Clinical practice guidelines

Treatment strategies to slow the progression of chronic renal failure in adults

September 2004
Treatment strategies to slow the progression of chronic renal failure in adults
## Synopsis

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<tr>
<td>Publication date</td>
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<td>Clinical practice guidelines</td>
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<tr>
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<td>All health professionals</td>
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<tr>
<td>Requested by</td>
<td>Collège universitaire des enseignants en néphrologie</td>
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<td>ANAES – French National Agency for Accreditation and Evaluation in Healthcare (Guidelines Department)</td>
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<td>Objectives</td>
<td>Propose treatment strategies to slow the progression of moderate chronic renal failure</td>
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| Assessment method | - Systematic review of the literature (with evidence levels)  
- Discussion among members of an ad hoc working group  
- External validation by peer reviewers |
| Literature search | 1992 - 2003  
127 cited out of 584 analysed |
| Project management | Project leaders: Dr Taraneh Shojaei-Brosseau and Dr Michel Laurence  
(Department head: Dr Patrice Dosquet)  
Literature search: Mireille Cecchin with the help of Renée Cardoso  
(Department head: Rabia Bazi)  
Secretarial work: Laetitia Gourbail |
| Collaborations and participants (annex 1) | - Learned societies  
- Steering committee  
- Working group (Chair: Professor Claude Jacobs, nephrologist, Paris)  
- Peer reviewers |
| Author of draft report | Dr Cécile Couchoud, epidemiologist, Paris |
| Internal validation | ANAES Scientific Council (Referee: Professor Muriel Rainfray)  
Validated on September 2004 |
| Related documents | Full report (in French)  
Available on ANAES website ([www.anaes.fr](http://www.anaes.fr)) |
| Other ANAES publications on the topic | Diagnosis of chronic renal failure in adults (Sept. 2002) |
10 key points

1. The disease
   - CRF is a progressive disease that remains silent for a long time.
   - End-stage renal disease (ESRD) requires dialysis or kidney transplantation.

2. Main targets to slow CRF progression
   - hypertension
   - proteinuria.

3. Treatment goals
   - blood pressure < 130/80 mmHg, lower if possible;
   - proteinuria < 0.5 g/day.

4. Recommended drugs
   - angiotensin converting enzyme inhibitors (ACE inhibitors)
   - angiotensin-II receptor antagonists (A2RA).
   ACE inhibitors are recommended in all patients except type 2 diabetics
   A2RA are recommended in type 2 diabetics

5. In addition to drug therapy
   - salt restriction to 100 mmol/day (6 g/day)

6. If treatment goals are not achieved
   - if blood pressure goal is not achieved: add a thiazide or loop diuretic;
   - if proteinuria goal is not achieved: give ACE inhibitor + A2RA;
   - if neither goal is achieved: add another class of antihypertensive to current regimen

7. Recommended protein intake
   - 0.8 g/kg/day
   A consultation with a dietician is recommended.

8. Intervals between clinical and laboratory monitoring
   - according to rate of CRF progression (GFR divided by 10 (in months), i.e. a patient with a GFR of 40 ml/min is monitored every 4 months).

9. Precautions in the use of other drugs
   - adjust doses to renal function, particularly for nephrotoxic drugs
     (aminoglycosides, NSAIDs, iodine-containing contrast media).

10. Patient management
    - by a multidisciplinary team, especially in diabetics.
I. Introduction

I.1 Objective and scope of the guidelines

These guidelines concern treatment strategies to slow the progression of chronic renal failure (CRF) in adults with moderate CRF i.e. glomerular filtration rate (GFR) between 30 and 60 ml/min.

They do not cover:
- detecting CRF at an early stage
- screening patients at risk of impaired renal function
- treating the cause of CRF
- treating complications of CRF
- preventing extrarenal complications
- CRF in renal transplant recipients
- CRF in children.

They are intended for all health professionals.

