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Prevention of Progression of Kidney Disease

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Dietary protein restriction

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GUIDELINES

a. A protein-controlled diet consisting of 0.75–1.0 g/kg/day, is recommended for adults with chronic kidney disease (CKD). The administration of a low protein diet (≤ 0.6 g/kg/day) to slow renal failure progression is not justified when the reported clinically modest benefit on glomerular filtration rate (GFR) decline is weighed against the concomitant significant declines in clinical and biochemical parameters of nutrition. (Level I evidence)

b. For children, reduction of dietary protein intake to the lowest safe amounts recommended by the World Health Organization (0.8–1.1 g/kg/day depending on age) has not been shown in a small randomised controlled trial (RCT) to decrease the progression of CKD and is therefore not currently recommended. (Level II evidence)

BACKGROUND

Low protein diets have been recommended as a treatment for retarding renal failure progression for over 50 years. The objective of the current guideline was to evaluate the available clinical evidence pertaining to the effect of protein-restricted diets on the progression of CKD.

SEARCH STRATEGY

Databases searched: Medline (1999 to November Week 2, 2003). MeSH terms for kidney diseases were combined with MeSH terms and text words for dietary protein restriction. The results were then combined with the Cochrane highly sensitive search strategy for randomised controlled trials and MeSH terms and text words for identifying meta-analyses and systematic reviews. The Cochrane Renal Group Specialized Register of Randomised Controlled Trials was also searched for relevant trials not indexed by Medline.
Date of search: 16 December 2003.

WHAT IS THE EVIDENCE?

The relationship between dietary protein restriction and non-diabetic renal failure progression has been examined by 4 meta-analyses,[1–4] 11 randomised controlled trials (RCTs),[5–12] 1 prospective double-blind cross-over study,[13] 8 prospective controlled trials,[14–21] 13 prospective non-controlled trials,[22–34] and 7 retrospective observational cohort studies.[35–40] In view of the potential for serious bias in the non-randomised studies, this review will be restricted to the RCTs and meta-analyses.

The Modification of Diet in Renal Disease (MDRD) study by Klahr *et al*[5] is the largest and best-designed prospective RCT to date. Patients were included in the study if their GFR was 25–55 mL/min/1.73 m^2 (Study A) or 13–24 mL/min/1.73 m^2 (Study B), their mean arterial pressure was less than 125 mmHg and their dietary protein intake was greater than or equal to 0.9 g/kg body weight/day (Study A only). Patients with body weight extremes (< 80% or > 160% of standard body weight), dubious compliance, insulin-dependent diabetes mellitus or heavy proteinuria (> 10 g/day) were excluded.

Study A patients ($n = 585$) were randomly assigned (with adequate allocation concealment) to a usual protein diet (1.3 g/kg/day) or a low protein diet (0.58 g/kg/day), while Study B patients ($n = 255$) were randomised to a low protein diet (0.58 g/kg/day) or a very low protein diet (0.28 g/kg/day). An open-label design was used. The groups were similar at the start of the trial. Only 3% of the patients had non-insulin–dependent diabetes mellitus and 24% of the patients had polycystic kidney disease. ACE

inhibitors were permitted and used by 32–44% of patients in each of the randomisation groups. Mean follow-up was 2.2 years (range 0–3.7 years) and the drop-out rate was very low (Study A = 1.9%, Study B = 1.2%). Compliance was reasonable, but the actual dietary intakes of the normal and low protein groups were 1.1 and 0.7 g/kg/day, respectively.

No significant differences in GFR decline, measured by ^{125}I-iothalamate clearance every 4 months, were found between the diet groups in either study. In Study A, a biphasic response of GFR to the low protein diet was noted, with a greater decline in the first 4 months (3.4 vs. 1.8 mL/min/4 months), followed by a significantly slower rate of decline (2.8 vs. 3.9 mL/min/year), which only resulted in a small absolute benefit of 1.1 mL/min/year. This effect of dietary intervention was unrelated to baseline GFR or urinary protein excretion. The time to occurrence of a rapid decline in GFR (>50% or ≥20 mL/min/1.73 m^2) or end-stage kidney disease (ESKD) did not differ significantly between the diet groups in either study, although these were secondary endpoints for which the study was not adequately powered.

In Study A, the low protein diet group had significantly lower energy intakes (males = 3.6 kcal/kg/day, females = 2.8 kcal/kg/day), body weight (males = 5.3 kg, females = 2.9 kg) and biochemical nutritional markers (transferrin, percent body fat, biceps skinfold thickness, triceps skinfold thickness, subscapular skinfold thickness and arm muscle area were all 5–10% lower than in the usual protein group).[41] A 15–20% decline in urinary creatinine excretion was also observed in the lower protein diet groups and was attributed to a reduction in dietary creatine and creatinine intake. However, the significant reductions in arm muscle area also suggests that there was an additional component due to reduced skeletal muscle mass.

The limitations of this study included: (a) overall GFR decline was relatively slow compared with that of other studies and roughly 25% of patients did not experience progressive renal function decline; (b) the study design may not have provided sufficient statistical power to find a positive result, particularly in view of the erratic GFR decline in Study A patients and the relatively high proportion of polycystic kidney disease patients (who may be less amenable to therapy); and (c) the separation of GFR decline into 2 phases represented a post hoc analysis.

Levey *et al*[42] subsequently reported a secondary analysis of the MDRD Study B in order to determine the relationship between achieved dietary protein intake (estimated from urinary urea nitrogen excretion) and renal failure progression. Total protein intake was slightly, but significantly, lower for the very low protein diet group (0.66 g/kg/day) compared with the low protein diet group (0.73 g/kg/day). Each 0.2 g/kg/day decrease in protein intake was associated with a slower mean GFR decline of 1.15 mL/min/year and an approximate halving of the risk of renal failure or death. Moreover, protein intake was directly correlated with final GFR prior to dialysis.

This study has serious limitations, which include: (a) the use of a secondary analysis rather than an intention-to-treat analysis is less valid for the clinical question of whether prescription of a low protein diet is an effective method of slowing renal failure progression; (b) the estimation of achieved protein intake assumes that patients are in a steady state of nitrogen balance but may have been affected by various factors such as acidosis, diuretics, acute illness or collection problems; (c) correlation analyses are limited by potential confounding effects from variables that are not controlled for in the regression model (this may be particularly relevant to post hoc secondary analyses which were not initially considered at the study inception); (d) the analysis may have been limited by the possible confounding effects of the presumed dependent variable (in other words, the association may have been explained by an effect of renal function on protein intake rather than vice versa); and (e) correlation analyses only detect an association and do not prove cause and effect. In short, extreme caution should be exercised with post hoc secondary analyses of initially negative studies.

