Methods for guideline development

AIM

The overall aim of this project was to develop an evidence-based CPG for the use of BP-lowering agents in individuals with CKD. The guideline consists of recommendation statements, rationale, and a summary of systematically generated evidence on relevant pre-defined clinical topics.

OVERVIEW OF PROCESS

The development process for the KDIGO *Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease* included the following steps:

- Appointing Work Group members and the ERT.
- Discussing process, methods, and results.
- Developing and refining topics.
- Identifying populations, interventions or predictors, and outcomes of interest.
- Selecting topics for systematic evidence review.
- Standardizing quality assessment methodology.
- Developing and implementing literature-search strategies.
- Screening abstracts and retrieving full-text articles on the basis of pre-defined eligibility criteria.
- Creating data extraction forms.
- Extracting data and performing critical appraisal of the literature.
- Grading the methodology and outcomes in individual studies.
- Tabulating data from individual studies into summary tables.
- Grading quality of evidence for each outcome across studies, and assessing the overall quality of evidence across outcomes with the aid of evidence profiles.
- Grading the strength of recommendations on the basis of the quality of evidence and other considerations.
- Finalizing guideline recommendations and supporting rationales.
- Sending the guideline draft for peer review to the KDIGO Board of Directors in December 2010 and for public review in July 2011.
- Publishing the final version of the guideline.

The Work Group, KDIGO Co-Chairs, ERT, and KDIGO support staff met for three 2-day meetings for training in the guideline development process, topic discussion, and consensus development.

Commissioning of Work Group and ERT

The KDIGO Co-Chairs appointed the Work Group Co-Chairs, who then assembled the Work Group of domain experts, including individuals with expertise in internal medicine, adult and pediatric nephrology, cardiology, hypertension, pharmacology, epidemiology, and endocrinology. The Tufts Center for Kidney Disease Guideline Development and Implementation at Tufts Medical Center in Boston, Massachusetts, USA, was contracted to conduct systematic evidence review and provide expertise in guideline development methodology. The ERT consisted of physician–methodologists with expertise in nephrology, a project coordinator and manager, and a research assistant. The ERT instructed and advised Work Group members in all steps of literature review, critical literature appraisal, and guideline development. The Work Group and the ERT collaborated closely throughout the project.

Defining scope and topics

The Work Group Co-Chairs first defined the overall scope and goals of the guideline and then drafted a preliminary list of topics and key clinical questions. The Work Group and ERT further developed and refined each topic and specified screening criteria, literature search strategies, and data extraction forms (Table 5).

Given the lack of robust evidence, the Work Group decided not to make guideline recommendations for patients with kidney failure (CKD 5D). The Work Group decided instead to refer readers to the KDIGO Controversies Conference paper on this topic.[4]

Establishing the process for guideline development

The ERT performed literature searches and organized abstract and article screening. The ERT also coordinated the methodological and analytical processes and defined and standardized the methodology for performing literature searches, data extraction, and summarizing the evidence. Throughout the project, the ERT offered suggestions for guideline development and led discussions on systematic review, literature searches, data extraction, assessment of quality and applicability of articles, evidence synthesis, grading of evidence and guideline recommendations, and consensus development. The Work Group took the primary role of writing the recommendation statements and rationale and retained final responsibility for their content.

The Work Group Co-Chairs prepared the first draft of the scope of work document as a series of open-ended questions to be considered by Work Group members. At their first 2-day meeting, members added further questions until the

Table 5 | Systematic review topics and screening criteria[a]

Diet or lifestyle modification

Population	CKD ND: CKD 1–5, non-dialysis, adults and children, with or without hypertension, any type of CKD
Intervention	Salt restriction, weight loss, diet, exercise
Comparator	Active or control
Outcome	Blood pressure, mortality, clinical cardiovascular events, kidney function (categorical or continuous), proteinuria or urine protein level (categorical or continuous), quality of life, adverse events
Study design	RCTs with parallel-group design; cross-over trials
Minimum duration of follow-up	6 weeks for blood pressure, 3 months for proteinuria, 1 year for other outcomes
Minimum N of subjects	≥50 per arm

Blood pressure targets

Population	CKD ND: CKD 1–5, non-dialysis, adults or children, with or without hypertension, any type of CKD[a] but organized by • DKD (DM and CKD) • Non-DKD • CKD in the kidney-transplant recipient (CKD T)
Intervention	Lower or low BP target
Comparator	Higher or usual BP target
Outcome	Mortality, clinical cardiovascular events, kidney function (categorical or continuous), proteinuria or urine protein level (categorical or continuous), quality of life, adverse events
Study design	RCTs with parallel-group design
Minimum duration of follow-up	3 months for proteinuria, 1 year for other outcomes
Minimum N of Subjects	≥50 per arm

Agents

Population	CKD ND: CKD 1–5, non-dialysis, adults or children, with or without hypertension, any type of CKD[a] but organized by • DKD (DM and CKD) • Non-DKD • CKD in the kidney-transplant recipient (CKD T)
Intervention	Any anti-hypertensive agent (single or in combination, any dose) as well as specific searches for ACE-I, ARB, aldosterone antagonist, beta-blocker, calcium-channel blocker, diuretic
Comparator	Active or placebo
Outcomes	Mortality, clinical cardiovascular events, kidney function (categorical or continuous), proteinuria or urine protein level (categorical or continuous), quality of life, adverse events
Study design	RCTs with parallel-group design
Minimum duration of follow-up	3 months for proteinuria, 1 year for other outcomes
Minimum N of Subjects	≥50 per arm