I.2 Definition and assessment of chronic renal failure (CRF)

In the guidelines on “Diagnosis of chronic renal failure in adults” (ANAES, September 2002), CRF was defined as a permanent reduction in GFR secondary to renal disease, and the Cockcroft-Gault formula was recommended for routine estimation of CRF in all patients.

$$\text{GFR} = \frac{\left[(140-\text{age}) \times \text{weight} / \text{serum creatinine}\right] \times \text{K}}{\text{K} = 1.23 \text{ for men} \text{ and } 1.04 \text{ for women}}$$

However, there has been little assessment of how well this formula works in subjects over 75 years of age, and further data on GFR measurement are needed to define the renal failure threshold accurately in the elderly (agreement among professionals).

In the 2002 guidelines, renal disease severity was classified as shown in Table 1.

Table 1. Classification of chronic renal disease and severity of chronic renal failure

<table>
<thead>
<tr>
<th>Stage</th>
<th>Definition</th>
<th>GFR (ml/min/1.73m²)</th>
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<tbody>
<tr>
<td>1</td>
<td>Chronic renal disease*</td>
<td>≥ 60</td>
</tr>
<tr>
<td>2</td>
<td>Moderate renal failure</td>
<td>30-59</td>
</tr>
<tr>
<td>3</td>
<td>Severe renal failure</td>
<td>15-29</td>
</tr>
<tr>
<td>4</td>
<td>End-stage renal disease (ESRD)†</td>
<td>&lt; 15</td>
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</tbody>
</table>
Treatment strategies to slow the progression of chronic renal failure in adults

* Abnormal laboratory values and/or histological findings and/or imaging findings for more than 3 months; † ESRD is defined as an estimated creatinine clearance of < 15 ml/min/1.73 m² irrespective of whether renal replacement therapy (dialysis or transplantation) has begun.

II. Assessment method

These guidelines were produced using a three-step method comprising:
(i) a critical review of the literature published from ..... to .......... This review was limited to studies of a high level of evidence (meta-analyses of randomised controlled trials, randomised controlled trials) and existing French or foreign guidelines;
(ii) discussions within a working group (3 meetings);
(iii) comments by peer reviewers.

They were graded on the basis of the level of evidence of the supporting studies (Annex 2). If no grade is given, they are based on agreement among professionals within the working group after taking into account the comments of peer reviewers.

There is no consensus definition for slowing of progression of CRF. Studies differ with respect to:
- endpoints (renal death, estimated renal function impairment as given by repeated measurements of serum creatinine or clearance of exogenous substances, use of combined endpoints);
- length of follow-up.

Preference was given to studies with progression to ESRD as the primary endpoint and with more than a year of follow-up. Possible sources of bias (error in endpoint measurement, patient selection, confounding variables and lacking information) were taken into account in the review. At times, the results had to be extrapolated (with agreement among professionals) to patients not included in the trial protocol, thus introducing an element of uncertainty.

III. Aims of management

CRF is a progressive disease that remains silent for a long time. End-stage CRF requires dialysis or kidney transplantation. The treatment strategies that have been assessed are management of hypertension, low-protein diet, management of dyslipidaemia, management of obesity and giving up smoking.

The main factors in CRF progression that can be corrected are:
- hypertension
- proteinuria.

Such correction slows progression, mainly in chronic glomerular disease (grade A).

In patients with moderate CRF with hypertension (BP > 130/80 mmHg) and proteinuria = 0.5 g/day, the only treatments that have been shown to be nephroprotective (i.e. have slowed progression of CRF) are:
- angiotensin-converting enzyme inhibitors (ACE inhibitors)
- angiotensin-II receptor antagonists (A2RA).

However, the other strategies mentioned above can help prevent cardiovascular risk.

The aim of management for moderate CRF is to delay dialysis or transplantation while maintaining the patient in a satisfactory state of health. This means:
- achieving and maintaining satisfactory nutritional status (blood albumin ≥ 35 g/l);
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- achieving and maintaining salt and water balance (no oedema);
- maintaining blood phosphorus ≤ 1.3 mmol/l;
- maintaining serum potassium ≤ 5.5 mmol/l;
- maintaining a satisfactory acid-base balance (plasma bicarbonate 23 - 27 mmol/l);
- regularly reviewing prescriptions (nephrotoxic drugs, dose adjustment according to GFR, etc.);
- maintaining haemoglobin concentration between 11 and 12 g/dl.

