CRITICAL APPRAISAL OF CLINICAL PRACTICE GUIDELINE (CPG)

Atiporn Ingsathit MD, PhD.

Moving from Evidence to Action
Rationale for Clinical Practice Guidelines

- Worldwide concerns about:
  - Unexplained variations in clinical practice
  - Rising health care costs
  - Exponential growth of information

Aim of Clinical Practice Guidelines

- To facilitate more consistent, effective and efficient practice and improve health outcomes for patients.

Suggestions, not rules
Developing recommendations

<table>
<thead>
<tr>
<th>Task</th>
<th>Method for achieving Task</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specify options and outcomes</td>
<td>Explicit question formulation</td>
</tr>
<tr>
<td>Use evidence to determine the link between options and outcomes in all relevant patient subgroups</td>
<td>Randomized controlled trials and other evidence → Systematic review</td>
</tr>
<tr>
<td>Incorporate values to decide on optimal course of action</td>
<td>Value → Decision analysis</td>
</tr>
<tr>
<td>If necessary, consider local circumstances and modify course of action</td>
<td>Local circumstance → Local guideline</td>
</tr>
</tbody>
</table>

Decision tree of health states resulting from having atrial fibrillation with utility values (median (interquartile range)) for each health state

Decision node
- Chance node
- Outcome (health state)
Clinical practice guidelines (CPG)

- Clinical practice guidelines are recommendations for clinicians about the care of patients with specific conditions.
- At their best they are based on the best available research evidence and practice experience.
- Described as "a new reality in medicine".

Component of CPG

- Guidelines have two parts:
  - A systematic review of the research evidence bearing on a clinical question, focused on the strength of the evidence on which clinical decision-making for that condition is based.
  - A set of recommendations for how patients with that condition should be managed.
Use and Users

- Clinicians use to help them take better care of patients.
- Insurers and administrators sometimes use guidelines to set policies on quality and payment for care.
- Lawyers may use well accepted national guidelines in malpractice litigation, arguing that physicians who have not followed such guidelines without a good reason are negligent.

Recognizing credible guidelines

1) Expertise
2) Evidence-based
3) Quality
4) Comprehensive
5) Recency
6) Sponsoring society: respected national bodies
7) Review
8) Conflict of interest
1) Expertise

- Full range of expertise
  - Generalist physicians
  - Subspecialists
  - Nurses, physician assistants
  - Public health specialists
  - Decision analysts
  - Behavioral scientists
  - Economists
  - Consumers
  - Ethicists

2) Evidence-based

- Guideline should be based on a systematic review of published research that is likely to include reports of all scientifically credible studies that relevant to the question.
- Expert opinion not supported by research evidence may be included, but should be labeled and not take precedence over stronger evidence.
3) Quality

- Expert groups have summarized the elements of quality for clinical practice guidelines. The Conference on Guideline Standardization proposed an 18-item checklist.

4) Comprehensive

- The magnitude of effect
- Harms from the intervention
- Convenience and side effects
- The clinical skills necessary to carry out the intervention successfully
- Patient preferences
- Cost
- Cost-effectiveness
Types of Economic Analysis

<table>
<thead>
<tr>
<th>Methodology</th>
<th>Cost measurement unit</th>
<th>Outcome unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost effectiveness</td>
<td>Dollars</td>
<td>Natural units (life years, mg/dl blood sugar, LDL cholesterol)</td>
</tr>
<tr>
<td>Cost benefit</td>
<td>Dollars</td>
<td>Dollars</td>
</tr>
<tr>
<td>Cost utility</td>
<td>Dollars</td>
<td>Quality adjusted life years</td>
</tr>
</tbody>
</table>

Perspective

- The “point of view” considered in economic analyses influences the outcomes and costs considered to be most relevant:
  - Provider
  - Patient
  - Payer
  - Society
Measurement of resource use

Direct Medical Costs
(Medications, hospital days, tests, procedures, etc.)

Other Direct (non-medical) Costs
(transportation to the doctor’s office, hiring a baby sitter so a parent can visit the doctor, etc.)

Indirect Costs
(Unpaid assistance, days lost from work, decreased productivity, etc.)

Intangible Costs
(Pain, suffering, etc.)