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; BP, blood pressure; CKD, chronic kidney disease; CKD ND, non-dialysis-dependent CKD; CKD T, non-dialysis-dependent CKD with a kidney transplant; DKD, diabetic kidney disease; DM, diabetes mellitus; N, number; RCTs, randomized controlled trials.
[a]Includes CKD subgroups from 'general population' studies (not exclusively in CKD patients).

initial working document included all topics of interest to the Work Group. The inclusive, combined set of questions formed the basis for the deliberation and discussion that followed. The Work Group strove to ensure that all topics deemed clinically relevant and worthy of review were identified and addressed.

Formulating questions of interest

Questions of interest were formulated according to the PICODD (Population, Intervention, Comparator, Outcome, study Design and Duration of follow-up) criteria. Details of the criteria are presented in Table 5.

Ranking of outcomes

The Work Group ranked outcomes of interest on the basis of their importance for informing clinical decision making (Table 6). Doubling of SCr level or halving of GFR was upgraded from 'high' to 'critical' importance in studies where the baseline GFR was <60 ml/min/1.73 m^2 (or the SCr was >2 mg/dl [>177 μmol/l]), given the known adverse consequences of advanced CKD.

Table 6 | Hierarchy of outcomes

Hierarchy[a]	Outcomes[b]
Critical importance	Mortality, cardiovascular mortality, cardiovascular events, kidney failure, composite including clinical events
High importance	Doubling of SCr or halving of GFR, proteinuria (categorical)
Moderate importance	Kidney function (continuous), urine protein level (continuous)
Importance dependent on severity	Adverse events: drug discontinuation or dose decrease, hyperkalemia, early rise of SCr or decrease of GFR

GFR, glomerular filtration rate; SCr, serum creatinine.
[a]Doubling of SCr or halving of GFR is of 'critical' importance in those studies with baseline GFR <60 ml/min/1.73 m^2 or SCr >2 mg/dl (177 μmol/l).
[b]The lists are not meant to reflect outcome ranking for other areas of kidney disease management. The Work Group acknowledges that not all clinicians, patients or families, or societies would rank all outcomes the same.

Literature searches and article selection

The Work Group sought to build on the evidence base from the previous *KDOQI Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease.*[1] As the first search for the KDOQI guideline was conducted in

Table 7 | Relevant systematic reviews and meta-analyses

Title	Reference	Databases and cut-off dates of literature search	Use in Work Group deliberation
Topic 1. Low sodium diet or lifestyle modification and change in BP			
Lifestyle interventions to reduce raised blood pressure: a systematic review of randomized controlled trials	Dickinson et al.[53]	Cochrane CENTRAL MEDLINE Embase 1998–2003	References used to check and supplement reference list of ERT systematic review
Systematic review of long term effects of advice to reduce dietary salt in adults	Hooper et al.[62]	Cochrane CENTRAL MEDLINE Embase CAB abstracts CVRCT registry SIGLE 1982–1998 Further search on sodium restriction and BP: Cochrane CENTRAL MEDLINE Embase Up to July 2002	References used to check and supplement reference list of ERT systematic review
Topic 2. BP target and kidney outcomes			
Progression of chronic kidney disease: the role of blood pressure control, proteinuria, and angiotensin-converting enzyme inhibition: a patient level meta-analysis	Jafar et al.[96]	MEDLINE 1977–1999	References used to check and supplement reference list of ERT systematic review
Topic 3. ACE-I or ARB on CVD and CKD progression			
RAS blockade and cardiovascular outcomes in patients with chronic kidney disease and proteinuria: a meta-analysis	Balamuthusamy et al.[97]	OVID MEDLINE Embase 1975–2006	References used to check and supplement reference list of ERT systematic review
Angiotensin receptor blockers as anti-hypertensive treatment for patients with diabetes mellitus: meta-analysis of controlled double-blind randomized trials	Siebenhofer et al.[450]	Cochrane CENTRAL MEDLINE Embase Cochrane Controlled Trials Register PubMed DARE NHSEED HTA 1992–2002	References used to check and supplement reference list of ERT systematic review
Topic 4. ACE-I or ARB on CKD progression			
Effect of inhibitors of the renin-angiotensin system and other anti-hypertensive drugs on renal outcomes: systematic review and meta-analysis	Casas et al.[451]	Cochrane CENTRAL MEDLINE Embase 1960–Jan. 31, 2005	References used to check and supplement reference list of ERT systematic review
Topic 5. ACE-I on CKD progression in CKD without DM			
Angiotensin-converting enzyme inhibitors and progression of non-diabetic renal disease. A meta-analysis of patient-level data	Jafar et al.[141]	MEDLINE May 1977–September 1997	References used to check and supplement reference list of ERT systematic review
Topic 6. Anti-hypertensive agents in kidney-transplant recipients			
Anti-hypertensives for kidney-transplant recipients: Systematic review and meta-analysis of randomized controlled trials	Cross et al.[301]	Cochrane Renal Group Specialized Register Cochrane CENTRAL MEDLINE Embase Up to July 1, 2008	References used to check and supplement reference list of ERT systematic review

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; BP, blood pressure; CKD, chronic kidney disease; CVD, cardiovascular disease; DM, diabetes mellitus; ERT, evidence review team; RAS, renin–angiotensin system.