IV. Treatment strategy

The treatment strategy proposed by the working group targets hypertension and proteinuria and was based on available data and current medical practice.

IV.1 Treatment goals

The aim is to slow CRF progression by achieving the following thresholds (extrapolated from randomised trials and agreed by consensus):
- blood pressure < 130/80 mmHg, lower if possible;
- residual proteinuria as low as possible, maximum 0.5 g/day.

IV.2 First-line treatment

- If proteinuria < 0.5g/day and BP < 130/80 mmHg: Clinical and laboratory value monitoring alone (agreement among professionals)

- In all other cases:
  - restrict salt to 100 mmol/day (6 g/day) (agreement among professionals);
  - A2RA for type 2 diabetics (grade A);
  - ACE inhibitor for all other patients (grade A for non-diabetics and grade B for type 1 diabetics).

IV.3 Prescribing an ACE inhibitor or A2RA

- Start with a low dose and increase gradually in steps of at least 4 weeks. This is particularly important in elderly patients or patients with impaired renal function. The dose should be increased until treatment goals are reached (agreement among professionals).

- Serum creatinine and serum potassium should be determined 7-15 days after starting treatment and after each dose adjustment because of the risk of a (functional) decrease in renal function under ACE inhibitors or A2RA:
  - If serum creatinine rises by more than 30%, withdraw ACE inhibitors temporarily. They may be reintroduced gradually after renal artery stenosis has been eliminated (agreement among professionals);
  - Treatment should be discontinued temporarily if serum potassium exceeds 6 mmol/L. If it is between 5-6 mmol/L, check for non-compliance with diet, then treat with a potassium-lowering diuretic (thiazide or loop diuretic) (agreement among professionals).
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- When a stable dose has been achieved, clinical and laboratory monitoring of treatment with ACE inhibitors or A2RA should be performed at the end of the first month, including measurement of blood pressure, 24-hour proteinuria, serum potassium and serum creatinine (see IV.7 below).

IV.4 Recommended strategy as a function of treatment outcome

The recommended strategies as a function of treatment outcome were:

- **Treatment goals have been achieved**: Continue treatment and monitoring. If there are any ACE inhibitor-specific side-effects, notably irritating cough, replace the ACE inhibitor with an A2RA (agreement among professionals).

- **If BP > 130/80 mmHg**: Check compliance with treatment and salt restriction. If necessary, add a thiazide or loop diuretic (depending on severity of renal failure) to ACE inhibitors (grade C). If this fails, add another therapeutic category (beta-blocker or calcium blocker) and seek the advice of a nephrologist (agreement among professionals).

- **If proteinuria > 0.5 g/day**: Gradually increase the dose of the ACE inhibitor or A2RA prescribed (up to the maximum dose in the Marketing Authorisation), provided that clinical and laboratory monitoring show that this is well tolerated (agreement among professionals). If high proteinuria persists (> 0.5 g/day), the working group recommended adding an ACE inhibitor to an A2RA (grade B).

IV.5 The case of diabetics

- Renal failure in a diabetic needs to be managed by a multidisciplinary team (general practitioner, nephrologist, diabetologist, cardiologist, ophthalmologist, dietician).

- Potassium levels need to be monitored closely if an ACE inhibitor or A2RA is used, as the incidence of hyperkalaemia is increased by renal failure and acidosis.

- Monitoring and management of diabetes are not covered by these guidelines. However, the working group noted that:
  - renal failure in diabetics modifies the metabolism of insulin and oral antidiabetics; doses will need to be adjusted according to progression of renal failure to avoid iatrogenic effects;
  - glycated haemoglobin goals are not modified by renal failure.

IV.6 Diet and lifestyle

The recommendations are:

- moderate restriction of protein intake (0.8 g/kg/day) (grade B);
- treatment of dyslipidaemia, if present, according to existing guidelines (agreement among professionals);
- basic fluid intake neither restricted nor excessive, approximately 1.5L/day (agreement among professionals);
- giving up smoking according to existing guidelines (agreement among professionals). Nicotine patches are not contraindicated;
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- energy intake 30-35 kcal/kg/day (agreement among professionals). Energy intake should be adjusted for obese patients. These recommendations require regular monitoring of diet. The working group recommended that consultations with a dietician should be reimbursed.