Measurement in cost-effectiveness analysis

- Comparing More than One Intervention

- Incremental Cost-Effectiveness Ratio (ICER)
  \[ \text{ICER} = \frac{C_1 - C_2}{E_1 - E_2} \]

  - \((C_1, E_1) = \text{(cost, effect) in the intervention/treatment group1}\)
  - \((C_2, E_2) = \text{(cost, effect) in the control/usual care group2}\)
Cost-effectiveness plane

5) Recency

- Need to update
6) Sponsoring society

- Respected national bodies
  - National Health Security Office: NHSO
- Organization
  - The Royal College of Physician of Thailand: RCPT
- Society
  - Thai Society of Nephrology

7) Review

- Review by sponsor organization, other than panel member.
8) Conflict of interest

- When an individual or organization is involved in multiple interests, one of which could possibly corrupt the motivation for an act in the other
- No conflict of interest
# Conflict of interest

## The Work Under Consideration for Publication

<table>
<thead>
<tr>
<th>Type</th>
<th>No</th>
<th>Money Paid to You</th>
<th>Money to Your Institution*</th>
<th>Name of Entity</th>
<th>Comments**</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Grant</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>2. Consulting fee or honorarium</td>
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<td></td>
<td></td>
<td></td>
<td>ADD</td>
</tr>
<tr>
<td>3. Support for travel to meetings for the study or other purposes</td>
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<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>4. Fees for participation in review activities such as data monitoring boards, statistical analysis, and point committees, and the like</td>
<td></td>
<td></td>
<td></td>
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<td>ADD</td>
</tr>
<tr>
<td>5. Payment for writing or reviewing the manuscript</td>
<td></td>
<td></td>
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<td>X</td>
</tr>
<tr>
<td>6. Provision of writing assistance, medicines, equipment, or administrative support</td>
<td></td>
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</table>

## Relevant financial activities outside the submitted work

<table>
<thead>
<tr>
<th>Type of Relationship (in alphabetical order)</th>
<th>No</th>
<th>Money Paid to You</th>
<th>Money to Your Institution*</th>
<th>Entity</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Board membership</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>2. Consultancy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ADD</td>
</tr>
<tr>
<td>3. Employment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>4. Expert testimony</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ADD</td>
</tr>
<tr>
<td>5. Grants/grants pending</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ADD</td>
</tr>
<tr>
<td>6. Payment for lectures including service on speakers bureaus</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>7. Payment for manuscript preparation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ADD</td>
</tr>
</tbody>
</table>
Disagreement among guidelines

- Guidelines on the same clinical question by different expert groups often disagree.
- Usually the differences are minor; with screening guidelines, for example, they might differ on the age at which screening should begin and end or the time interval between screening examinations.
- Disagreement may be a barrier to acceptance of guidelines.
- Disagreement among recommendations is not necessarily a sign of poor quality because a weak evidence base may lead to various conclusions.

Attitudes and acceptance

- Clinicians are most likely to accept recommendations from their own specialty society, less likely to trust those prepared by government agencies, and least likely to believe in guidelines prepared by managed care organizations and insurance companies.
- Clinicians are more likely to trust guidelines if they have had a hand in developing them.
  - However, it is neither practical nor necessary for local physicians to build new guidelines from the ground up if guidelines by national groups already exist.
Grading guidelines

- A common approach is to grade the strength of the evidence and the strength of the recommendation separately.
- There are many grading systems.
  - The US Preventive Services Task Force (USPSTF)
  - The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system
  - Guideline recommendation and evidence grading (GREG)

USPSTF grading scheme for recommendations

<table>
<thead>
<tr>
<th>Classification</th>
<th>USPSTF grading scheme for recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>The USPSTF <strong>strongly recommends</strong> that clinicians provide [the service] to eligible patients. The USPSTF found good evidence that [the service] improves important health outcomes and concludes that benefits substantially outweigh harms.</td>
</tr>
<tr>
<td>B</td>
<td>The USPSTF <strong>recommends</strong> that clinicians provide [this service] to eligible patients. The USPSTF found at least fair evidence that [the service] improves important health outcomes and concludes that benefits outweigh harms.</td>
</tr>
<tr>
<td>C</td>
<td>The USPSTF makes <strong>no recommendation</strong> for or against routine provision of [the service]. The USPSTF found at least fair evidence that [the service] can improve health outcomes but concludes that the balance of benefits and harms is too close to justify a general recommendation.</td>
</tr>
<tr>
<td>D</td>
<td>The USPSTF <strong>recommends against</strong> routinely providing [the service] to asymptomatic patients. The USPSTF found at least fair evidence that [the service] is ineffective or that harms outweigh benefits.</td>
</tr>
<tr>
<td>I</td>
<td>The USPSTF concludes that the evidence is <strong>insufficient</strong> to recommend for or against routinely providing [the service]. Evidence that the [service] is effective is lacking, of poor quality, or conflicting and the balance of benefits and harms cannot be determined.</td>
</tr>
</tbody>
</table>
## USPSTF grading scheme for quality of evidence

