NEPHROLOGY

Nephrology **19** (2014) 53–55

Original Article

Commentary on the KDIGO Clinical Practice Guideline for the management of blood pressure in chronic kidney disease

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Accepted for publication 7 October 2013.
Accepted manuscript online 15 October 2013.

doi:10.1111/nep.12168

Elevated blood pressure is an important modifiable risk factor for both cardiovascular disease (CVD) and progression to end-stage kidney disease (ESKD).[1] Much time and effort in chronic kidney disease (CKD) clinics is spent on measuring blood pressure, deciding whether to escalate treatment, and which agent to use. Blood pressure is therefore an essential topic for the Kidney Disease Improving Global Outcomes (KDIGO) group[2] to tackle. Their Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease, published in *Kidney International* in December 2012,[3] makes 21 recommendation statements based on the available evidence presented by the Tufts Medical Centre-based Evidence Review Team (summarized in 62 supplemental tables).

The KDIGO Blood Pressure Guideline illustrates some of the challenges of writing evidence-based guidelines, which are: (i) distilling a complicated clinical issue into a practical guideline statement that can be implemented; (ii) adjudicating the quality of evidence for each statement; and (iii) remaining consistent within the guideline and with guidelines for other topics.

GUIDELINE SUMMARY

This KDIGO Guideline deals with patients with CKD who do not require dialysis and includes chapters on kidney transplant recipients, children and the elderly. Nine of the 21 recommendation statements are contained in two separate chapters regarding CKD patients according to diabetes status. Blood pressure in patients receiving dialysis was discussed at a KDIGO Controversies Conference that resulted in no recommendation statements but many recommendations for research.[4] The key recommendations for non-dialysis CKD are:

- Treat adult patients without albuminuria to keep office blood pressure consistently ≤140/90 mmHg (with and without diabetes);
- Treat adult patients with any level of albuminuria to keep office blood pressure consistently ≤130/80 mmHg, and include an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) in the treatment regimen (with and without diabetes);
- Treat adult kidney transplant recipients to keep office blood pressure consistently ≤130/80 mmHg;
- Treat children with an ACEi or ARB if blood pressure is consistently >90th percentile, aiming for systolic and diastolic readings ≤50th percentile for age, sex and height.

COMMENTARY

This KDIGO Guideline provides a more rigorous analysis of the evidence for a lower target blood pressure (i.e. 130/80 *vs* 140/90 mmHg) in patients without proteinuria than most other guidelines (Table 1).[5–11] The Evidence Review Team performed a systematic review of blood pressure targets and found eight reports of three trials that randomized 2272 patients with CKD to different blood pressure targets but could not generate summary estimates as proteinuria and outcome definitions were too dissimilar between the trials.[12] In diverging from most other guidelines, the KDIGO Work Group considered the nature of the endpoints (predominantly renal), that subgroup analyses of two of the trials demonstrated no benefit in the groups without proteinuria, possible adverse effects of antihypertensive therapy and reduced patient adherence to therapy when more agents are required to reach a lower target. For patients with proteinuria, the KDIGO Work Group recommended the lower target

Table 1 The KDIGO Blood Pressure in chronic kidney disease (CKD) Guideline, current Australian and New Zealand guidelines (ANZ) and other international (INT) guideline statements regarding goal blood pressure in CKD†

	No diabetes			Diabetes		
ACR:	Normal	Micro	Macro	Normal	Micro	Macro
KDIGO 2012[3]	140/90 (1B)	130/80 (2D)	130/80 (2C)	140/90 (1B)	130/80 (2D)	130/80 (2D)
ANZ						
KHA-CARI[6]	140/90 (1B)	130/80 (1B)	130/80 (1B)	130/80 (1B)	130/80 (1B)	130/80 (1B)
NHF Aus 2008[8]	130/80	130/80	125/75‡	130/80	130/80	125/75
NZ Guidelines Group 2012[10]	130/80	130/80	130/80	130/80	130/80	130/80
NVDPA 2012[9]	140/90	130/80	130/80	130/80	130/80	130/80
International						
JNC VII 2003[5]	130/80	130/80	130/80	130/80	130/80	130/80
NICE CG73[11]	140/90	140/90	130/80‡	130/80	130/80	130/80
UK Renal Association 2011[7]	140/90 (2C)	140/90 (2C)	130/80 (2C)	130/80 (2C)	130/80 (2C)	130/80 (2C)

†Grade for evidence in parentheses where stated are according to the GRADE system. ‡Recommendation if proteinuria >1 g/day (not 300 mg/day). ACR, albumin to creatinine ratio; GRADE, Grading of Recommendations Assessment, Development and Evaluation; KDIGO, Kidney Disease Improving Global Outcomes.