Table 8 | Literature yield

Intervention	Abstracts identified	Articles retrieved	Studies with data extracted	Studies included in summary tables			General population studies in summary tables	Summary tables
				DKD	Non-DKD	Transplant		
Agents	10, 657	247	55	23	22	6	13	45
Targets				0	8	0	1	3

DKD, diabetic kidney disease.

Table 9 | Work products for BP guideline*

Topic	Summary table of RCTs	Evidence profile
Diet or lifestyle modification		
Exercise	+	− (single study)
BP targets in CKD without DM		
BP target in adults	+	+ (3 studies)
BP target in children	+	− (single study)
Adverse events of target RCTs	+	—[a]
Agents in CKD without DM, non-transplant		
ACE-I or ARB versus CCB	+	+ (7 studies)
ACE-I or ARB versus placebo	+	+ (6 studies)
High-dose ACE-I versus low-dose ACE-I	+	+ (2 studies)
ACE-I versus ARB	+	+ (3 studies)
ACE-I versus beta-blocker	+	− (single study)
High-dose ARB versus low-dose ARB	+	+ (3 studies)
(ACE-I + CCB) versus ACE-I	+	− (single study)
(ACE-I + CCB) versus CCB	+	− (single study)
Beta-blocker versus CCB	+	− (single study)
CCB versus CCB	+	− (single study)
Central-acting agent versus CCB	+	− (single study)
Adverse events of agent RCTs	+	—[a]
Agents in CKD with DM, non-transplant		
Aldosterone antagonist versus placebo	+	− (single study)
ACE-I or ARB versus CCB	+	+ (7 studies)
ACE-I or ARB versus placebo	+	+ (9 studies)
ACE-I versus ARB	+	+ (3 studies)
ARB versus ARB	+	+ (3 studies)
CCB versus placebo	+	− (single study)
Direct renin inhibitor versus placebo	+	− (single study)
Endothelin antagonist versus endothelin antagonist	+	− (single study)
Endothelin antagonist versus placebo	+	− (single study)
Adverse events of agents in RCTs	+	—[a]
Agents in CKD in kidney transplant recipient		
ACE-I versus ARB	+	− (single study)
ARB versus placebo	+	− (single study)
ACE-I versus CCB	+	+ (2 studies)
CCB versus placebo	+	+ (3 studies)
Adverse events of agent RCTs	+	—[a]
CKD subgroups from general population studies		
BP target	+ (1 study)	
ACE-I + diuretic versus placebo in DM	+ (4 studies)	
ACE-I or ARB versus control	+ (5 studies)	
ACE + ARB or ARB versus ACE-I	+ (1 study)	
ARB versus CCB	+ (1 study)	
CCB versus control	+ (2 studies)	

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; BP, blood pressure; CCB, calcium-channel blocker; CKD, chronic kidney disease; DM, diabetes mellitus; RCTs, randomized controlled trials; +, work product is indicated for the topic of interest; −, work product is not indicated for the topic of interest.
[a]Included in evidence profile for other outcomes.

July 2002, the search for the current KDIGO Guideline included publications since January 2002. Search strategies were developed by the ERT with input from the Work Group. The text words or medical subject headings (MeSH) that were included are provided in the Supplementary Appendix 1 online. Non-human studies and those focusing on dialysis, pregnancy, neonates, malignant hypertension, acute kidney injury, or drug pharmacology were excluded.

The MEDLINE, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews were searched by the ERT to capture all RCTs on the use of

BP-lowering agents in CKD. The first search was conducted in November 2009 and was subsequently updated in April and August of 2010; the final update was done in January 2011. Additional focused searches were conducted to identify RCTs evaluating lifestyle interventions of salt restriction, weight loss, and diet and exercise in CKD and to look for reviews of adverse effects of anti-hypertensive agents. The ERT relied on Work Group members to identify large, general population RCTs reporting on subgroup analyses based on CKD, GFR, or proteinuria status. Additional pertinent articles were added from the reference lists of JNC 7 and relevant meta-analyses and systematic reviews (Table 7). The search yield was also supplemented by articles provided by Work Group members through February 2012.

A total of 10,657 citations were initially screened. Journal articles reporting original data, meta-analyses, and systematic reviews were selected for evidence review. Editorials, letters, abstracts, unpublished reports, and articles published in non–peer-reviewed journals were not included. The Work Group also decided to exclude publications from journal supplements because of potential differences in the process of how they get solicited, selected, reviewed, and edited compared to peer-reviewed publications. *Post hoc* analyses were also excluded, however, after discussion with the Work Group, it was decided that exception would be made for post-trial observational follow-up reports from RCTs looking at BP targets as BP interventions may take longer time to influence outcomes. These studies were downgraded one level to designate that they are of lesser quality than the original RCT. The overall search yield along with the number of abstracts identified and articles reviewed for each topic are presented in Table 8.

Data extraction

Data extraction was done by the ERT. The ERT, in consultation with the Work Group, designed forms to capture data on design, methodology, sample characteristics, interventions, comparators, outcomes, results, and limitations of individual studies. Methodology and outcomes were also systematically graded (see the section on grading below) and recorded during the data extraction process.