<table>
<thead>
<tr>
<th>Scale</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Good</strong></td>
<td>Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes.</td>
</tr>
<tr>
<td><strong>Fair</strong></td>
<td>Evidence is sufficient to determine effects on health outcomes, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies, generalizability to routine practice, or indirect nature of the evidence on health outcomes.</td>
</tr>
<tr>
<td><strong>Poor</strong></td>
<td>Evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.</td>
</tr>
</tbody>
</table>

## The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system

- In GRADE, grades have two components,
  - A number (1 or 2) reflecting the strength of the recommendation.
    - 1 Strong
    - 2 Weak
  - A letter (A, B, C, or D) reflecting the quality of the evidence supporting that recommendation.
# The GRADE system

## Strength of recommendations

<table>
<thead>
<tr>
<th>Level</th>
<th>Group</th>
<th>Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Strong</td>
<td>For clinicians</td>
<td>Most individuals should receive the intervention.</td>
</tr>
<tr>
<td></td>
<td>For patients</td>
<td>Most individuals want the recommended course of action.</td>
</tr>
<tr>
<td></td>
<td>For quality monitors</td>
<td>Adherence to this recommendation could be used as a quality criterion indicator of your practice.</td>
</tr>
<tr>
<td>2 Weak</td>
<td>For clinicians</td>
<td>Offering the suggested action and helping individuals to make a decision. Use decision aids.</td>
</tr>
<tr>
<td></td>
<td>For patients</td>
<td>The majority of individual in this situation would want the suggested course of action, but many would not.</td>
</tr>
<tr>
<td></td>
<td>For quality monitors</td>
<td>Consider clinicians’ discussion of the pros and cons of the intervention with the patients as a quality criterion.</td>
</tr>
</tbody>
</table>

## Quality of Evidence

<table>
<thead>
<tr>
<th>Quality rating</th>
<th>Definition</th>
<th>Underlying methodology</th>
</tr>
</thead>
<tbody>
<tr>
<td>A High</td>
<td>Further research is unlikely to change our confidence in the estimate of effect.</td>
<td>- RCTs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Well-done observational studies</td>
</tr>
<tr>
<td>B Moderate</td>
<td>Further research is likely to have an important influence on our confidence and may change the estimate.</td>
<td>- RCTs with important limitation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Well-done observational studies</td>
</tr>
<tr>
<td>C Low</td>
<td>Further research is very likely to have an important influence on our confidence and is likely to change the estimate.</td>
<td>RCTs with serious limitations</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Observational studies</td>
</tr>
<tr>
<td>D Very low</td>
<td>Any estimate of effect is uncertain.</td>
<td>- Poorly controlled observational studies</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Case series, case report</td>
</tr>
</tbody>
</table>
Guideline recommendation and evidence grading (GREG)

<table>
<thead>
<tr>
<th>Recommendation grade</th>
<th>Evidence grading</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (Recommendation)</td>
<td>I (High)</td>
</tr>
<tr>
<td>B (Provisional</td>
<td>II (Intermediate)</td>
</tr>
<tr>
<td>recommendation)</td>
<td></td>
</tr>
<tr>
<td>C (Consensus opinion)</td>
<td>III (Low)</td>
</tr>
</tbody>
</table>

- **Recommendation grade:**
  - A (Recommendation): there is robust evidence to recommend a pattern of care
  - B (Provisional recommendation): on balance of evidence, a pattern of care is recommended with caution
  - C (Consensus opinion): evidence being inadequate, a pattern of care is recommended by consensus

