer follow-up of patients in RCTs, which minimizes the risk of serious adverse events such as dangerous levels of hyperkalaemia, acute deterioration of kidney function or hypotension. In both RENAAL and the Chinese RCT, the patients were relatively young (mean age 60 years and 45 years, respectively) and were moderately hypertensive (systolic blood pressure around 154 and 152 mmHg, respectively) at baseline, giving a blood pressure and safety margin for ACE-Is/ARBs. In contrast, a >25% increase in estimated glomerular filtration rate (eGFR) in 62% of patients and a >50% increase in 37% of patients was seen on stopping the ACE-I/ARB in an observational study [10] in older patients (mean age 73 years) with lower blood pressure (134/69 mmHg) and more severe CKD (average eGFR 16 mL/min). This suggests that consideration should be given to stopping ACE-I/ARB in patients with advanced CKD when there are no other hard indications for these agents (such as heart failure), especially in patients with renovascular disease (excluded from RCTs) or when discontinuation of the drug may enable the start of renal replacement therapy to be postponed or avoided.

As the majority of CKD patients needs more than one drug to control blood pressure, other classes also deserve some comments.

Calcium-channel blockers. In addition to ACE-Is and ARBs, non-dihydropyridine calcium channel blockers have been shown to reduce proteinuria [11, 12]. In contrast, dihydropyridines completely abolish renal autoregulation [13], which is already impaired in CKD, and may thus aggravate proteinuria when used as a single agent. In the opinion of the ERBP Work Group, non-dihydropyridine calcium channel

blockers can be used as a valid additive or alternative to ACE-Is or ARBs in proteinuric patients. The use of dihydropyridines is not advisable in this situation, without concomitant use of an ACE-I or ARB.

Beta-blockers. In the NICE guideline, beta-blockers are no longer considered as a first-choice agent for the treatment of hypertension in the general population [4]. However, the question arises whether this is only a case against atenolol, the most frequently used comparator in RCTs. It was shown over 20 years ago that once daily atenolol does not provide a 24-h antihypertensive effect in a substantial number of patients. The patient can be prone to high blood pressure levels, and possibly also to beta-blocker withdrawal effects, for several hours per day [14]. It is not clear whether the negative effects seen with atenolol and older short-acting beta-blockers are due to beta-blockade or to the lack of sustained beta-blockade. In addition, classical beta-blockers have less effect on central blood pressure than other antihypertensive drugs, which may be an alternative explanation for their inferior effect on hard end points as put forward by the CAFÉ-ASCOT study [15]. However, beta-blockers are not a homogeneous class of drugs and some compounds like celiprolol, carvedilol and nebivolol have vasodilating properties and do not share the negative properties described above. Apart from its vasodilating and long-acting properties for a similar antihypertensive effect, nebivolol lowers heart rate less compared with atenolol [16], which may be advantageous when it is combined with a non-dihydropyridine calcium channel blocker like diltiazem.

In patients with advanced CKD and a high risk of sudden death, beta-blockers might provide beneficial effects in addition to blood pressure lowering by attenuating sympathetic hyperactivity and preventing ventricular arrhythmias in the setting of increased adrenergic stimulation [17, 18].

Diuretics. Hydrochlorothiazide (HCTZ) is the most widely used thiazide-type diuretic, often at doses of 12.5–25 mg daily as a component of fixed-dose combination products. Nevertheless, in the NICE guideline [4], preference is given to agents with a thiazide-like action, such as chlorthalidone and indapamide, for reasons that may also be relevant to the CKD population. Hard outcome data of HCTZ only exist for doses ≥ 25 mg per day, the dose at which also metabolic side effects become significant, while more evidence for efficacy exists for the thiazide-like agents. Chlorthalidone is 1.5–2 times more potent than HCTZ and has a longer duration of action [19]. In the ALLHAT study [20], the largest RCT in hypertension including >30 000 patients, chlorthalidone 12.5–25.0 mg/day was equally effective as amlodipine or lisinopril in preventing fatal coronary artery disease or non-fatal myocardial infarction. In the Hypertension in the Very Elderly Trial (HYVET) [21], antihypertensive treatment with indapamide (with or without perindopril as optional add-on) in 3845 patients aged ≥ 80 years conferred a 30% reduction in the rate of fatal or non-fatal stroke as well as a 23 and 21% reduction in cardiovascular and all-cause mortality. The combination of indapamide and perindopril also reduced the risk of stroke in another large multicentre trial [22]. Compared with HCTZ,

indapamide has a neutral effect on blood glucose and lipids [23], but a more pronounced potassium-depleting effect [24], which might be convenient when it is combined with ACE-Is or ARBs, especially in CKD.