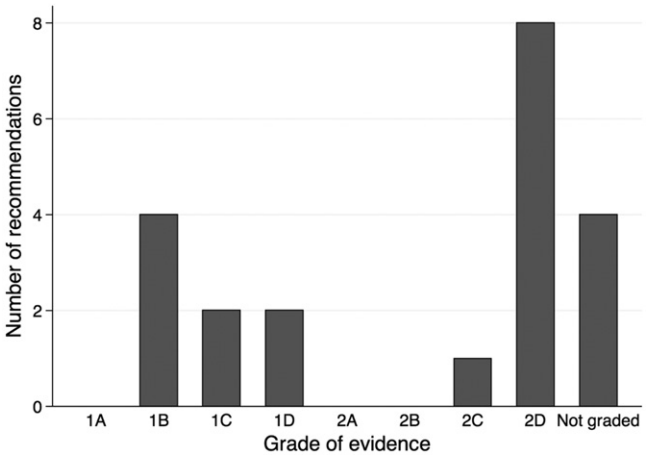

Fig. 1 Number of KDIGO guideline recommendations[3] by grade of evidence†. KDIGO, Kidney Disease: Improving Global Outcomes. †Using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.

of ≤130/80 mmHg, albeit with lower levels of evidence given that this was based on post-hoc analyses of subgroups with proteinuria in two of the trials[13,14] included in the systematic review.

Sound evidence regarding treatment of blood pressure in CKD, as evaluated by the KDIGO Work Group, appears to be lacking (Fig. 1). No '1A' recommendation is made in this guideline and the predominant grading for the statements is '2D'. Given that evidence for '2D' statements is considered to be 'very low' in quality and the estimate of effect 'often will be far from the truth',[3] this should be of concern to physicians managing patients with CKD and stimulate interest in conducting randomized controlled trials (RCT) to further clarify what blood pressure to target in which patients.

While we clearly do not have enough RCT data to underpin this guideline, has this guideline group been particularly severe in its grading of the evidence? The evidence behind the statements for patients with microalbuminuria or overt proteinuria is graded 2D and 2C using the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE)' tool but the recent KHA-CARI guideline on Early Chronic Kidney Disease grades the evidence for a similar statement as 1B[6] (Table 1). Furthermore, an RCT is considered to be a 'High' level of evidence in the GRADE system but the guideline statements regarding blood pressure targets and agents in the chapter on children are graded 2D. The guideline statements are based on a single RCT, the 'Effect of Strict Blood Pressure Control and ACE Inhibition of Progression of CRF in Paediatric Patients (ESCAPE)' trial.[15] This trial demonstrated that intensified blood pressure control in children, targeting a mean arterial pressure below the 50th percentile, delayed progression to doubling of serum creatinine or ESKD, with a hazard ratio of 0.65 (95% confidence interval 0.44–0.94, $P = 0.02$) compared with usual blood pressure control. Although this was a large, well-designed RCT without serious limitations and rated by the Evidence Review Team to be of 'Good' quality for this outcome, the Work Group 'downgraded' the evidence because it was based on a single trial in a predominantly Caucasian population. In contrast, the first statement regarding kidney transplant recipients recommends a blood pressure target of ≤130/80 mmHg and grades the evidence 2D, the same as for blood pressure in children. However, this '2D' is based on observational data only as there has not been an RCT in kidney transplant recipients comparing blood pressure targets. The rigour applied to interpreting the data for the adult CKD blood pressure targets (Chapters 3 and 4) has not been applied to kidney transplant recipients (Chapter 5). The most likely reason is what is stated in the text: that a blood pressure target has already been stated in another KDIGO Guideline.[16] The KDIGO Management of Blood Pressure in CKD Work Group state that there is no new data to contradict the previous statement, although they reduced the grade from

2C to 2D. Consistency is not just a problem for KDIGO, as management of blood pressure permeates many areas of nephrology and therefore, many guidelines. For example, the KHA-CARI Guideline for the Detection, Prevention and Management of Early Chronic Kidney Disease, which recommends blood pressure targets[6] (Table 1) was preceded by five different guidelines that are now 'out of date' and three guidelines that remain current, all of which make statements about issues covered in the KDIGO BP Guideline (see http://www.cari.org.au/ckd_prevent_list_published.php accessed 15/7/2013).

The KDIGO Clinical Practice Guideline on the Management of Blood Pressure in CKD makes reasonable statements about the management of blood pressure in CKD and is less accepting of the evidence for lower blood pressure targets than previous guidelines. By providing a blood pressure target for most patient groups, they are able to be implemented by clinicians. This guideline is useful to illustrate the paucity of evidence in a fundamental area of nephrology practice but highlights the difficulties of maintaining consistency in the grading of that evidence for a topic that transcends different areas of nephrology practice and therefore appears in different guidelines.

ACKNOWLEDGEMENT

I thank Dr Elisabeth Hodson of the Centre for Kidney Research, The Sydney Children's Hospital Network (Westmead), for reviewing the Paediatric Chapter and for her comments on this manuscript.

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