- **Evidence grade:**
  - I (High): the described effect is plausible, precisely quantified and not vulnerable to bias
  - II (Intermediate): the described effect is plausible but is not quantified precisely or may be vulnerable to bias
  - III (Low): concerns about plausibility or vulnerability to bias severely limit the value of the effect being described and quantified

Guideline recommendation and evidence grading (GREG)

- **Recommendation grade:**
  - A (Recommendation): there is robust evidence to recommend a pattern of care
  - B (Provisional recommendation): on balance of evidence, a pattern of care is recommended with caution
  - C (Consensus opinion): evidence being inadequate, a pattern of care is recommended by consensus

- **Evidence grade:**
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  - II (Intermediate): the described effect is plausible but is not quantified precisely or may be vulnerable to bias
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The Conference on Guideline Standardization (COGS)
Checklist for Reporting Clinical Practice Guidelines

Standardized Reporting of Clinical Practice Guidelines: A Proposal
from the Conference on Guideline Standardization*

Richard N. Shiffman, MD, MSc; Paul Shekelle, MD, PhD; J. Marc Overhage, MD, PhD; Joan Slutsky, PA, MSPH;
Jeremy Grimshaw, MB, ChB, PhD; and Aniruddha M. Deshpande, MD


Standardization elements of a complete
report on clinical practice guidelines

<table>
<thead>
<tr>
<th>Topic</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Overview material</td>
<td>Provide a <strong>structured abstract</strong> that includes the guideline's release date, status (original, revised, updated), and print and electronic sources.</td>
</tr>
<tr>
<td>2. Focus</td>
<td>Describe the <strong>primary disease/condition and intervention/service/technology that the guideline addresses</strong>. Indicate any alternative preventive, diagnostic or therapeutic interventions that were considered during development.</td>
</tr>
<tr>
<td>3. Goal</td>
<td>Describe the goal that following the guideline is <strong>expected to achieve</strong>, including the rationale for development of a guideline on this topic.</td>
</tr>
</tbody>
</table>
### Standardization elements of a complete report on clinical practice guidelines

<table>
<thead>
<tr>
<th>Topic</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>4. Users/setting</td>
<td>Describe the intended <strong>users of the guideline</strong> (eg, provider types, patients) and the settings in which the guideline is intended to be used.</td>
</tr>
<tr>
<td>5. Target population</td>
<td>Describe the <strong>patient population</strong> eligible for guideline recommendations and list any exclusion criteria.</td>
</tr>
<tr>
<td>6. Developer</td>
<td>Identify the <strong>organization(s) responsible for guideline development</strong> and the names/credentials/potential conflicts of interest of individuals involved in the guideline's development.</td>
</tr>
</tbody>
</table>

### Standardization elements of a complete report on clinical practice guidelines

<table>
<thead>
<tr>
<th>Topic</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>7. Funding source/sponsor</td>
<td>Identify the funding source/sponsor and describe its <strong>role in developing</strong>, and/or reporting the guideline. Disclose potential conflict of interest.</td>
</tr>
<tr>
<td>8. Evidence collection</td>
<td>Describe the <strong>methods used</strong> to search the scientific literature, including the range of dates and databases searched, and criteria applied to filter the retrieved evidence.</td>
</tr>
<tr>
<td>9. Recommendation grading criteria</td>
<td>Describe the <strong>criteria used to rate the quality</strong> 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 or harms.</td>
</tr>
</tbody>
</table>
### Standardization elements of a complete report on clinical practice guidelines

