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

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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.

### Table 1. Summary of KDIGO recommendation statements

<table>
<thead>
<tr>
<th>Chapter</th>
<th>Number</th>
<th>Intervention (threshold)</th>
<th>Target</th>
<th>Grading</th>
</tr>
</thead>
<tbody>
<tr>
<td>(2) Lifestyle and pharmacological treatments</td>
<td>General strategies</td>
<td>2.1</td>
<td>Individualize of targets and agents according to age, CVD, comorbidities, risk of CKD progression, retinopathy (DM) and tolerance of treatment</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lifestyle modification</td>
<td>2.2</td>
<td>Inquire about postural dizzinessCheck for postural hypotension regularly</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.3.1</td>
<td>Lower salt intake &lt;90 mmol/day (&lt;2 g/day) of sodium</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.3.2</td>
<td>Exercise Programme ≥30', 5×/week</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.3.3</td>
<td>Exercise Programme ≥30', 5×/week</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.3.4</td>
<td>Limit alcohol intake ≤2 drinks/day (male); ≤1 drink/day (female)</td>
<td></td>
</tr>
<tr>
<td>(3/4) CKD patients without/with diabetes (DM−/DM+)</td>
<td>DM−/DM+</td>
<td>3.1/4.1</td>
<td>Ualb (Uprot)a BP thresholdb BP targetc</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&lt;30 (&lt;150) &gt;140/90 ≤140/90</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Agent: no recommendation</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.2; 3.3/4.2</td>
<td>≥30 (≥150) &gt;130/80 ≤130/80</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Agent: ACE-I or ARB</td>
<td></td>
</tr>
<tr>
<td>(5) Kidney transplants</td>
<td>5.1</td>
<td>Any &gt;130/80 ≤130/80</td>
<td></td>
<td>2D</td>
</tr>
<tr>
<td></td>
<td>5.2</td>
<td>Agent: time after transplantation, use of calcineurin inhibitors, albuminuria, comorbidities</td>
<td></td>
<td>Not graded</td>
</tr>
<tr>
<td>(6) Children</td>
<td>6.1/6.2</td>
<td>Any &gt;90th percentilea ≤50th percentiled</td>
<td></td>
<td>1C/2D</td>
</tr>
<tr>
<td></td>
<td>6.3</td>
<td>Agent: ACE-I or ARB</td>
<td></td>
<td>2D</td>
</tr>
<tr>
<td>(7) Elderly</td>
<td>7.1</td>
<td>Tailor, age, co-morbidities, other therapies</td>
<td></td>
<td>Not graded</td>
</tr>
</tbody>
</table>

*Ualb, albuminuria; Uprot, proteinuria; in g/24 h or g/g urinary creatinine.

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

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

*Thresholds and targets for mean arterial pressure, percentiles for height, age and sex.
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/m² 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 kg/m² 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.

### Table 2. Study acronyms and characteristics (to convert creatinine from mg/dl to µmol/l, please multiply by 88.4)

<table>
<thead>
<tr>
<th>Study</th>
<th>Disease and inclusion criteria</th>
<th>Renal function</th>
<th>Age (years)</th>
<th>Intervention</th>
<th>n</th>
<th>FU (years)</th>
<th>Primary end point</th>
</tr>
</thead>
<tbody>
<tr>
<td>RENAL</td>
<td>Diabetic nephropathy (type 2 diabetes); UACR ≥300</td>
<td>Screat ≥1.3–3.0 mg/dl</td>
<td>31–70</td>
<td>Losartan versus placebo</td>
<td>1513</td>
<td>3.4</td>
<td>Doubling Screat, ESRD or death</td>
</tr>
<tr>
<td>ALLHAT</td>
<td>Stage 1 or 2 hypertension ≥1 other CV risk factor</td>
<td>Screat &lt;2.0 mg/dl</td>
<td>≥55</td>
<td>Chlorthalidone, amlodipine, lisinopril or doxazosin</td>
<td>33357</td>
<td>4.9</td>
<td>Fatal coronary heart disease or non-fatal MI</td>
</tr>
<tr>
<td>ESCAPE</td>
<td>CKD + 24-h MAP &gt;95th percentile or antihypertensive medication</td>
<td>CKD II–IV</td>
<td>3–18</td>
<td>Intensified versus conventional BP control (fixed dose ramipril + other</td>
<td>468</td>
<td>5.0</td>
<td>Time to 50% ↓ GFR or ESRD</td>
</tr>
<tr>
<td>HYVET</td>
<td>Hypertension (systolic BP ≥160 mmHg)</td>
<td>Screat ≤1.7 mg/dl</td>
<td>≥80</td>
<td>Indapamide versus placebo + perindopril versus placebo to target BP 150/80</td>
<td>3845</td>
<td>2.1</td>
<td>Fatal or non-fatal stroke</td>
</tr>
</tbody>
</table>

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.
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 RENAL 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), respectively. 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 amilor dine 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.

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 ≤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 ≤50th 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
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.

**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.

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