Loop diuretics are particularly useful for the treatment of hypertension in advanced CKD (Stages 4–5) since fluid overload is almost always a major contributing factor in this situation. Dosing should be sufficiently high, taking into account the reduced glomerular filtration in renal failure and the intratubular protein binding of the drug in the case of proteinuria.

For the use of spironolactone, the KDIGO GDG does not provide clear guidance, except the recommendation that its place as an add-on therapy should be explored in further studies. This viewpoint seems reasonable to the ERBP Work Group, and several trials in this regard are currently running.

Other treatment modalities

Recently, renal denervation has been forwarded as a means to lower blood pressure. This technique is in its early stages of development, and evidence on its longer term effects on hard outcomes such as progression of renal function, cardiovascular end points or mortality is limited. The ERBP Work Group suggests that this technique should only be offered in the setting of a well-controlled randomized trial.

CHAPTERS 3 AND 4: BLOOD PRESSURE MANAGEMENT IN ADULT CKD PATIENTS WITHOUT AND WITH DIABETES

In many charts and scoring systems developed to assess total cardiovascular risk, the presence of CKD (Stage 3 or higher) or diabetes categorizes the patient into the highest risk group, irrespective of the level of other risk factors. In previous guidelines, this has been the rationale for recommending lower thresholds and targets for the treatment of cardiovascular risk factors including dyslipidaemia and hypertension. The recommendations were not different for patients with or without diabetes, with macroalbuminuria or microalbuminuria or for different stages of CKD.

In the new KDIGO blood pressure guideline, the presence or absence of microalbuminuria (or the equivalent as proteinuria) has become the principle criterion on which to stratify target blood pressure. For instance, KDIGO currently recommends a threshold of 140/90 mmHg for all CKD patients without microalbuminuria, including those with diabetes and/or advanced CKD (Stage 3 or higher). This is at variance with most existing guidelines that recommend a lower target in such patients. The use of the patient's measured albuminuria to guide blood pressure management fits well with the concept of individualized therapy, although it is acknowledged that this is not the only factor to take into account. The KDIGO GDG stresses that factors discussed in Chapter 2, such as age and cardiovascular co-morbidities, should also be considered. It should also be stressed that only pre-treatment albuminuria is considered here and not its evolution over time, with or without treatment.

CHAPTER 5: BLOOD PRESSURE MANAGEMENT IN KIDNEY TRANSPLANT RECIPIENTS

In keeping with the KDIGO guideline for kidney transplant recipients, the recommended blood pressure target is $\leq 130/80$ mmHg based on observational data, hence the 2D grading. However, the ERBP Work Group questions whether this is a realistic goal and whether 'one size fits all'. In an unselected cohort of renal transplant patients from two tertiary hospitals in Belgium recruited to a study of the predictive values of arterial stiffness [25], only 37.5% achieved this target with a median number of two antihypertensive drugs (personal data). Moreover, 20% of the cohort were older than 65 years, which would also categorize these patients in the scope of the hypertension recommendation for the elderly (see below), and 31% had a history of cardiovascular disease.

The choice of blood pressure lowering agent in this population is not straightforward. ACE-Is and ARBs are often avoided in the first months after transplantation because they can cause a rise in serum creatinine due to haemodynamic effects, which may be difficult to distinguish from acute rejection. Calcium channel blockers (particularly the non-dihydropyridine subclass), on the other hand, may affect immunosuppressive drug levels such as calcineurin and mTOR inhibitors.

CHAPTER 6: BLOOD PRESSURE MANAGEMENT IN CHILDREN WITH CKD

For adults, the KDIGO GDG recommends the same blood pressure levels for the threshold for starting treatment and for blood pressure targets. For children, it is recommended that blood pressure lowering treatment should be started when blood pressure is above the 90th percentile for height, age and sex, but to a blood pressure target of ≤ 50 th percentile. This will lead to confusion regarding the treatment of children whose blood pressure is between these two limits. In children, ACE-Is or ARBs are suggested as first-line blood pressure-lowering drug, irrespective of the level of proteinuria. The ERBP Work Group suggests that this recommendation may be inappropriate, particularly when there is no significant proteinuria, as the evidence is derived from a single RCT (Effect of Strict Blood Pressure Control and ACE Inhibition on the Progression of CRF in Pediatric Patients [26]). In this trial, both arms received a fixed maximum dose of ramipril so that the potential superiority of ACE-I treatment cannot be determined.