<table>
<thead>
<tr>
<th>Topic Description</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>10. Method for synthesizing evidence</td>
<td>Describe <strong>how evidence was used</strong> to create recommendations, eg, evidence tables, meta-analysis, decision analysis.</td>
</tr>
<tr>
<td>11. Pre-release review</td>
<td>Describe how the guideline developer reviewed and/or tested the guidelines <strong>prior to release</strong>.</td>
</tr>
<tr>
<td>12. Update plan</td>
<td>State whether or not there is a <strong>plan to update</strong> the guideline and, if applicable, an expiration date for this version of the guideline.</td>
</tr>
<tr>
<td>13. Definitions</td>
<td><strong>Define unfamiliar terms</strong> and those critical to correct application of the guideline that might be subject to misinterpretation.</td>
</tr>
<tr>
<td>14. Recommendations and rationale</td>
<td>State the <strong>recommended action precisely</strong> 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 9.</td>
</tr>
<tr>
<td>15. Potential benefits and harms</td>
<td>Describe <strong>anticipated benefits and potential risks</strong> associated with implementation of guideline recommendations.</td>
</tr>
<tr>
<td>16. Patient preferences</td>
<td>Describe the <strong>role of patient preferences</strong> when a recommendation involves a substantial element of personal choice or values.</td>
</tr>
<tr>
<td>17. Algorithm</td>
<td>Provide (when appropriate) a <strong>graphical description</strong> of the stages and decisions in clinical care described by the guideline.</td>
</tr>
<tr>
<td>18. Implementation considerations</td>
<td>Describe <strong>anticipated barriers to application</strong> 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.</td>
</tr>
</tbody>
</table>
Example
Methods for guideline development


AIM

The overall aim of this project was to develop an evidence-based clinical practice guideline for evaluation and management of CKD. The guideline consists of recommendation statements, rationales, and a summary of systematically generated evidence on relevant pre-defined clinical topics. To a large extent the guideline builds on the output of the KDIGO Controversies Conference in 2009, which generated epidemiological data to support a revision of the classification and staging system. The vision for this KDIGO guideline is that it would endorse the current CKD definition as an imperfect convention for describing a state of function, revise classification based on risk, revise risk states, and revise and update action plans in view of the revised classifications. Additional systematic evidence review focused on specific topics.

OVERVIEW PROCESS

The guideline development process 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 predefined 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 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 January 2012 and for public review in May 2012
- Publishing the final version of the guideline
APPROACH TO EVIDENCE REVIEW TOPICS
Formulating Questions of Interest
Questions of interest were formulated according to the PICODD (Population, Intervention or Predictor, Comparator, Outcome, study Design, and Duration of follow-up) criteria. Details of the PICODD criteria are presented in Table 37.

Literature Searches and Article Selection for Evidence Review Topics
Search strategies were developed by the ERT, with input from the Work Group, for each topic of interest (whether treatment or non-treatment topics). The ERT performed literature searches and conducted abstract and article screening. The ERT also coordinated the methodological and analytic processes, data extraction, and summarizing of the evidence. Before initiating our own de novo systematic review, we searched for existing systematic reviews that could be used. The searches and search terms are provided in Supplemental Table 1 and the search dates and yields for all topics are presented in Table 38.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Question</th>
<th>Population</th>
<th>Treatment, predictors or explanatory test</th>
<th>Comparator or alternatives</th>
<th>Outcome measured by importance</th>
<th>Study design</th>
<th>Inclusion criteria</th>
<th>Methodological approach</th>
<th>No. of relevant articles retrieved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment with bicarbonate</td>
<td>Does treatment with bicarbonate in CKD improve clinical outcomes?</td>
<td>GFR &gt; 30 ml/min/1.73 m² and/or kidney transplant</td>
<td>Bicarbonate or choline</td>
<td>No bicarbonate or choline</td>
<td>GFR, categorical or continuous kidney function, QOL, and BP controlled as adverse events</td>
<td>RCT</td>
<td>N &gt; 500</td>
<td>Review of Cochrane SR plus systematic search for RCTs published after search dates in most recent Cochrane SR</td>
<td>1</td>
</tr>
<tr>
<td>Treatment with allopurinol</td>
<td>Does treatment with allopurinol in CKD improve clinical outcomes?</td>
<td>GFR &gt; 30 ml/min/1.73 m² and/or kidney transplant</td>
<td>Allopurinol</td>
<td>No allopurinol</td>
<td>Morbidity, cardiovascular events, ESRD, CKD progression, post-transplant QOL, and BP controlled as adverse events</td>
<td>RCT</td>
<td>N &gt; 500</td>
<td>SR</td>
<td>1</td>
</tr>
<tr>
<td>Timing of initiation of RT in CKD</td>
<td>Should dialysis be started early or late?</td>
<td>GFR &gt; 30 ml/min/1.73 m² and/or kidney transplant</td>
<td>Early start of dialysis</td>
<td>Late start of dialysis</td>
<td>Morbidity, ESRD</td>
<td>RCT</td>
<td>N &gt; 500</td>
<td>Review of studies identified by RCT</td>
<td>1</td>
</tr>
<tr>
<td>Renal restriction</td>
<td>Should patients with CKD be on a protein-restricted diet?</td>
<td>GFR &gt; 30 ml/min/1.73 m² and/or kidney transplant</td>
<td>Reduced protein intake</td>
<td>Usual protein intake</td>
<td>GFR, mortality, categorical or continuous kidney function</td>
<td>RCT</td>
<td>N &gt; 500</td>
<td>Review of Cochrane SR plus systematic search for RCTs published after search dates in most recent Cochrane SR</td>
<td>1</td>
</tr>
</tbody>
</table>
Grading the Quality of Evidence and the Strength of Guideline Recommendations