Locatelli *et al*[8] conducted a prospective, multicentre, open-label, RCT of 456 patients randomised to a low protein diet (0.4 g/kg/day) or a normal controlled-protein diet (1 g/kg/day). Patients were included if their creatinine clearance was less than 60 mL/min, 24- h protein excretion was less than 3 g/day and body weight was between 45 and 90 kg. ACE inhibitors were avoided as much as possible. Allocation concealment was adequate. Baseline demographic, clinical and laboratory characteristics of each group were not provided. Patients were followed-up for 2 years or until an end-point (doubling of baseline plasma creatinine or dialysis) was reached. Seventeen percent of patients were withdrawn from the study (non-compliance 13%, intolerance of low protein diet 1%, concomitant disease 1%, death 1%, other causes 1%). No differences in actuarial renal survival rate, creatinine clearance decline or slope of plasma creatinine reciprocal were noted between the two diet groups. No correlation was found between the progression of renal failure and protein catabolic rate. The potentially significant pitfalls of the study included: (a) indirect measurement of GFR by creatinine clearance (which is often inaccurate and significantly affected by diet); (b) a moderately high drop-out rate (17%); (c) non-compliance with protein restriction minimized the difference in dietary intake between control and treated groups (0.16 g/kg/day vs. intended 0.4 g/kg/day); and (d) the clinically important outcome of effect of diet on nutritional status was not considered.

Rosman[6] conducted a prospective, single centre, open-label RCT of 228 patients with creatinine clearances between 10 and 60 mL/min/1.73 m^2. Patients were stratified for sex, age and renal function and then randomly allocated to receive either a low protein diet (0.4 g/kg/day if creatinine clearance 10–30 mL/min/1.73 m^2 [Group C] or 0.6 g/kg/day if creatinine clearance 31–60 mL/min/1.73 m^2 [Group B]) or their usual diet (averaging 55 g/day for A2 and 70 g/day for A1). Allocation concealment was adequate (sealed envelopes). ACE inhibitors were not prescribed.

The groups were comparable at baseline but 23 (10%) patients (A1 $n = 4$, A2 $n = 7$, B $n = 1$, C $n = 7$) were subsequently removed from the study due either to death, trans-

plantation or dialysis. The initial results published in 1984 were favourable with protein restriction reducing the median rate of progression of renal insufficiency, determined by reciprocals of median plasma creatinine, by a factor of 3 (group C) to 5 (group B). However, after another 4 years of follow-up, no significant differences were found between the groups (except for the subset of patients with chronic glomerulonephritis). The authors concluded that protein restriction is of limited value and should only be used in selected patient groups. Patient dissatisfaction with the low protein diets was very high, especially in the early stages. The major pitfall of the study was the use of reciprocal plasma creatinine as a marker of GFR.

Ihle *et al*[10] conducted a prospective, single centre, randomised study of 72 patients with serum creatinine concentrations between 0.35 and 1.0 mmol/L. Diabetics and patients receiving angiotensin-converting enzyme (ACE) inhibitors were excluded. Patients were randomly allocated to receive either a regular diet (at least 0.75 g/kg/day) or a protein-restricted diet (0.4 g/kg/day). Allocation concealment was adequate. GFR was assessed every 6 months by ^{51}Cr-EDTA clearance. The study lasted 18 months, during which time 3 patients (4%) withdrew voluntarily and 5 patients (6%) were withdrawn because of non-compliance. Compliance in the remaining patients was reasonable. A significantly higher proportion of control patients reached ESKD compared with the protein-restricted group (27% vs. 6%, $P < 0.05$). This, however, is a misleading end-point since this may have reflected differences in the development of uraemic symptoms rather than progression of renal impairment *per se*. Moreover, given the lack of blinding, it is conceivable that clinicians caring for patients on a low protein diet may have been more prone to delay initiation of dialysis. Nevertheless, mean ^{51}Cr-EDTA clearance did not change in the low protein group, but significantly decreased by 60% in the control group. Of major concern were the significant falls in body weight, serum albumin, serum transferrin and lymphocyte counts in the protein-restricted group suggesting an adverse effect of the dietary intervention on nutrition. The limitations of the study were (a) its small numbers and short follow-up; (b) the exclusion of diabetics; (c) the withdrawal of non-compliant patients rather than analysing on an intention-to-treat basis; and (d) the disallowance of ACE inhibitors.

A prospective, single-centre, open-label, RCT of a severe (0.30 g/kg/day) protein-restricted diet supplemented with a preparation of ketoanalogues, hydroxyanalogues of amino acids and amino acids (Group A) vs. a moderate protein-restricted diet (0.65 g/kg/day, Group B) was conducted in 50 patients with a GFR < 19 mL/min/1.73 m^2.[43] Follow-up ranged between 3 months and 3 years. There were no statistically significant differences between the two dietary regimens with respect to renal survival, although a Type 2 statistical error could not be excluded.

Pijls *et al*[44] conducted a prospective, single-centre, open-label RCT of protein restriction (0.8 g/kg/day) vs. usual dietary advice in 131 patients with Type 2 diabetes mellitus and microalbuminuria or known diabetes duration in excess of 5 years. Patients were followed for at least 12 months. No significant differences were seen between the two groups with respect to decline in cimetidine creatinine clearance. However, the difference in dietary protein intake between the two groups at 6 months was only 0.08 g/kg/day and disappeared over time.

Several small RCTs[3,7,11] have all reported essentially negative results with respect to the effects of protein restriction. Protein intakes ranged from 0.3 to 0.6 g/kg/day in the treated groups and 0.6 to >0.8 g/kg/day in the control group. These studies have all been significantly limited by their small numbers, short follow-up times (12–18 months) and the use of inappropriate measures of GFR (plasma creatinine, reciprocal plasma creatinine or arithmetic mean of urinary urea and creatinine clearance).

A more recent small, prospective, randomised trial of 128 non-diabetic patients with CKD by D'Amico *et al*,[9] suggested that dietary protein restriction conferred a modest benefit. Over a 2.3 year follow-up, a 50% reduction in creatinine clearance was observed in 40% of the control group (mean protein intake 1.06 g/kg/day) compared with 29% in the low protein diet group (mean protein intake 0.8 g/kg/day). The major limitation of this study was the use of creatinine clearance as a marker of GFR.