CHAPTER 7: BLOOD PRESSURE MANAGEMENT IN ELDERLY PERSONS WITH CKD

The HYVET trial [21] has had an important impact on hypertension guidelines, providing evidence to positively recommend anti-hypertensive drug treatment in patients aged 80 years or older. A large prospective meta-analysis, published in the same year as HYVET, showed that patients aged under or

over 65 years gain a similar benefit from an achieved blood pressure reduction. These data counter the nihilistic idea that treating hypertension in the elderly without substantial comorbidity is not worth the effort. The HYVET study population, however, was not a (typical) CKD population as patients with a serum creatinine of >1.7 mg/dL (>170 μmol/L) were excluded. In addition, HYVET only recruited patients without cardiovascular disease and in good general condition. Furthermore, it is worth noting that the achieved blood pressure in the intervention arm was 145/79 mmHg, well above the traditional 140 mmHg target for systolic blood pressure. The results of HYVET can thus not be directly generalized to elderly patients with CKD. Two recent RCTs in Asiatic elderly populations failed to show a benefit of strict blood pressure control (systolic blood pressure <140 mmHg) when compared with achieving a target systolic blood pressure of 140–150 mmHg. Treatment should thus be individually tailored to match potential benefits and harms especially in this frail and elderly population. As a general rule, attempts should be made to treat high blood pressure in the elderly, but only when this treatment is well tolerated and considered safe. Postural dizziness for example can lead to falls and associated fractures, which carry a high mortality risk in themselves. As long as the debate on the J-shaped diastolic blood pressure–risk curve is ongoing [27], the lowering of diastolic blood pressure when attempting to decrease high systolic blood pressure should be considered. Particular caution is required in patients with isolated systolic hypertension and coronary artery disease, both highly prevalent in CKD.

CONCLUSION

The KDIGO GDG reviewed all available evidence on the management of hypertension in CKD patients in a rigorous and transparent way. The recommendations were made after applying stringent criteria for data selection and grading the evidence. The ERBP Work group endorses the spirit of the recommendation statements. However, the Work Group also wants to draw attention to a number of considerations that enhance the clinical relevance of the guideline:

- Individualization of treatment is felt to be crucial, taking into account (cardiovascular) co-morbidities, age, gender and race.
- Postural hypotension should be monitored closely, particularly in elderly, diabetics and patients with arterial stiffness.
- The importance of salt restriction is stressed.
- Although ACE-Is and ARBs remain a cornerstone in the management of hypertension, their use remains controversial in some particular situations such as in advanced CKD and in patients without proteinuria.
- As most CKD patients need more than one antihypertensive drug to achieve blood pressure control, the specific (renal) advantages of other classes than ACE-I or ARB should not be neglected.

- The level of albuminuria/proteinuria has become the principal criterion on which to stratify target blood pressure, irrespective of diabetes status or CKD stage, but without neglecting other important individual factors mentioned in the general strategies section.
- Optimal blood pressure thresholds and targets in elderly CKD patients, a large and growing population, remain to be determined.

ACKNOWLEDGEMENTS

Among the authors, R.V., G.L., E.L., P.C., A.W., D.F. and W.V. B. are members of the ERBP Advisory Board. Other members of the ERBP Advisory Board are D. Abramovicz, J.B. Cannata, A. Covic, K.U. Eckardt, O. Heimbürger, K.J. Jager, S. Jenkins, E.J. Lindley, F. Locatelli, G. London, A. Marti, G. Spasovski, J. E. Tattersall, C. Wanner and C. Zoccali. This document has been submitted for comments to, and approved by, the Advisory Board of ERBP.

CONFLICT OF INTEREST STATEMENT

F.V. and L.V.B.: none declared. The declarations of R.V., G.L., P.C., A.W., D.F. and W.V.B. can be found at www.European-renal-best-practice.org.