A structured approach, based on the GRADE approach, was used to grade the quality of the overall evidence and the strength of recommendations for each topic. This grading scheme—with two levels for the strength of a recommendation together with four levels of grading for 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.
## Strength of recommendation

<table>
<thead>
<tr>
<th>Grade*</th>
<th>Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Level 1</strong>&lt;br&gt;<strong>We recommend</strong>&lt;br&gt;Most people in your situation would want the recommended course of action and only a small proportion would not.</td>
<td><strong>Patients</strong>&lt;br&gt;Most patients should receive the recommended course of action.</td>
</tr>
<tr>
<td><strong>Level 2</strong>&lt;br&gt;<strong>We suggest</strong>&lt;br&gt;The majority of people in your situation would want the recommended course of action, but many would not.</td>
<td><strong>Patients</strong>&lt;br&gt;</td>
</tr>
</tbody>
</table>

## Quality of the supporting evidence

<table>
<thead>
<tr>
<th>Grade</th>
<th>Quality of evidence</th>
<th>Meaning</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>High</td>
<td>We are confident that the true effect lies close to that of the estimate of the effect.</td>
</tr>
<tr>
<td>B</td>
<td>Moderate</td>
<td>The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.</td>
</tr>
<tr>
<td>C</td>
<td>Low</td>
<td>The true effect may be substantially different from the estimate of the effect.</td>
</tr>
<tr>
<td>D</td>
<td>Very low</td>
<td>The estimate of effect is very uncertain, and often will be far from the truth.</td>
</tr>
</tbody>
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**EVIDENCE REVIEW TEAM**

Tufts Center for Kidney Disease Guideline Development and Implementation
Tufts Medical Center, Boston, MA, USA:

- Katrin Uhlig, MD, MS, Project Director; Director, Guideline Development
- Dana Miskulin, MD, MS, Staff Nephrologist
- Amy Earley, BS, Project Coordinator
- Shana Haynes, MS, DHSc, Research Assistant
- Jenny Lamont, MS, Project Manager

In addition, support and supervision were provided by:

- Ethan M Balk, MD, MPH; Program Director, Evidence Based Medicine
Prevention of CKD progression

Protein intake

3.1.13: We suggest lowering protein intake to 0.8 g/kg/day in adults with diabetes (2C) or without diabetes (2B) and GFR < 30 ml/min/1.73 m² (GFR categories G4-G5), with appropriate education.

3.1.14: We suggest avoiding high protein intake (>1.3 g/kg/day) in adults with CKD at risk of progression. (2C)

Glycemic control

3.1.15: We recommend a target hemoglobin A₁c (HbA₁c) of ~7.0% (53 mmol/mol) to prevent or delay progression of the microvascular complications of diabetes, including diabetic kidney disease. (1A)

3.1.16: We recommend not treating to an HbA₁c target of <7.0% (<53 mmol/mol) in patients at risk of hypoglycemia. (1B)

3.1.17: We suggest that target HbA₁c be extended above 7.0% (53 mmol/mol) in individuals with comorbidities or limited life expectancy and risk of hypoglycemia. (2C)

3.1.18: In people with CKD and diabetes, glycemic control should be part of a multifactorial intervention strategy addressing blood pressure control and cardiovascular risk, promoting the use of angiotensin-converting enzyme inhibition or angiotensin receptor blockade, statins, and antiplatelet therapy where clinically indicated. (Not Graded)

Rationale

These statements are worded to reflect the potential benefits and dangers of varying dietary protein intake (DPI) in people with CKD. Excess dietary protein leads to the accumulation of uremic toxins, conversely insufficient protein intake may lead to loss of lean body mass, and malnutrition (the latter more frequent in the elderly). The benefits of dietary protein restriction include reduction of accumulation of metabolic waste products that may suppress the appetite and stimulate muscle protein wasting. The role of dietary protein restriction in slowing progression of CKD is more controversial and advanced CKD is associated with a protein wasting syndrome which is directly correlated with morbidity and mortality. Note that statements about reduction in dietary protein do not apply to pediatric populations given issues related to growth and nutrition.