Summary tables

Summary tables were developed for each comparison of interest (Table 9). Studies included in the evidence base for the *KDOQI Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease*[1] were also incorporated if they fulfilled the inclusion criteria for the current KDIGO Guideline.

Summary tables contain outcomes of interest, relevant population characteristics, description of intervention and comparator, results, and quality grading for each outcome. Categorical and continuous outcomes were summarized separately. Studies done exclusively in patients of a single race or ethnicity and studies reporting effect modifications by baseline urine protein level were annotated. Studies were also

categorized by baseline proteinuria status in summary tables for the CKD with diabetes mellitus topic.

For studies not exclusively examining CKD population, only those reporting analysis by CKD subgroups were tabulated. Studies including both diabetes mellitus and non-diabetes mellitus populations were included in summary tables for the CKD without diabetes mellitus topic unless results of subgroup analysis by diabetes mellitus status was provided.

Work Group members proofed all summary table data and quality assessments. Summary tables are available at www.kdigo.org.

Evidence profiles

Evidence profiles were constructed to assess the quality and record quality grades and descriptions of effect for each outcome across studies, as well as the quality of overall evidence and description of net benefits or harms of the intervention or comparator across all outcomes. These profiles aim to make the evidence synthesis process transparent. Decisions in the evidence profiles were based

on data from the primary studies listed in corresponding summary tables and on judgments of the ERT and the Work Group. When the body of evidence for a particular comparison of interest consisted of only one study, the summary table provided the final level of synthesis and an evidence profile was not generated. Evidence profiles were also not created for studies that did not exclusively examine CKD population. Each evidence profile was initially constructed by the ERT and then reviewed, edited, and approved by the Work Group. The work products created by the ERT for summarizing the evidence base are listed in Table 9.

Grading of quality of evidence for outcomes of individual studies

Methodological quality. Methodological quality (internal validity) refers to the design, conduct, and reporting of outcomes of a clinical study. A previously devised three-level classification system for quality assessment was used to grade the overall study quality and quality of all relevant outcomes in the study (Table 10). Variations of this system have been used in most KDOQI and all KDIGO guidelines and have been recommended for the US Agency for Healthcare Research and Quality Evidence-based Practice Center program.[444]

Each study was given an overall quality grade based on its design, methodology (randomization, allocation, blinding, definition of outcomes, appropriate use of statistical methods, etc.), conduct (dropout percentage, outcome assessment methodologies, etc.) and reporting (internal consistency, clarity, thoroughness and precision, etc.). Each reported outcome was then evaluated and given an individual grade depending on the quality of reporting and methodological issues specific to that outcome. However, the quality

Table 10 | Classification of study quality

Good quality	Low risk of bias and no obvious reporting errors; complete reporting of data. Must be prospective. If study of intervention, must be RCT.
Fair quality	Moderate risk of bias, but problems with study or paper are unlikely to cause major bias. If study of intervention, must be prospective.
Poor quality	High risk of bias or cannot exclude possible significant biases. Poor methods, incomplete data, reporting errors. Prospective or retrospective.

RCT, randomized controlled trial.

Table 11 | GRADE system for grading quality of evidence

Step 1: Starting grade for quality of evidence based on study design	Step 2: Reduce grade	Step 3: Raise grade	Final grade for quality of evidence and definition
Randomized trials = High	*Study quality* −1 level if serious limitations −2 levels if very serious limitations	*Strength of association* +1 level if strong[a], no plausible confounders +2 levels if very strong[b], no major threats to validity	High = Further research is unlikely to change confidence in the estimate of the effect
	Consistency −1 level if important inconsistency	*Other* +1 level if evidence of a dose–response gradient	Moderate = Further research is likely to have an important impact on confidence in the estimate of effect, and may change the estimate
Observational study = Low	*Directness* −1 level if some uncertainty −2 levels if major uncertainty		
	Other −1 level if sparse or imprecise data[c] −1 level if high probability of reporting bias	+1 level if all residual plausible confounders would have reduced the observed effect	Low = Further research is very likely to have an important impact on confidence in the estimate, and may change the estimate
Any other evidence = Very Low			
			Very Low = Any estimate of effect is very uncertain

GRADE, Grading of Recommendations Assessment, Development and Evaluation.
[a]Strong evidence of association is defined as 'significant relative risk of >2 (<0.5)' based on consistent evidence from two or more observational studies, with no plausible confounders.
[b]Very strong evidence of association is defined as 'significant relative risk of >5 (<0.2)' based on direct evidence with no major threats to validity.
[c]Sparse if there is only one study or if total N <500. Imprecise if there is a low event rate (0 or 1 event) in either arm or confidence interval spanning a range >1.
Adapted by permission from Macmillan Publishers Ltd, *Kidney International*. Uhlig K, Macleod A, Craig J *et al.* Grading evidence and recommendations for clinical practice guidelines in nephrology. A position statement from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int* 2006; **70**: 2058–2065;[157] accessed http://www.nature.com/ki/journal/v70/n12/pdf/5001875a.pdf.

grade of an individual outcome could not exceed the quality grade for the overall study.