Fouque *et al*[3] published a meta-analysis of 6 RCTs[6–8,10,11] in 1992, prior to the publication of the results of the MDRD study. The criteria and methods used to select articles for inclusion were appropriate and it is unlikely that important relevant studies were missed. Although of limited sensitivity, the chi-squared heterogeneity test between odds ratios was not significant. A total of 890 patients with mild to severe CKD were followed-up for at least 1 year. Sixty-one renal deaths, defined as the commencement of dialysis or patient death, were recorded in the low protein diet group and 95 in the control group, leading to an odds ratio of 0.54 (95% CI: 0.37–0.79) in favour of protein restriction. The authors concluded that low protein diets are effective in delaying the onset of ESKD, but it is impossible to tell from this analysis whether or not the reduction in renal death was the consequence of a reduction in uraemic symptoms (thereby delaying the need for dialysis) or a reduction in the progression of renal insufficiency. Another limitation of the meta-analysis was the heterogeneity of the studies with respect to treatments (for example, the protein intake in the control group of 1 study was the same as that in the treatment group of another study). Furthermore, not all clinically important outcomes were considered, since the effect of treatment on nutritional status was not evaluated.

Finally, the validity of meta-analyses may be threatened by publication bias, which may be suggested, among other things, by an inverse association between trial size and treatment. Such an analysis was not performed in Fouque's meta-analysis. However, a funnel plot of odds ratio vs. trial size does raise the possibility of a positive publication bias. Fouque *et al*[4] have subsequently published a systematic review of only 7 RCTs since 1975, which concluded that low protein diets are associated with a significantly lower incidence of renal death compared with higher protein diets (odds ratio 0.62, 95% CI: 0.46–0.83, P = 0.006). This Cochrane review suffered the

same limitations as the 1992 meta-analysis and did not include all available RCTs.

Another meta-analysis which included the MDRD study (making up 40% of its patients) was subsequently published by Pedrini *et al*.[2] Only full-length published studies were included in the analysis, raising the possibility that important relevant studies were missed. As an example of this, Pedrini *et al*[2] only included 4 of the 6 studies used in the meta-analysis of Fouque *et al*,[3] even though the latter was published 4 years earlier. Assessments of the reproducibility of study inclusion between the 2 investigators were not made, although there must have been some disparity as the paper states that differences were resolved in a conference. The analysis included 5 RCTs[5,6,8,10,11] and found that a low protein diet significantly reduced the risk of renal failure or death (RR 0.67, 95% CI: 0.50–0.89). Significant heterogeneity of treatment effects was unlikely as the results were similar using both random-effects and fixed-effects models. However, this meta-analysis suffered the same serious limitations as those of Fouque and coworkers.[3]

The most recent meta-analysis of the effects of dietary protein restriction on the rate of decline of renal function was reported by Kasiske *et al*.[1] The meta-analysis only considered published studies between 1980 and 1996 using Medline and bibliographies found in published reviews. The results of 13 RCTs (including 4 trials in purely diabetic populations) were pooled ($n = 1919$) and found that dietary protein restriction reduced the rate of decline in estimated GFR by a meagre 0.53 mL/min/year (95% CI: 0.08–0.98 mL/min/year). The unweighted mean dietary protein content was 0.68 ± 0.11 g/kg/day in the low protein groups and 1.01 ± 0.32 g/kg/day in the control groups. Interestingly, the magnitude and variability of the treatment effects were inversely proportional to the size of the studies, indicating a possible publication bias in favour of low-protein diets. A weighted regression analysis of 13 RCTs compared with 11 other non-randomised trials demonstrated that the effect of dietary protein restriction was significantly less in the former and relatively greater among diabetic vs. non-diabetic patients. The impact of restricted protein diets on nutrition was not considered in this meta-analysis, but is clearly crucial given the very modest beneficial effect on GFR decline.

Another concern regarding dietary protein restriction in patients with CKD is the spontaneous reduction in dietary protein intake with declining GFR. Ikizler *et al*[46] noted that mean spontaneous dietary intakes averaged 1.1 g/kg/day for patients with creatinine clearances >50 mL/min, 0.85 g/kg/day at 25–50 mL/min, 0.70 g/kg/day at 10–25 mL/min and 0.54 g/kg/day at <10 mL/min. These changes presumably reflect uraemic anorexia and raise questions regarding the safety of further restricting protein intake.

What is the evidence in children?

In a recent, multicentre trial by Wingen *et al*,[47] 191 children with CKD were randomly allocated to the lowest safe protein intake recommended by the World Health Organization (1.1 g/kg/day in infants to 0.8 g/kg/day in adolescents) or to a regular diet. ACE inhibitors were allowed. Over the 2-year follow-up, no benefit was noted with respect to decline in creatinine clearance. The actual mean protein intakes of the two groups were 125% and 181% of the WHO recommendations, respectively. Calculation of protein intake by urinary urea nitrogen excretion found that patients in the diet group under-reported their protein intake (141% of WHO recommendations) whereas controls did not (181%). One hundred and twelve patients completed an optional third year of the study with still no significant difference apparent between the two groups with respect to decline in creatinine clearance. Growth was also comparable between the two groups. The main limitations of the study were the use of creatinine clearance as a GFR marker and the fact that the study was probably under-powered.

SUMMARY OF THE EVIDENCE

In summary, there is no convincing or conclusive evidence that long-term protein restriction delays the progression of CKD. The longest lasting, largest and best-designed RCT (MDRD study) argues against an important benefit. Four meta-analyses have demonstrated either a modest or substantial benefit of protein-restricted diets, but three of these used an inappropriate outcome measure (renal survival), which does not allow distinction between delay of dialysis due to suppression of uraemic symptoms vs. slowing renal failure progression. The only meta-analysis which used estimated GFR as an outcome measure found only a very weak benefit of dietary protein restriction. It also found evidence of possible publication bias favouring a beneficial effect of low protein diets. The trials showed some heterogeneity and cannot substitute for properly conducted RCTs. Moreover, the possibility of a modest benefit of low-protein diets on renal failure progression must be weighed against the risk of a concomitant decline in nutritional parameters. Only three of the 11 RCTs in non-diabetics have addressed the effect of restricted protein diets on nutrition[5,10,43] and two have found statistically important reductions in nutritional parameters (the other observed neither a benefit nor adverse effect of dietary protein restriction).

WHAT DO THE OTHER GUIDELINES SAY?

Kidney Disease Outcomes Quality Initiative: For individuals with chronic renal failure (GFR < 25 mL/min) who are not undergoing maintenance dialysis, the institution of a planned low-protein diet providing 0.6 g protein/kg/d should be considered. For individuals who will not accept such a diet or who are unable to maintain adequate dietary energy intake with such a diet, an intake of up to 0.75 g protein/kg/d may be prescribed (Evidence and Opinion).