IV.7 Monitoring of CRF

- Clinical and laboratory monitoring of CRF and of treatment should be performed every 3-6 months. Intervals between monitoring (months) are determined by dividing estimated GFR by 10 (e.g. a patient with a GFR of 40 ml/min should be monitored every 4 months). If possible, samples of venous blood should be taken from the back of the hand to preserve the vein stock.

- Laboratory values to be monitored:
  - estimated glomerular filtration rate using the Cockcroft-Gault formula to assess progression of CRF
  - plasma electrolytes including serum potassium, blood sodium and bicarbonates
  - blood phosphorus, blood calcium
  - full blood count
  - plasma proteins
  - blood albumin
  - 24-hour proteinuria
  - 24-hour urinary urea, sodium and creatinine.
Chronic Renal Failure
GFR 30-60 ml/min

Yes

Proteinuria <0.5 /day and
BP<< 130/80 mmHg

Monitoring

Yes

ACE or A2RA*
+ salt restriction (6g/day)

No

Proteinuria <0.5 g/day and
BP<< 130/80 mmHg

Yes

Continue treatment

No

Proteinuria >0.5 g/day

Increase dose of ACE inhibitor or A2RA*

Yes

Proteinuria < 0.5 g/day

Continue treatment

No

Combine ACE + A2RA

BP >130/80 mmHg

Add diuretic°

Yes

BP<< 130/80 mmHg

Continue treatment

No

Add beta-blocker or calcium-blocker

<<: < 130/80 mmHg, lower if possible
*A2RA if type 2 diabetic, ACE inhibitor in other patients
° thiazide or loop diuretic depending on severity of CRF

Figure 1. Treatment strategy
Annex 1 – Participants

Learned societies consulted

Société française de néphrologie
Société francophone de dialyse
Collège national des généralistes enseignants
Société française de médecine générale
Société de formation thérapeutique du généraliste
Centre de documentation et de recherche en médecine générale

Steering committee

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Dr Évelyne Carre, general practitioner, Reims
Professor Jacques Chanard, nephrologist, Reims
Dr Raymond Frayssinet, nephrologist, Aix-en-Provence
Professor Maurice Laville, nephrologist, Lyon
Professor Bruno Moulin, nephrologist, Strasbourg
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Working group

Professor Claude Jacobs, nephrologist, Paris – Chair
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Dr Michel Laurence, ANAES, Saint-Denis La Plaine – Project manager

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Professor Gérard Friélander, physiologist, Paris
Professor Thierry Hannedouche, nephrologist, Strasbourg
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Dr Bertrand Prouff, general practitioner, Anglet
Professor Philippe Zacui, endocrinologist, Grenoble
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Professor Michel Aparicio, nephrologist, Bordeaux
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Dr Georges Badoc, endocrinologist, Paris
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Jocelyne Bertoglio, dietician, Nice
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Dr Bruno Coevoet, nephrologist, Saint-Quentin
Professor Christian Combe, nephrologist, Bordeaux
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Dr Jean-François Dézier, laboratory analyst, Bain-de-Bretagne
Dr Éric Drahi, general practitioner, Saint-Jean-de-Braye
Dr François Dumel, general practitioner, Audincourt

Professor Michel Godin, nephrologist, Rouen
Dr Samy Hadjadj, diabetologist, Poitiers
Dr Alain Kanfer, nephrologist, Paris
Professor Michèle Kessler, nephrologist, Vandœuvre-les-Nancy
Dr Jean-Louis Lacombe, nephrologist, Toulouse
Dr Etienne Larger, endocrinologist/diabetologist, Paris
Dr Catherine Lasseur, nephrologist, Bordeaux
Dr Sylvie Lavaud, nephrologist, Reims
Dr Jacques Maire, specialist in internal medicine, Dijon
Evelyne Matheron, dietician, Rennes
Professor Françoise Mignon, nephrologist, Paris
Dr Joseph Pollini, nephrologist, Avignon
Professor Muriel Rainfray, geriatrician, Pessac
Professor Jérome Rossert, nephrologist, Paris
Dr Emmanuel Roubertie, general practitioner, Vendôme
Dr Roland Servel, general practitioner, Vitry-le-François
Dr Pierre Simon, nephrologist, Saint-Brieuc
Dr Paul Stroumza, nephrologist, Marseille
Dr Philippe Vanhille, nephrologist, Valenciennes
Annex 2 – Assessment method