Evidence Base

A number of systematic reviews and meta-analyses have pooled the available RCT data. Pedrini et al. compared a low-protein diet (LPD), defined as a DPI of 0.4 to 0.6 g/kg/day, with a usual diet (5 RCTs, N = 1413) over a period of follow-up ranging between 18-36 months in people with non-diabetic CKD and GFR < 30 ml/min/1.73 m². Pousset et al. updated this analysis to include 8 RCTs in people with non-diabetic CKD (N = 1528). DPI in their low-protein group was between 0.3-0.6 g/kg/day and follow-up ranged from 12-24 months (5 of 8 studies were in people with GFR categories G4-G5 (GFR < 30 ml/min/1.73 m²). Robertson et al. compared diabetic subjects (8 studies in type 1 diabetes, N = 322; 1 study in type 2 diabetes, N = 263). DPI in the low-protein subjects was 0.3-0.8 g/kg/day and usual protein intake ranged from 1.2 g/kg/day. Mean follow-up ranged from 4.5 months to 4 years. In all studies, compliance with a low DPI was poor. There was
<table>
<thead>
<tr>
<th>Topic</th>
<th>Discussed in KDIGO CKD Guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Overview material</td>
<td>Abstract and Methods for Guideline Development.</td>
</tr>
<tr>
<td>2. Focus</td>
<td>Evaluation and management of adults and children with CKD.</td>
</tr>
<tr>
<td>3. Goal</td>
<td>This clinical practice guideline is intended to assist the practitioner caring for patients with CKD and to prevent deaths, cardiovascular disease events and progression to kidney failure while optimizing patients' quality of life.</td>
</tr>
<tr>
<td>4. User-setting</td>
<td>Providers: Nephrologists (adult and pediatric), Dialysis providers (including nurses), Internists, and Pediatricians. Patients: Adult and pediatric individuals at risk for or with CKD. Policy Makers: Those in related health fields.</td>
</tr>
<tr>
<td>5. Target population</td>
<td>Individuals at risk for or with CKD.</td>
</tr>
<tr>
<td>6. Developer</td>
<td>Organization: KDIGO. Refer to Biographic and Disclosure Information section.</td>
</tr>
<tr>
<td>7. Funding source/sponsor</td>
<td>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 Calk</td>
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<tr>
<td>8. Evidence collection</td>
<td>Screening criteria are outlined in the methods chapter. The search was updated through June 2011 and supplemented by articles identified by Work Group members through November 2012. We also searched for pertinent existing guidelines and systematic reviews.</td>
</tr>
<tr>
<td>9. Recommendation grading criteria</td>
<td>Quality of individual studies was graded in a three-tiered grading system (see Table 39). Quality of evidence (Table 40) was graded following the GRADE approach. Strength of the recommendation was graded in a two-level grading system which was adapted from GRADE for KDIGO with the quality of overall evidence graded on a four-tiered system (Tables 41 and 43). The Work Group could provide general guidance in ungraded statements.</td>
</tr>
<tr>
<td>10. Method for synthesizing evidence</td>
<td>For systematic review topics, summary tables and evidence profiles were generated. For recommendations on treatment interventions, the steps outlined by GRADE were followed.</td>
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<tr>
<td>11. Pre-release review</td>
<td>The guideline had undergone internal review by the KDIGO Board of Directors in January 2012 and external review in May 2012. Public review comments were compiled and fed back to the Work Group, which considered comments in its revision of the guideline.</td>
</tr>
<tr>
<td>12. Update plan</td>
<td>There is no date set for updating this entire guideline. 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. Specific sections may be updated separately from the entire guideline within the next 3-5 years depending on the evidence base.</td>
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Algorithm for further investigation of a positive reagent trip test
Treatment AF algorithm