When properly implemented and monitored, low-protein, high-energy diets maintain nutritional status while limiting the generation of potentially toxic nitrogenous metabolites, the development of uraemic symptoms, and the occurrence of other metabolic complications.

Evidence suggests that low protein diets may retard the progression of renal failure or delay the need for dialysis therapy.

When patients with chronic renal failure consume uncontrolled diets, a decline in protein intake and indices of nutritional status is often observed.

British Dietetic Association Renal Nutrition Group: Recommends 0.6–1.0 g protein/kg/day.

European Dialysis and Transplant Nurses Association – European Renal Care Association: Recommends 0.6–1 0 g protein/kg/day.

European Society of Parenteral and Enteral Nutrition: Recommends 0.55–0.6 g protein/kg/day.

IMPLEMENTATION AND AUDIT

No recommendation.

SUGGESTIONS FOR FUTURE RESEARCH

No recommendation.

REFERENCES

1. Kasiske BL, Lakatua JD, Ma JZ *et al*. A meta-analysis of the effects of dietary protein restriction on the rate of decline in renal function. *Am. J. Kidney Dis* 1998; **31**: 954–61.
2. Pedrini MT, Levey AS, Lau J *et al*. The effect of dietary protein restriction on the progression of diabetic and nondiabetic renal diseases: a meta-analysis. *Ann. Intern. Med*. 1996; **124**: 627–32.
3. Fouque D, Laville M, Boissel JP *et al*. Controlled low protein diets in chronic renal insufficiency: meta-analysis. *BMJ*. 1992; **304**: 216–20.
4. Fouque D, Wang PH, Laville M *et al*. Low protein diets for chronic renal failure in non diabetic adults. *The Cochrane Database of Systematic Reviews* 2000, Issue 4. Art. No. CD001892. DOI: 10.1002/14651858. CD001892.
5. Klahr S, Levey AS, Beck GJ *et al*. The effects of dietary protein restriction and blood-pressure control on the progression of chronic renal disease. Modification of Diet in Renal Disease Study Group. *N Engl. J. Med*. 1994; **330**: 877–84.
6. Rosman JB. Dietary protein restriction in chronic renal failure: an update. *Klin Wochenschr* 1989; **67**: 882–8.
7. Jungers P, Chauveau P, Ployard F *et al*. Comparison of ketoacids and low protein diet on advanced chronic renal failure progression. *Kidney Int. Suppl* 1987; **22**: S67–S71.
8. Locatelli F, Alberti D, Graziani G *et al*. Prospective, randomised, multicentre trial of effect of protein restriction on progression of chronic renal insufficiency. Northern Italian Cooperative Study Group. *Lancet* 1991; **337**: 1299–304.
9. D'Amico G, Gentile MG, Fellin G *et al*. Effect of dietary protein restriction on the progression of renal failure: a prospective randomized trial. *Nephrol. Dial Transplant* 1994; **9**: 1590–94.
10. Ihle BU, Becker GJ, Whitworth JA *et al*. The effect of protein restriction on the progression of renal insufficiency. *N Engl. J. Med*. 1989; **321**: 1773–7.
11. Williams PS, Stevens ME, Fass G *et al*. Failure of dietary protein and phosphate restriction to retard the rate of progression of chronic renal failure: a prospective, randomized, controlled trial. *Q J. Med*. 1991; **81**: 837–55.
12. Bergstrom J, Alvestrand A, Bucht H *et al*. Stockholm clinical study on progression of chronic renal failure – an interim report. *Kidney Int. Suppl* 1989; **27**: S110–S114.
13. Hecking E, Andrzejewski L, Prellwitz W *et al*. Double-blind crossover study with oral alpha-ketoacids in patients with chronic renal failure. *Am. J. Clin. Nutr* 1980; **33**: 1678–81.
14. Frohling PT, Schmicker R, Vetter K *et al*. Conservative treatment with ketoacid and amino acid supplemented low-protein diets in chronic renal failure. *Am. J. Clin. Nutr* 1980; **33**: 1667–72.
15. Maschio G, Oldrizzi L, Tessitore N *et al*. Effects of dietary protein and phosphorus restriction on the progression of early renal failure. *Kidney Int*. 1982; **22**: 371–6.
16. Gretz N, Korb E, Strauch M. Low-protein diet supplemented by keto acids in chronic renal failure: a prospective controlled study. *Kidney Int. Suppl* 1983; **16**: S263–S267.
17. Oldrizzi L, Rugiu C, Valvo E *et al*. Progression of renal failure in patients with renal disease of diverse etiology on protein-restricted diet. *Kidney Int*. 1985; **27**: 553–7.
18. Di Landro D, Perin N, Bertoli M *et al*. Clinical effects of a low protein diet supplemented with essential amino acids and keto analogues in uremic patients. *Contrib Nephrol*. 1986; **53**: 137–43.
19. Schmicker R, Froehling PT, Goetz KH *et al*. Influence of low protein diet supplemented with amino acids and keto acids on the progression of chronic renal failure. *Contrib Nephrol*. 1986; **53**: 121–7.
20. Frohling PT, Lindenau K, Vetter K *et al*. What can be safely said about predialysis treatment? *Blood Purif* 1989; **7**: 28–32.
21. Walser M. Ketoacids in the treatment of uremia. *Clin. Nephrol*. 1975; **3**: 180–6.
22. Mallick NP. Dietary protein and progression of chronic renal disease. *BMJ*. 1994; **309**: 1101–2.
23. Burns J, Cresswell E, Ell S *et al*. Comparison of the effects of keto acid analogues and essential amino acids on nitrogen homeostasis in uremic patients on moderately protein-restricted diets. *Am. J. Clin. Nutr* 1978; **31**: 1767–75.
24. Kampf D, Fischer HC, Kessel M. Efficacy of an unselected protein diet (25 g) with minor oral supply of essential amino acids and keto analogues compared with a selective protein diet (40 g) in chronic renal failure. *Am. J. Clin. Nutr* 1980; **33**: 1673–7.
25. Attman PO, Bucht H, Larsson O *et al*. Protein-reduced diet in diabetic renal failure. *Clin. Nephrol*. 1983; **19**: 217–20.
26. Frohling PT, Kokot F, Schmicker R *et al*. Influence of keto acids on serum parathyroid hormone levels in patients with chronic renal failure. *Clin. Nephrol*. 1983; **20**: 212–5.
27. El Nahas AM, Masters TA, Brady SA *et al*. Selective effect of low protein diets in chronic renal diseases. *Br. Medical J Clin. Res. Ed*. 1984; **289**: 1337–41.
28. Mitch WE, Walser M, Steinman TI *et al*. The effect of a keto acid-amino acid supplement to a restricted diet on the progression of chronic renal failure. *N Engl. J. Med*. 1984; **311**: 623–9.
29. Lucas PA, Meadows JH, Roberts DE *et al*. The risks and benefits of a low protein-essential amino acid-keto acid diet. *Kidney Int*. 1986; **29**: 995–1003.
30. Walser M, LaFrance N, Ward L *et al*. Progression of chronic renal failure in patients given keto acids following amino acids. *Infusionsther Klin Ernahr* 1987; **14** (Suppl. 5): S17–S20.
31. Ciardella F, Morelli E, Cupisti A *et al*. Metabolic effects of a very-low-protein, low-phosphorus diet supplemented with essential amino acids and keto analogues in end-stage renal diseases. *Contrib Nephrol*. 1988; **65**: 72–80.
32. Barsotti G, Ciardella F, Morelli E *et al*. Nutritional treatment of renal failure in type 1 diabetic nephropathy. *Clin. Nephrol*. 1988; **29**: 280–7.
33. Levine SE, D'Elia JA, Bistrian B *et al*. Protein-restricted diets in diabetic nephropathy. *Nephron* 1989; **52**: 55–61.