Grading the quality of evidence and the strength of a guideline recommendation

A structured approach, based on Grading of Recommendations Assessment, Development and Evaluation (GRADE)[156,157,445] and facilitated by the use of evidence profiles was used to grade the quality of the overall evidence and the strength of recommendations. For each topic, the discussion on grading of the quality of the evidence was led by the ERT, and the discussion regarding the strength of the recommendations was led by the Work Group Co-Chairs. The 'strength of a recommendation' indicates the extent to which one can be confident that adherence to the recommendation will do more good than harm. The 'quality of a body of evidence' refers to the extent to which our confidence in an estimate of effect is sufficient to support a particular recommendation.[445]

Table 12 | Final grade for overall quality of evidence

Grade	Quality of Evidence	Meaning
A	High	We are confident that the true effect lies close to that of the estimate of the effect.
B	Moderate	The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
C	Low	The true effect may be substantially different from the estimate of the effect.
D	Very low	The estimate of effect is very uncertain, and often will be far from the truth.

Table 13 | Balance of benefits and harms

When there was evidence to determine the balance of medical benefits and harms of an intervention to a patient, conclusions were categorized as follows:
- For statistically significant benefit or harm, report as 'benefit [or harm] of drug X.'
- For non–statistically significant benefit or harm, report as 'possible benefit [or harm] of drug X.'
- In instances where studies are inconsistent, report as 'possible benefit [or harm] of drug X.'
- 'No difference' can only be reported if a study is not imprecise.
- 'Insufficient evidence' is reported if imprecision is a factor.

Grading the quality of evidence for each outcome across studies. Following GRADE, the quality of a body of evidence pertaining to a particular outcome of interest was initially categorized on the basis of study design. For questions of interventions, the initial quality grade was 'High' if the body of evidence consisted of RCTs, 'Low' if it consisted of observational studies, and 'Very Low' if it consisted of studies of other study designs. For questions of interventions, the Work Group decided to use only RCTs. The grade for the quality of evidence for each intervention–outcome pair was then lowered if there were serious limitations to the methodological quality of the aggregate of studies, if there were important inconsistencies in the results across studies, if there was uncertainty about the directness of evidence including limited applicability of the findings to the population of interest, if the data were imprecise (a low event rate in either arm or a CI spanning a range >1) or sparse (only 1 study or total $N < 500$), or if there was thought to be a high likelihood of bias. The final grade for the quality of the evidence for an intervention–outcome pair could be one of the following four grades: 'High', 'Moderate', 'Low' or 'Very Low' (Table 11).

Grading the overall quality of evidence. The quality of the overall body of evidence was then determined on the basis of the quality grades for all outcomes of interest, taking into

Table 15 | Determinants of strength of recommendation

Factor	Comment
Balance between desirable and undesirable effects	The larger the difference between the desirable and undesirable effects, the more likely a strong recommendation is warranted. The narrower the gradient, the more likely a weak recommendation is warranted.
Quality of the evidence	The higher the quality of evidence, the more likely a strong recommendation is warranted.
Values and preferences	The more variability in values and preferences, or the more uncertainty in values and preferences, the more likely a weak recommendation is warranted.
Costs (resource allocation)	The higher the costs of an intervention—that is, the more resources consumed—the less likely a strong recommendation is warranted.

Table 14 | KDIGO nomenclature and description for grading recommendations

| Grade* | Implications | | |
	Patients	Clinicians	Policy
Level 1 'We recommend'	Most people in your situation would want the recommended course of action and only a small proportion would not.	Most patients should receive the recommended course of action.	The recommendation can be evaluated as a candidate for developing a policy or a performance measure.
Level 2 'We suggest'	The majority of people in your situation would want the recommended course of action, but many would not.	Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision consistent with her or his values and preferences.	The recommendation is likely to require substantial debate and involvement of stakeholders before policy can be determined.

*The additional category 'Not Graded' was used, typically, to provide guidance based on common sense or where the topic does not allow adequate application of evidence. The most common examples include recommendations regarding monitoring intervals, counseling, and referral to other clinical specialists. The ungraded recommendations are generally written as simple declarative statements, but are not meant to be interpreted as being stronger recommendations than Level 1 or 2 recommendations.

Table 16 | Existing major guidelines and recommendations on hypertension and anti-hypertensive agents in CKD