The ANAES method for producing these clinical practice guidelines\(^1\) comprised the following steps:

**Defining the scope of the guidelines (Steering committee).** ANAES invited representatives from learned societies concerned by the topic to take part in a steering committee whose job was to define the scope of the guidelines, to review previous work on the subject and to nominate professionals to take part in a working group or act as peer reviewers.

**Literature search (ANAES Documentation Department):** See below

**Drafting the guidelines (Working group).** The ANAES project manager formed a working group of 13 professionals from a number of disciplines, working in different types of practice, from all over the country. The chair of the working group coordinated the production of the guidelines with the help of the project manager whose job was to ensure conformity with the methodological principles of guideline production. Two members of the working group identified, selected, and analysed relevant studies (from a literature search performed by the ANAES Documentation Department) and wrote a draft report. This draft report was discussed by the working group over 3 meetings and amended in the light of comments from other members of the working group and from peer reviewers. Proposals for future studies and action were made.

**External validation (Peer reviewers).** Peer reviewers were appointed according to the same criteria as working group members. They were consulted by post after the second working group meeting, primarily with regard to the readability and applicability of the guidelines (scores from 1 to 9). The ANAES project manager summarized their comments and submitted them to the working group prior to the third meeting. Peer reviewers were asked to sign the final document.

**Internal validation (Evaluation Section of the ANAES Scientific Council).** One member of the Council acted as referees reporting to the Council, together with the ANAES report manager. The working group finalized the guidelines with due regard to the Council’s suggestions.

- **Literature search and analysis (general procedure)**

The scope of the literature search was defined by the steering committee and the project manager. The search was carried out by the ANAES Documentation Department and focused on searching:

- medical and scientific databases over an appropriate period, with special emphasis on retrieving clinical practice guidelines, consensus conferences, articles on medical decision-making, systematic reviews, meta-analyses and other assessments already published nationally or internationally (articles in French or English)

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\(^1\) Full details are given in “Recommandations pour la pratique clinique – base méthodologique pour leur réalisation en France – 1999” (ANAES)
specific and/or financial/economic databases, if necessary
- all relevant websites (government agencies, professional societies, etc.)
- the grey literature (documents not identified through the usual information
distribution circuits)
- legislative and regulatory texts
Further references were obtained from citations in the articles retrieved above and
from working group members' and peer reviewers' own reference sources. The
search was updated until the project was completed.

The articles selected were analysed according to the principles of a critical appraisal
of the literature, using a checklist, to allocate a level of scientific evidence to each
study. Whenever possible, the working group based their guidelines on this review of
the literature. Guidelines were graded from A to C as shown in Table 1 depending on
the level of the evidence of the supporting studies. If no grading is given, they are
based on agreement among professionals.

<table>
<thead>
<tr>
<th>Level of published scientific evidence</th>
<th>Grade</th>
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<tbody>
<tr>
<td><strong>Level 1</strong></td>
<td>A: Established scientific evidence</td>
</tr>
<tr>
<td>Randomised controlled trials of high power</td>
<td></td>
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<tr>
<td>Meta-analyses of randomised controlled trials</td>
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<tr>
<td>Decision analyses based on properly conducted studies</td>
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<tr>
<td><strong>Level 2</strong></td>
<td>B: Presumption of scientific foundation</td>
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<tr>
<td>Randomised controlled trials of low power</td>
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<tr>
<td>Properly conducted non-randomised controlled trials</td>
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<tr>
<td>Cohort studies</td>
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<tr>
<td><strong>Level 3</strong></td>
<td>C: Low level of evidence</td>
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<td>Case-control studies</td>
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<td><strong>Level 4</strong></td>
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<td>Comparative studies with major bias</td>
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<td>Retrospective studies</td>
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