34. Zeller K, Whittaker E, Sullivan L *et al*. Effect of restricting dietary protein on the progression of renal failure in patients with insulin-dependent diabetes mellitus. *N Engl. J. Med*. 1991; **324**: 78–84.
35. Alvestrand A, Ahlberg M, Furst P *et al*. Clinical experience with amino acid and keto acid diets. *Am. J. Clin. Nutr* 1980; **33**: 1654–9.
36. Barsotti G, Guiducci A, Ciardella F *et al*. Effects on renal function of a low-nitrogen diet supplemented with essential amino acids and ketoanalogues and of hemodialysis and free protein supply in patients with chronic renal failure. *Nephron* 1981; **27**: 113–7.
37. Alvestrand A, Ahlberg M, Bergstrom J. Retardation of the progression of renal insufficiency in patients treated with low-protein diets. *Kidney Int. Suppl* 1983; **16**: S268–72.
38. Bennett SE, Russell GI, Walls J. Low protein diets in uraemia. *Br. Med. J. Clin. Res. Ed* 1983; **287**: 1344–5.
39. Attman PO. Long-term treatment with low protein diet in uremia. *Contrib Nephrol*. 1986; **53**: 128–36.
40. Hannedouche T, Chauveau P, Fehrat A *et al*. Effect of moderate protein restriction on the rate of progression of chronic renal failure. *Kidney Int. Suppl* 1989; **27**: S91–5.
41. Kopple JD, Levey AS, Greene T *et al*. Effect of dietary protein restriction on nutritional status in the Modification of Diet in Renal Disease Study. *Kidney Int*. 1997; **52**: 778–91.
42. Levey AS, Adler S, Caggiula AW *et al*. Effects of dietary protein restriction on the progression of advanced renal disease in the Modification of Diet in Renal Disease Study. *Am. J. Kidney Dis* 1996; **27**: 652–63.
43. Malvy D, Maingourd C, Pengloan J *et al*. Effects of severe protein restriction with ketoanalogues in advanced renal failure. *J. Am. Coll Nutr* 1999; **18**: 481–6.
44. Pijls LT, de Vries H, van Eijk JT *et al*. Protein restriction, glomerular filtration rate and albuminuria in patients with type 2 diabetes mellitus: a randomized trial. *Eur J. Clin. Nutr* 2002; **56**: 1200–7.
45. Ikizler TA, Greene JH, Wingard RL *et al*. Spontaneous dietary protein intake during progression of chronic renal failure. *J. Am. Soc. Nephrol*. 1995; **6**: 1386–91.
46. Wingen AM, Fabian-Bach C, Schaefer F *et al*. Randomised multicentre study of a low-protein diet on the progression of chronic renal failure in children. European Study Group of Nutritional Treatment of Chronic Renal Failure in Childhood. *Lancet* 1997; **349**: 1117–23.

APPENDICES

Table 1 Characteristics of included studies

Study ID (author, year)	*N*	Study design	Setting	Participants	Intervention (experimental group)	Intervention (control group)	Follow up (months)	Comments
Malvy *et al*, 1999[43]	50	Prospective randomised controlled study	Single centre	50 uremic outpatients with GFR <19 mL/min/1.73m^2	Severe protein restriction diet (0.3 g/kg/day) with a supplement of ketoanalogues and hydroxyanalogues of amino acids (0.17 g/kg/day)	0.65 g/kg/day protein intake	Min. 3	
Pijls *et al*, 2002[44]	160	Randomised single-blind controlled study	Single centre	160 patients with type II diabetes and micro-albuminuria or detectable albuminuria aged <79 years	Dietary counselling on protein restriction (to reduce protein intake to 0.8 g/kg/day) + normal dietary advice	Normal dietary advice about restriction of saturated fat intake	28 ± 7	
Wingen *et al*, 1997[47]	191	Randomised prospective controlled study	Multicentre	191 children (aged 2–18 years) with creatinine clearances between 15 and 60 mL/min/1.73m^2	Patients were advised to decrease their protein intake to 0.8–1.1 g/kg	No restrictions on protein intake	24–36	
D'Amico *et al*, 1994[9]	128	Prospective randomised controlled study	Single centre (outpatient clinic)	128 adult patients with chronic renal failure (creatinine clearance between 70 and 15 mL/min/1.73m^2).	Low protein diet (0.6 g protein/kg with an energy supplement of 30 kcal/kg daily)	Control diet (1.0 g protein/kg with an energy supplement of 35 kcal/kg daily)	27.1 ± 21.8	
Jungers *et al*, 1987[7]	19	Randomised controlled trial	Single centre	19 adult patients with advanced chronic renal failure with a creatine clearance of 5–15 mL/min/1.73m^2	0.4 g/kg/day of mixed quality proteins with a phosphate intake <600 mg/day + keto acids administered as a calcium salt (1 tablet/6 kg/day divided into 3 equal doses taken with meals)	0.6 g/kg/day proteins with a phosphate intake <750 mg/day. Caloric intake was maintained at 35–40 kcal/kg/day	18	