Year	Group	Target CKD population	Recommended BP goal (mm Hg)	Recommended preferred anti-hypertensive agent(s)
2003	Seventh report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure[143] http://jama.ama-assn.org/content/289/19/2560.abstract (accessed July 17, 2012)	Stage 3 CKD, macroalbuminuria, kidney-transplant recipients	<130/80	CKD 3 or macroalbuminuria: ACE-I or ARB in combination with a diuretic Kidney-transplant recipients: No particular class of agents superior
2003	World Health Organization/International Society of Hypertension Statement on Management of Hypertension[243] http://www.who.int/cardiovascular_diseases/guidelines/hypertension_guidelines.pdf (accessed July 17, 2012)	Type 1 DM with nephropathy Type 2 DM with nephropathy Non-diabetic nephropathy	<130/80	Type 1 DM with nephropathy: ACE-I Type 2 DM with nephropathy: ARB Non-diabetic nephropathy: ACE-I
2003	European Society of Hypertension–European Society of Cardiology Guidelines for the Management of Arterial Hypertension[236] http://www.eshonline.org/asset.axd?id=d1381ab0-63ce-4427-bd8f-f44ef5281c5f&t=633770299529000000 (accessed July 17, 2012)	DM, CKD	<130/80 (if urine protein >1 g/d is present, lower target to lower protein if possible)	CKD: Diuretic Type 1 DM with nephropathy: ACE-I Type 2 DM with nephropathy: ARB Non-diabetic nephropathy: ACE-I Proteinuria: ACE-I or ARB
2006	Caring for Australasians with Renal Impairment (CARI) Guidelines: Prevention of Progression of Kidney Disease http://www.cari.org.au/ckd_prevent_list_published.php (accessed August 20, 2012)	DM, CKD	CKD in general: <125/75 (or mean BP <92) if urine protein >1 g/d <130/80 (or mean BP <97) if urine protein 0.25–1 g/d <130/85 (or mean BP <100) if urine protein <0.25 g/d DKD: <130/85 for patients >50 years of age <120/70–75 for those <50 years of age	Non-DKD: Regimens including ACE-I more effective than those not including ACE-I in slowing CKD progression in non-DKD Combination therapy of ACE-I and ARB slows progression of non-DKD more effectively than either single agent ACE-I more effective than beta-blockers and dihydropyridine CCB in slowing progression of CKD Beta-blockers more effective than dihydropyridine CCB in slowing CKD progression, especially in the presence of proteinuria DKD: ACE-I for all patients with diabetes and hypertension ACE-I for all patients with diabetes and microalbuminuria or overt nephropathy, independent of BP and GFR ARB provides specific renoprotection in diabetic nephropathy, beyond their anti-hypertensive benefit There is insufficient evidence that ACE-I and ARB combination are of additive specific benefit in diabetic nephropathy, beyond additional anti-hypertensive benefit
2008	Canadian Society of Nephrology Guidelines on Management of CKD[238] http://www.cmaj.ca/cgi/content/full/179/11/1154 (accessed July 17, 2012)	DM, CKD	<130/80	Non-DKD: ACE-I or ARB should be included in the regimen if urine ACR >30 mg/mmol (>300 mg/g) ACE-I, ARB, thiazides, long-acting CCB, or beta-blockers (for patients older than 60 years) should be included in the regimen if urine ACR <30 mg/mmol (<300 mg/g) DKD: ACE-I or ARB should be included in the regimen
2009	Reappraisal of European Guidelines on Hypertension Management: a European Society of Hypertension Task Force Document[353] http://www.ish.org.il/2009GuidelinesESH.pdf (accessed July 17, 2012)	DM, CKD	Initiate treatment for systolic BP >130 and diastolic BP >85	ACE-I or ARB, but combination therapy with other agents most likely needed to control BP
2009	Japanese Society of Hypertension Guidelines for the Management of Hypertension[452] http://www.nature.com/hr/journal/v32/n1/abs/hr200818a.html (accessed July 17, 2012)	CKD	<130/80 For those with urine protein ≥1 g/d: target <125/75	ACE-I or ARB should be the first choice of therapy and dose should be titrated by urinary albumin excretion (<30 mg/g for diabetic nephropathy and <300 mg/g for glomerulonephritis) For diuretics, thiazides should be used if GFR ≥30 ml/min/1.73 m^2, and loop diuretics should be used if GFR <30 ml/min/1.73 m^2

Table 16 | Continued

Year	Group	Target CKD population	Recommended BP goal (mm Hg)	Recommended preferred anti-hypertensive agent(s)
2011	The Renal Association (UK) CKD Guidelines[396] http://www.renal.org/Clinical/GuidelinesSection/ Detection-Monitoring-and-Care-of-Patients-with-CKD.aspx (accessed August 28, 2012)	CKD	For the majority, systolic BP: <140 mm Hg (target range 120–139 mm Hg) and diastolic BP: <90 mm Hg for the majority. For those with DM or proteinuria ⩾1g/24 h, systolic BP: <130 mm Hg (target range 120–129 mm Hg) and diastolic BP: <80 mm Hg unless the risks are considered to outweigh the potential benefits. Antihypertensive therapy should be individualized and lowering the systolic blood pressure to <120 mm Hg should be avoided	ACE-I or ARB
2012	Canadian Hypertension Education Program Recommendations http://www.hypertension.ca/chep-recommendations (accessed August 20, 2012)	Non-DKD and DKD	CKD in general: <140/90 DKD: <130/80	Non-DKD: ACE-I or ARB (if ACE-I intolerant) as a first choice agent if urine ACR >30 mg/mmol (>300 mg/g) or urine protein >500 mg/24 h. DKD: For patients with persistent microalbuminuria (urine ACR >2 mg/mmol [>20 mg/g] in men and >2.8 mg/mmol [>28 mg/g] in women), ACE-I or or ARB is recommended as initial therapy
2012	American Diabetes Association[453] http://care.diabetesjournals.org/content/35/Supplement_1/ S11.full.pdf (accessed August 20, 2012)	DM with microalbuminuria or overt nephropathy	<130/80	ACE-I or ARB should be considered for patients with microalbuminuria or macroalbuminaria. If ACE-I or ARB is not tolerated, then diuretics, CCBs, and beta-blockers should be considered

ACE-I, angiotensin-converting enzyme inhibitor; ACR, albumin/creatinine ratio; ARB, angiotensin-receptor blocker; BP, blood pressure; CCB, calcium-channel blocker; CKD, chronic kidney disease; DKD, diabetic kidney disease; DM, diabetes mellitus; GFR, glomerular filtration rate.

account explicit judgments about the relative importance of each outcome. The resulting four final categories for the quality of overall evidence were: 'A', 'B', 'C' or 'D' (Table 12).