Treatment strategy decision tree

- Confirmed diagnosis of AF
- Further investigations and clinical assessment including risk stratification for stroke/thromboembolism
  - Paroxysmal AF
  - Persistent AF
  - Permanent AF

- Rhythm or rate?
- Rhythm control
  - Remains symptomatic
    - Failure of rhythm control
      - Try rhythm control first for patients with persistent AF:
        - who are symptomatic
        - who are younger
        - presenting for the first time with lone AF
        - secondary to a treated or corrected precipitant
        - with congestive heart failure.
      - By rate-control first for patients with persistent AF:
        - over 65
        - with coronary artery disease
        - with contraindications to antiarrhythmic drugs
        - unsuitable for cardioversion?
Thromboprophylaxis

Antithrombotic therapy for persistent AF

- Before cardioversion, maintain patients on therapeutic anticoagulation with warfarin (INR 2.5, range 2.0 to 3.0) for at least 3 weeks.
- After successful cardioversion, maintain patients on therapeutic anticoagulation with warfarin (INR 2.5, range 2.0 to 3.0) for at least 4 weeks.
- If cardioversion cannot be postponed for 3 weeks:
  - give heparin before cardioversion
  - give warfarin for at least 4 weeks after cardioversion.
- After cardioversion, continue anticoagulation long term in patients with a high risk of AF recurrence or where it is recommended by the stroke risk stratification algorithm (see page 7). Factors indicating a high risk of AF recurrence include:
  - a history of failed cardioversion attempts
  - mitral valve disease, LV dysfunction or enlarged left atrium.
- Anticoagulation is not required when cardioversion successfully restores sinus rhythm in a patient with AF of confirmed duration of less than 48 hours.

Critical appraisal
Users’ guides for the validity of recommendations

1. Do the recommendations consider **all relevant** patient groups, management options, and possible outcomes?
2. Are there **systemic reviews** of evidence that estimate the relative effect of management options on relevant outcome?
3. Is there an appropriate specification of values and **preferences** associate with outcomes?
4. Do the authors **grade the strength** of their recommendation?

1) Do the recommendations consider **all relevant** patient groups, management options, and possible outcomes?

- Did the recommendation consider all relevant patient groups?
  - Low risk and high risk
  - More and less susceptible to adverse effects
- Did the recommendation consider all relevant management options?
  - Surgical and medical
  - No-treatment option
- Did the recommendation consider all patient-important outcomes?
  - Morbidity and mortality
  - Quality of life
  - Toxicity and adverse effects
  - Inconvenience
  - Psychological burden
  - Cost to the patient or to society
2) Are there **systemic reviews** of evidence that estimate the relative effect of management options on relevant outcome?

- Systematic review: high quality
- Recommendations may deal with the best (often low-quality) evidence available → weak recommendation

3) Is there an appropriate specification of **values and preferences** associate with outcomes

- Relative importance of diseases is vary.
- Example:
  - **HRT**  
    - Risk of developing breast cancer 
    - Decreased in perimenopausal hot flashes
4) Do the authors **grade the strength** of their recommendation?

- The grades of recommendation, assessment, development, and evaluation (GRADE) system
- Classify recommendation in 2 levels
  - **Strong**
  - **Weak**
- Quality of evidence classification
  - **High**
  - **Moderate**
  - **Low**
  - **Very low**

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### Factors affect the quality of evidence

- Decrease the quality of evidence
  - Poor quality of planning or implementation of the available studies, suggesting high likelihood of bias
  - Inconsistency of results
  - Indirectness of evidence
  - Imprecise estimates
  - Publication bias
- Increase the quality of evidence
  - Large magnitude of effect
  - All plausible confounding would reduce a demonstrated effect
  - Dose-response gradient
Conclusion

- Clinical practice guidelines are recommendations for clinicians about the care of patients with specific conditions.

- Guideline development should involve a systematic review of the research evidence related to decision-making for the targeted condition/question.
  - recommendations about patient management based on the evidence and value judgments that should be explicitly identified.

Conclusion

- Guidelines are suggestions for care, not rules.
  - There will always be individual patients who should be managed differently for reasons including biologic differences (in drug metabolism, immune response or genetic endowment); comorbidities; availability of resources and cultural differences; and patient preferences.

- Guidelines vary widely in quality.