Bergstrom *et al*, 1989[12]	57	Prospective randomised controlled trial	Single centre	57 adult patients with chronic renal disease and an approximately linear progression of renal failure with a creatinine clearance of <70 mL/min/1.73 m^2	0.4 g/kg bwt/day protein, 0.1 g/kg bwt/day essential amino acids	Unrestricted protein intake	12–24	
Locatelli *et al*, 1991[8]	456	Prospective randomised controlled trial	Multicentre (Northern Italian Cooperative Study Group)	456 adult outpatients with chronic renal insufficiency as defined by a creatine clearance level below 60 mL/min.	Low protein diet (0.6 g/kg bwt/day + energy supplement of 35 kcal/kg/day)	Normal controlled-protein diet (1.0 g/kg bwt/day + energy supplement of 30 kcal/kg/day)	24	
Klahr *et al*, 1994[5]	840	Randomised controlled trial	Multicentre	840 adult patients with various chronic renal diseases/insufficiencies	Low protein diet (0.58 g/kg/day) or very low protein diet (0.28 g/kg/day)	Normal protein diet (1.3 g/kg/day)	18–45 Mean = 26	2 simultaneous studies stratified by GFR
Ihle *et al*, 1989[10]	64	Prospective randomised controlled study	Single centre	72 adult patients with chronic renal insufficiency (serum creatinine concentrations between 350–1000 µmol/L	Protein-restricted diet (0.4 g/kg/day protein)	Regular diet (at least 0.75g/kg/day protein)	18	

Table 1 *Continued*

Study ID (author, year)	*N*	Study design	Setting	Participants	Intervention (experimental group)	Intervention (control group)	Follow up (months)	Comments
Williams *et al*, 1991[11]	95	Prospective randomised controlled trial	Multicentre (2 nephrology clinic units)	95 adult patients with chronic renal failure (plasma creatinine <900 µmol/L)	Dietary protein and phosphate restriction: 0.6 g/kg/day protein, 800 mg phosphate, energy intake =30 kCal/kg/day	Dietary phosphate restriction only: 1000 mg/day + oral phosphate binders with each meal	3	3 arm study: 3rd group had no protein or phosphate restriction
Rosman, 1989[6]	228	Prospective open-label randomised controlled trial	Single centre	Adult patients with chronic renal insufficiency (serum creatinine clearance between 10–60 mL/min/1.73 m^2	Low protein diet of 0.4g/kg/day if Cr 10–30 mL/min/1.73m^2 or 0.6 g/kg/day if Cr 31–60 mL/min/1.73 m^2	Normal diet: 55 g/day (group 1) or 70 g/day (group 2)	48	
Levey *et al*, 1996[42]	255	Randomised controlled trial	Multicentre (15 university hospital outpatient nephrology practices)	Adult patients with chronic renal insufficiency and baseline GFR between 13–24 mL/min/1.73 m^2	Very low protein diet (0.28 g/kg/day) supplemented with keto acids and amino acids (0.28 g/kg/day)	Low protein diet (0.58 g/kg/day)	Av. = 26	

Table 2 Quality of randomised trials

Study ID (author, year)	Method of allocation concealment	Blinding			Intention-to-treat analysis	Loss to follow up (%)
		(participants)	(investigators)	(outcome assessors)		
Levey *et al*, 1996[42]	Not specified	No	Blinded to GFR measurements only	No	No	Unclear
Rosman, 1989[6]	Sealed envelopes	No	No	No	Unclear	Unclear
Williams *et al*, 1991[11]	Pack of numbered cards and random numbers table	No	No	No	Unclear	0
Ihle *et al*, 1989[10]	Not specified	No	No	No	Unclear	0
Klahr *et al*, 1994[5]	Not specified	No	No	No	Yes	1.7 (14/840)
Locatelli *et al*, 1991[8]	Central	No	No	No	Yes	31.8 (145/456)
Bergstrom *et al*, 1989[12]	Not specified	No	No	No	Unclear	0
Jungers *et al*, 1987[7]	Not specified	No	No	No	Unclear	21.1 (4/19)
Pijls *et al*, 2002[44]	Randomisation by computer software	No	Yes	No	Yes	18 (29/160)
Malvy *et al*, 1999[43]	Not specified	No	No	No	Unclear	0
D'Amico *et al*, 1994[9]	Not specified	No	No	No	Unclear	0
Wingen *et al*, 1997[47]	Computerised randomisation	No	No	No	No	15.5 (35/226)