REFERENCES

1. KDIGO Blood Pressure Work Group. KDIGO clinical practice guideline for the management of blood pressure in chronic kidney disease. *Kidney Int* 2012; 2(Suppl.): 337–414
2. Brewster LM, van Montfrans GA, Kleijnen J. Systematic review: antihypertensive drug therapy in black patients. *Ann Intern Med* 2004; 141: 614–627
3. Alberti KG, Eckel RH, Grundy SM *et al*. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation* 2009; 120: 1640–1645
4. National Clinical Guideline Center. The clinical management of primary hypertension in adults. Commissioned by the National Institute of Health and Clinical Excellence. *Hypertension Clinical Guideline 127* 2011 (NICE CG 127), 2011. <http://publications.nice.org.uk/hypertension-cg127/guidance#diagnosing-hypertension-2>
5. van Popele NM, Bos WJ, de Beer NAM *et al*. Arterial stiffness as underlying mechanism of disagreement between an oscillometric blood pressure monitor and a sphygmomanometer. *Hypertension* 2000; 36: 484–488
6. Yusuf S, Teo KK, Pogue J *et al*. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med* 2008; 358: 1547–1559
7. Parving HH, Brenner BM, McMurray JJ *et al*. Cardiorenal end points in a trial of aliskiren for type 2 diabetes. *N Engl J Med* 2012; 367: 2204–2213
8. Remuzzi G, Ruggenenti P, Perna A *et al*. Continuum of renoprotection with losartan at all stages of type 2 diabetic nephropathy: a post hoc analysis of the RENAAL trial results. *J Am Soc Nephrol* 2004; 15: 3117–3125
9. Hou FF, Zhang X, Zhang GH *et al*. Efficacy and safety of benazepril for advanced chronic renal insufficiency. *N Engl J Med* 2006; 354: 131–140
10. Ahmed AK, Kamath NS, El KM *et al*. The impact of stopping inhibitors of the renin-angiotensin system in patients with advanced chronic kidney disease. *Nephrol Dial Transplant* 2010; 25: 3977–3982

11. Smith AC, Toto R, Bakris GL. Differential effects of calcium channel blockers on size selectivity of proteinuria in diabetic glomerulopathy. *Kidney Int* 1998; 54: 889–896
12. Bakris GL, Weir MR, Secic M *et al*. Differential effects of calcium antagonist subclasses on markers of nephropathy progression. *Kidney Int* 2004; 65: 1991–2002
13. Griffin KA, Picken MM, Bakris GL *et al*. Class differences in the effects of calcium channel blockers in the rat remnant kidney model. *Kidney Int* 1999; 55: 1849–1860
14. Neutel JM, Schnaper H, Cheung DG *et al*. Antihypertensive effects of beta-blockers administered once daily: 24-hour measurements. *Am Heart J* 1990; 120: 166–171
15. Williams B, Lacy PS, Thom SM *et al*. Differential impact of blood pressure-lowering drugs on central aortic pressure and clinical outcomes: principal results of the Conduit Artery Function Evaluation (CAFE) study. *Circulation* 2006; 113: 1213–1225
16. Zanchetti A. Clinical pharmacodynamics of nebivolol: new evidence of nitric oxide-mediated vasodilating activity and peculiar haemodynamic properties in hypertensive patients. *Blood Press Suppl* 2004; 1: 17–32
17. Neumann J, Ligtenberg G, Klein II *et al*. Sympathetic hyperactivity in chronic kidney disease: pathogenesis, clinical relevance, and treatment. *Kidney Int* 2004; 65: 1568–1576
18. Bleyer AJ, Hartman J, Brannon PC *et al*. Characteristics of sudden death in hemodialysis patients. *Kidney Int* 2006; 69: 2268–2273
19. Carter BL, Ernst ME, Cohen JD. Hydrochlorothiazide versus chlorthalidone: evidence supporting their interchangeability. *Hypertension* 2004; 43: 4–9
20. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 2002; 288: 2981–2997
21. Beckett NS, Peters R, Fletcher AE *et al*. Treatment of hypertension in patients 80 years of age or older. *N Engl J Med* 2008; 358: 1887–1898
22. PROGRESS Collaborative Group. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. *Lancet* 2001; 358: 1033–1041
23. Ambrosioni E, Safar M, Degaute JP *et al*. Low-dose antihypertensive therapy with 1.5 mg sustained-release indapamide: results of randomised double-blind controlled studies. European study group. *J Hypertens* 1998; 16: 1677–1684
24. Krum H, Skiba M, Gilbert RE. Comparative metabolic effects of hydrochlorothiazide and indapamide in hypertensive diabetic patients receiving ACE inhibitor therapy. *Diabet Med* 2003; 20: 708–712
25. Verbeke F, Marechal C, Van LS *et al*. Aortic stiffness and central wave reflections predict outcome in renal transplant recipients. *Hypertension* 2011; 58: 833–838
26. Wuhl E, Trivelli A, Picca S *et al*. Strict blood-pressure control and progression of renal failure in children. *N Engl J Med* 2009; 361: 1639–1650
27. Messerli FH, Panjra GS. The J-curve between blood pressure and coronary artery disease or essential hypertension: exactly how essential? *J Am Coll Cardiol* 2009; 54: 1827–1834

Received for publication: 3.5.2013; Accepted in revised form: 22.6.2013