Assessment of the net health benefit across all important clinical outcomes. The net health benefit was determined on the basis of the anticipated balance of benefits and harms across all clinically important outcomes (Table 13). The assessment of net benefit also involved the judgment of the Work Group and the ERT.

Grading the strength of the recommendations. The strength of a recommendation is graded as level 1 or level 2. Table 14 shows the KDIGO nomenclature for grading the strength of a recommendation and the implications of each level for patients, clinicians, and policy makers. Recommendations can be for or against doing something. Table 15 shows that the strength of a recommendation is determined not only by the quality of the evidence but also by other, often complex judgments regarding the size of the net medical benefit, values, and preferences, and costs. Formal decision analyses including cost analysis were not conducted.

Ungraded statements. This category was designed to allow the Work Group to issue general advice. Typically an ungraded statement meets the following criteria: it provides guidance based on common sense; it provides reminders of the obvious; and it is not sufficiently specific to allow for application of evidence to the issue and therefore it is not based on systematic evidence review. Common examples include recommendations about frequency of testing, referral to specialists, and routine medical care. We strove to minimize the use of ungraded recommendations.

This grading scheme, with two levels for the strength of a recommendation together with four levels of grading the quality of the evidence, as well as the option of an ungraded statement for general guidance, was adopted by the KDIGO Board in December 2008. The Work Group took on the primary role of writing the recommendations and rationale and retained final responsibility for the content of the guideline statements and the accompanying narrative. The ERT reviewed draft recommendations and grades for consistency with the conclusions of the evidence review.

Format for guideline recommendations. Each chapter contains one or more specific recommendations. Within each recommendation, the strength of recommendation is indicated as level 1 or level 2 and the quality of the supporting evidence is shown as A, B, C, or D. The recommendation statements and grades are followed by a brief background with relevant definitions of terms and then the rationale starting with a 'chain of logic,' which consists of declarative sentences summarizing the key points of the

Table 17 | The Conference on Guideline Standardization (COGS) checklist for reporting clinical practice guidelines

Topic	Description	Discussed in KDIGO Management of Blood Pressure in Chronic Kidney Disease Guideline
1. Overview material	Provide a structured abstract that includes the guideline's release date, status (original, revised, updated), and print and electronic sources.	Abstract and Methods for Guideline Development.
2. Focus	Describe the primary disease/condition and intervention/service/technology that the guideline addresses. Indicate any alternative preventative, diagnostic or therapeutic interventions that were considered during development.	Management of blood pressure and the use of anti-hypertensive agents in adults and children with CKD ND, including those with kidney transplants.
3. Goal	Describe the goal that following the guideline is expected to achieve, including the rationale for development of a guideline on this topic.	This clinical practice guideline is intended to assist the practitioner caring for patients with non-dialysis CKD and hypertension and to prevent deaths, CVD events, and progression to kidney failure while optimizing patients' quality of life.
4. User/setting	Describe the intended users of the guideline (e.g., provider types, patients) and the settings in which the guideline is intended to be used.	Providers: Nephrologists (adult and pediatric), Internists, and Pediatricians. Patients: Adults and children with CKD at risk for hypertension. Policy Makers: Those in related health fields.
5. Target population	Describe the patient population eligible for guideline recommendations and list any exclusion criteria.	Adults and children with CKD, not on dialysis; kidney transplant recipients.
6. Developer	Identify the organization(s) responsible for guideline development and the names/credentials/potential conflicts of interest of individuals involved in the guideline's development.	Organization: KDIGO Names/credentials/potential conflicts of interest of individuals involved in the guideline's development are disclosed in the Biographic and Disclosure Information.
7. Funding source/sponsor	Identify the funding source/sponsor and describe its role in developing and/or reporting the guideline. Disclose potential conflict of interest.	KDIGO is supported by the following consortium of sponsors: Abbott, Amgen, Bayer Schering Pharma, Belo Foundation, Bristol-Myers Squibb, Chugai Pharmaceutical, Coca-Cola Company, Dole Food Company, Fresenius Medical Care, Genzyme, Hoffmann-LaRoche, JC Penney, Kyowa Hakko Kirin, NATCO—The Organization for Transplant Professionals, NKF-Board of Directors, Novartis, Pharmacosmos, PUMC Pharmaceutical, Robert and Jane Cizik Foundation, Shire, Takeda Pharmaceutical, Transwestern Commercial Services, Vifor Pharma, and Wyeth. No funding is accepted for the development or reporting of specific guidelines. All stakeholders could participate in open review.
8. Evidence collection	Describe the methods used to search the scientific literature, including the range of dates and databases searched, and criteria applied to filter the retrieved evidence.	Topics were triaged either to a) systematic review, b) systematic search followed by narrative summary, or c) narrative summary. For systematic reviews on treatment with different anti-hypertensive agents or to different BP targets, we searched for RCTs in MEDLINE, Cochrane Central Registry for trials, and Cochrane database of systematic reviews. Screening criteria are outlined in the *Methods for Guideline Development* chapter. The search was updated through January 2011 and supplemented by articles identified by Work Group members through February 2012. We also searched for pertinent existing guidelines and systematic reviews.
9. Recommendation grading criteria	Describe the criteria used to rate the quality of evidence that supports the recommendations and the system for describing the strength of the recommendations. Recommendation strength communicates the importance of adherence to a recommendation and is based on both the quality of the evidence and the magnitude of anticipated benefits and harms.	Quality of individual studies was graded in a three-tiered grading system (see Table 10). Quality of evidence and strength of recommendations were graded following the GRADE approach (Tables 12 and 14). The Work Group could provide general guidance in unngraded statements.
10. Method for synthesizing evidence	Describe how evidence was used to create recommendations, e.g., evidence tables, meta-analysis, decision analysis.	For systematic review topics, summary tables and evidence profiles were generated. For recommendations on treatment interventions, the steps outlined by GRADE were followed.
11. Prerelease review	Describe how the guideline developer reviewed and/or tested the guidelines prior to release.	The guideline had undergone internal review at the 2010 KDIGO Board of Directors meeting and external public review in July 2011. Public review comments were compiled and fed back to the Work Group, which considered comments in its revision of the guideline.
12. Update plan	State whether or not there is a plan to update the guideline and, if applicable, an expiration date for this version of the guideline.	There is no date set for updating. The need for updating of the guideline will depend on the publication of new evidence that would change the quality of the evidence or the estimates for the benefits and harms. Results from registered ongoing studies and other publications will be reviewed periodically to evaluate their potential to impact on the recommendations in this guideline.