Table 3 Results for continuous outcomes

Study ID (author, year)	Outcomes	Intervention group (mean [SD])	Control group (mean [SD])	Difference in means [95% CI]
Ihle *et al.* 1989	Serum creatinine (μmol/L) at 18 mo	790 (1169.23)	930 (1436.14)	–140.00 (95%CI: –77.92, 499.92)
	^{51}Cr-EDTA (mL/sec) at 18 mo	0.20 (0.28)	0.10 (0.29)	0.10 (95%CI: –0.04, 0.24)
	SBP (mmHg) at 18 mo	132 (61.25)	129 (63.19)	3.00 (95%CI: –27.49, 33.49)
	DBP (mmHg) at 18 mo	84 (44.54)	87 (45.96)	–3.00 (95%CI: –25.17, 19.17)
	Serum Ca (mmol/l) at 18 mo	2.35 (0.61)	2.29 (1.90)	0.06 (95%CI: –0.62, 0.74)
	Serum P (mmol/L) at 18 mo	1.36 (3.34)	1.41 (1.72)	–0.05 (95%CI: –1.36, 1.26)
	PTH (IU/L) at 18 mo	208 (428.72)	264 (637.65)	–56.00 (95%CI: –320.78, 208.78)
	Cholesterol (mmol/L) at 18 mo	7.3 (4.45)	7.2 (4.60)	0.10 (95%CI: –2.12, 2.32)
	Triglyceride (mmol/L) at 18 mo	2.0 (4.45)	2.3 (2.30)	–0.30 (95%CI: –2.05, 1.45)
Jungers *et al.* 1987	Serum Cr (μmol/L) at end of study	927 (145)	953 (172)	–26.00 (95%CI: –192.65, 140.65)
	C_{Cr} (mL/min) at end of study	5.1 (1.6)	5.1 (1.0)	0.00 (95%CI: –1.40, 1.40)
	Urea (mmol/l) at end of study	32.5 (14) 7	38.8 (9.4) 8	–6.30 (95%CI: –18.55, 5.95)
	Bicarbonate (mmo/l) at end of study	24.0 (2.7)	23.4 (3.8)	0.60 (95%CI: –2.71, 3.91)
	Potassium (mmol/l) at end of study	5.0 (0.4)	5.1 (0.4)	–0.10 (95%CI: –0.51, 0.31)
	Calcium (mmol/l) at end of study	2.47 (0.34)	2.40 (0.17)	0.07 (95%CI: –0.21, 0.35)
	Phosphate (mmol/l) at end of study	1.62 (0.43)	1.73 (0.38)	–0.11 (95%CI: –0.52, 0.30)
	Ca × P (mmol/l) at end of study	3.90 (0.69)	4.16 (0.67)	–0.26 (95%CI: –0.95, 0.43)
	Total cholesterol at end of study	4.70 (1.7)	6.50 (1.9)	–1.80 (95%CI: –3.62, 0.02)
	Triglycerides at end of study	1.10 (0.37)	1.06 (0.22)	0.04 (95%CI: –0.27, 0.35)
	MAP (mmHg) at end of study	118 (11)	113 (12)	5.00 (95%CI: –6.64, 16.64)
	Body weight (kg) at end of study	68.3 (19.2)	59.5 (11)	8.80 (95%CI: –7.34, 24.94)
	AMC (cm) at end of study	24 (2.7)	24.7 (4)	–0.70 (95%CI: –4.12, 2.72)
	Proteins (g/L) at end of study	68.2 (4)	69.5 (8.7)	–1.30 (95%CI: –8.02, 5.42)
	Albumin (g/L) at end of study	39.2 (4.9)	41.4 (7.2)	–2.20 (95%CI: –8.37, 3.97)
	Transferrin (g/L) at end of study	2.1 (0.4)	2.1 (0.5)	0.00 (95%CI: –0.46, 0.46)
Klahr *et al.* 1996	Rate of change in GFR at 4 mo in study A (mL/min per month)	–0.32 (0.3)	–0.23 (0.3)	0.09 (95%CI: 0.04, 0.14)
Locatelli *et al.* 1991	Urinary urea excretion (g) at 24 mo	14.2 (5.8)	17.3 (5.9)	–3.10 (95%CI: –4.46, –1.74)
Malvy *et al.* 1999	Uraemia (mmol/l) at end of study	18.5 (6.7)	34.9 (9.9)	–16.40 (95%CI: –21.09, –11.71)
	Calcemia (mmol/L) at end of study	2.42 (0.17)	2.25 (0.17)	0.17 (95%CI: 0.08, 0.26)
	Phosphatemia (mmol/L) at end of study	1.39 (0.30)	1.80 (0.65)	–0.41 (95%CI: –0.69, –0.13)
	Alkaline phosphatase at end of study	61.42 (22.93)	78.8 (27.0)	–17.38 (95%CI: –31.27, –3.49)
	PTH plasma (ng/mL) at end of study	2.71 (1.55)	5.91 (1.41)	–3.20 (95%CI: –4.02, –2.38)
	Body weight (kg) at end of study	57.7 (10.6)	61.8 (9.6)	–4.10 (95%CI: –9.71, 1.51)
	Albumin (g/L) at end of study	43.7 (3.8)	41.54 (3.38)	2.16 (95%CI: 0.17, 4.15)
	Cholesterol (mmol/L) at end of study	5.92 (1.53)	5.67 (11.03)	0.25 (95%CI: –4.12, 4.62)
	Urinary urea excretion (mmol/L)	131.2 (69.2)	213.8 (67.1)	–82.60 (95%CI: –120.38, –44.82)
Pjils *et al.* 2002	Decrease in GFR at 6 mo (mL/min/1.73 m^2)	2.9 (17)	1.3 (5)	1.60 (95%CI: –2.76, 5.96)
	Change rate (per yr) of GFR (mL/min/1.73 m^2) at 12 mo	–4.8 (12)	–6.4 (14)	1.60 (95%CI: –2.86, 6.06)

Williams *et al.* 1991	**Low Protein vs Control**			
	Mean SBP (mmHg)	150 (17.23)	146 (16.97)	4.00 (95%CI: –4.31, 12.31)
	Mean DBP (mmHg)	89 (5.74)	87 (5.66)	2.00 (95%CI: –0.77, 4.77)
	Protein catabolic rate (g/kg/day)	0.71 (0.11)	0.95 (0.23)	–0.24 (95%CI: –0.33, –0.15)
	Plasma carbonate (mmol/l)	24.8 (5.17)	23.2 (6.79)	1.60 (95%CI: –1.34, 4.54)
	Creatinine clearance (mL/min/1.73 m^2)	13.9 (10.05)	16.5 (11.43)	–2.60 (95%CI: –8.30, 3.10)
	Low Phosphate vs Control			
	Mean SBP (mmHg)	148 (16.43)	146 (16.97)	2.00 (95%CI: –6.31, 10.31)
	Mean DBP (mmHg)	87 (5.48)	87 (5.66)	0.00 (95%CI: –2.77, 2.77)
	Protein catabolic rate (g/kg/day)	0.92 (0.16)	0.95 (0.23)	–0.03 (95%CI: –0.13, 0.07)
	Plasma carbonate (mmol/l)	23.0 (6.02)	23.2 (6.79)	–0.20 (95%CI: –3.39, 2.99)
	Creatinine clearance (mL/min/1.73 m^2)	18.3 (17.15)	16.5 (11.43)	1.80 (95%CI: –6.30, 9.90)
Wingen *et al.* 1997	SBP (mmHg) non progressive, at 2 yrs	109 (10)	110 (10)	–1.00 (95%CI: –4.92, 2.92)
	SBP (mmHg) progressive, at 2 yrs	116 (11)	118 (13)	–2.00 (95%CI: –6.96, 2.96)
	DBP (mmHg) non progressive, at 2 yrs	68 (9)	70 (9)	–2.00 (95%CI: –5.53, 1.53)
	DBP (mmHg) progressive, at 2 yrs	77 (9)	76 (11)	1.00 (95%CI: –3.15, 5.15)
	Proteinuria (mg/kg) non progressive, at 2 yrs	32 (63)	24 (24)	8.00 (95%CI: –10.69, 26.69)
	Proteinuria (mg/kg) progressive, at 2 yrs	38 (31)	44 (46)	–6.00 (95%CI: –23.43, 11.43)
	Cr Clearance (mL/min/1.73 m^2) non progressive, at 2 yrs	–4.3 (13.5)	–6.4 (11.8)	2.10 (95%CI: –2.87, 7.07)
	Cr Clearance (mL/min/1.73 m^2) progressive, at 2 yrs	–10.6 (10.4)	–10.7 (19.3)	0.10 (95%CI: –6.33, 6.53)
	SBP (mmHg) non progressive, at 3 yrs	107.5 (10.3)	108.7 (9.8)	–1.20 (95%CI: –6.04, 3.64)
	SBP (mmHg) progressive, at 3 yrs	113.8 (10.4)	115.7 (11.5)	1.90 (95%CI: –8.30, 4.50)
	Proteinuria (mg/kg) non progressive, at 3 yrs	21 (27)	23 (22)	–2.00 (95%CI: –13.92, 9.92)
	Proteinuria (mg/kg) progressive, at 3 yrs	25 (23)	23 (25)	2.00 (95%CI: –12.03, 16.03)
	Cr Clearance (mL/min/1.73 m^2) non progressive, at 3 yrs	–2.4 (6.5)	–5.7 (10.5)	3.30 (95%CI: –0.82, 7.42)
	Cr Clearance (mL/min/1.73 m^2) progressive, at 3 yrs	–10.1 (8)	–7.7 (9.9)	–2.40 (95%CI: –7.65, 2.85)
	Protein (g/L) non progressive, at 2 yrs	69 (6) 50	72 (6) 50	–3.00 (95%CI: –5.35, –0.65)
	Protein (g/L) progressive, at 2 yrs	69 (6) 47	72 (9) 44	–3.00 (95%CI: –6.16, 0.16)
	Albumin (g/L) non progressive, at 2 yrs	44 (6) 50	44 (5) 50	0.00 (95%CI: –2.16, 2.16)
	Albumin (g/L) progressive, at 2 yrs	43 (5) 47	44 (7) 44	–1.00 (95%CI: –3.51, 1.51)
	Cholesterol (mmol/L) non progressive, at 2 yrs	4.89 (1.55) 50	5.04 (1.01) 50	–0.15 (95%CI: –0.66, 0.36)
	Cholesterol (mmol/L) progressive, at 2 yrs	5.04 (1.34) 47	5.17 (1.11) 44	–0.13 (95%CI: –20.53, 20.57)