Table 17 | Continued

Topic	Description	Discussed in KDIGO Management of Blood Pressure in Chronic Kidney Disease Guideline
13. Definitions	Define unfamiliar terms and those critical to correct application of the guideline that might be subject to misinterpretation.	Abbreviations and Acronyms.
14. Recommendations and rationale	State the recommended action precisely and the specific circumstances under which to perform it. Justify each recommendation by describing the linkage between the recommendation and its supporting evidence. Indicate the quality of evidence and the recommendation strength, based on the criteria described in Topic 9.	Each guideline chapter contains recommendations for blood pressure management of CKD patients. Each recommendation builds on a supporting rationale with evidence tables if available. The strength of the recommendation and the quality of evidence are provided in parenthesis within each recommendation.
15. Potential benefits and harms	Describe anticipated benefits and potential risks associated with implementation of guideline recommendations.	The benefits and harm for each comparison of interventions are provided in summary tables and summarized in evidence profiles. The estimated balance between potential benefits and harm was considered when formulating the recommendations.
16. Patient preferences	Describe the role of patient preferences when a recommendation involves a substantial element of personal choice or values.	Many recommendations are level 2 or "discretionary," which indicates a greater need to help each patient arrive at a management decision consistent with her or his values and preferences.
17. Algorithm	Provide (when appropriate) a graphical description of the stages and decisions in clinical care described by the guideline.	No overall algorithm.
18. Implementation considerations	Describe anticipated barriers to application of the recommendations. Provide reference to any auxiliary documents for providers or patients that are intended to facilitate implementation. Suggest review criteria for measuring changes in care when the guideline is implemented.	These recommendations are global. Review criteria were not suggested because implementation with prioritization and development of review criteria have to proceed locally. Furthermore, most recommendations are discretionary, requiring substantial discussion among stakeholders before they can be adopted as review criteria. Suggestions were provided for future research.

BP, blood pressure; CKD, chronic kidney disease; CKD ND, non–dialysis-dependent CKD; CVD, cardiovascular disease; GRADE, Grading of Recommendations Assessment, Development and Evaluation; KDIGO, Kidney Disease: Improving Global Outcomes; RCT, randomized controlled trial.

evidence base and the judgments supporting the recommendation. This is followed by a narrative in support of the rationale. In relevant sections, research recommendations suggest future research to resolve current uncertainties.

Comparison with other guidelines

We tabulated recommendations from other key English-language guidelines pertinent to the use of blood-pressure–lowering agents in individuals with CKD (Table 16). This served to inform topic selection and scope. Also, after recommendations had been drafted, the Work Group reviewed them in the context of the existing guideline recommendations to avoid unnecessary or unwarranted discrepancies.

Limitations of approach

Although the literature searches were intended to be comprehensive, they were not exhaustive. MEDLINE was the only database searched. Hand searches of journals were not performed, and review articles and textbook chapters were not systematically searched. However, important studies known to domain experts that were missed by the electronic literature searches were added to retrieved articles and reviewed by the Work Group.

Review of guideline development process

Several tools and checklists have been developed to assess the quality of the methodological process for guideline development. These include the Appraisal of Guidelines for Research and Evaluation (AGREE) criteria,[446] the Conference on Guideline Standardization (COGS) checklist,[447] and the Institute of Medicine's recent *Standards for Systematic Reviews*,[448] and *Clinical Practice Guideines We Can Trust*.[449] Table 17 and Supplementary Appdenix 2 online show, respectively, the COGS criteria and the Institute of Medicine standards, and how each one of them is addressed in this Guideline.

SUPPLEMENTARY MATERIAL
Supplementary Appendix 1. Online search strategies.
Supplementary Appendix 2. Concurrence with Institute of Medicine standards for systematic reviews and for guidelines.
Supplementary material is linked to the online version of the paper at http://www.kdigo.org/clinical_practice_guidelines/bp.php