Table 4 Results for dichotomous outcomes

Study ID (author, year)	Outcomes	Intervention group (number of patients with events/number of patients exposed)	Control group (number of patients with events/number of patients not exposed)	Relative risk (RR) [95% CI]	Risk difference (RD) [95% CI]
Locatelli *et al.* 1991	Mortality	2/226	2/230	1.02 (95%CI: 0.14, 716)	0.00 (95%CI: −0.02, 0.02)
Pjils *et al.* 2002	Mortality	1/63	2/68	0.54 (95%CI: 0.05, 5.81)	−0.01 (95%CI: −0.06, 0.04)
Williams *et al.* 1991	**Low Protein vs Control**				
	Increased or commenced hypertensive agent	23/33	20/32	1.12 (95%CI: 0.79, 1.58)	0.07 (95%CI: −0.16, 0.30)
	Angiotensin-converting enzyme inhibitors	6/33	6/32	0.97 (95%CI: 0.35, 2.69)	−0.01 (95%CI: −0.19, 0.18)
	Progress of renal failure retarded	6/33	4/32	1.45 (95%CI: 0.45, 4.68)	0.06 (95%CI: −0.12, 0.23)
	No change	21/33	22/32	0.93 (95%CI: 0.65, 1.31)	−0.05 (95%CI: −0.28, 0.18)
	Acceleration of renal failure	3/33	3/32	0.97 (95%CI: 0.21. 4.45)	0.00 (95%CI: −0.14, 0.14)
	Dialysis	17/33	15/32	1.10 (95%CI: 0.67, 1.80)	0.05 (95%CI: −0.20, 0.29)
	Mortality	1/33	1/32	0.97 (95%CI: 0.06, 14.85)	0.00 (95%CI: −0.08, 0.08)
	Low Phosphate vs Control				
	Increased or commenced hypertensive agent	18/30	20/32	0.96 (95%CI: 0.65, 1.43)	−0.03 (95%CI: −0.27, 0.22)
	Angiotensin-converting enzyme inhibitors	4/30	6/32	0.71 (95%CI: 0.22, 2.28)	−0.05 (95%CI: −0.24, 0.13)
	Progress of renal failure retarded	7/30	4/32	1.87 (95%CI: 0.60, 1.27)	0.11 (95%CI: −0.08, 0.30)
	No change	18/30	22/32	0.87 (95%CI: 0.60, 1.27)	−0.09 (95%CI: −0.33, 0.15)
	Acceleration of renal failure	1/30	3/32	0.53 (95%CI: 0.05, 5.58)	−0.06 (95%CI: −0.18, 0.06)
	Dialysis	14/30	15/32	1.00 (95%CI: 0.59, 1.69)	0.00 (95%CI: −0.25, 0.25)
	Mortality	4/30	1/32	4.27 (95%CI: 0.51, 36.05)	0.10 (95%CI: −0.03, 0.24)

Lipids

Date written: February 2004
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Author: David Johnson

GUIDELINES

a. HMGCoA reductase inhibitors may retard the progression of renal failure (Level I evidence, 9 RCTs and 1 meta-analysis; mostly clinically relevant outcomes; inconsistent effects)

BACKGROUND

Chronic kidney diseases (CKD) are associated commonly with substantial abnormalities of lipid metabolism, including increased low-density lipoproteins, triglycerides, very-low-density lipoproteins, and lipoprotein(a), and reduced levels of high-density lipoprotein cholesterol. Other abnormalities consist of increased apolipoprotein B, reduced HDL2 cholesterol, and increased Apo C-to-Apo C-II ratio. Dyslipidemia is more severe in patients with proteinuria, particularly those with nephrotic syndrome.

Hypercholesterolemia is a predictor of loss of kidney function in diabetic and non-diabetic kidney disease.[1–3] Studies in experimental CKD have suggested that treatment with statins retards the progression of kidney disease in animals.[4] The objective of this guideline is to review the available clinical evidence pertaining to the effect of lipid-lowering agents on the progression of CKD.

SEARCH STRATEGY

Databases searched: Medline (1999 to November Week 2, 2003). MeSH terms for kidney diseases were combined with MeSH terms and text words for antilipemic agents. The results were then combined with the Cochrane highly sensitive search strategy for randomised controlled trials and MeSH terms and text words for identifying meta-analyses and systematic reviews. The Cochrane Renal Group Specialized Register of Randomised Controlled Trials was also searched for relevant trials not indexed by Medline.
Date of search: 16 December 2003.

WHAT IS THE EVIDENCE?

There have been 9 randomised controlled trials (RCTs);[5–14] 1 meta-analysis;[13] 1 prospective controlled study;[15] 2 prospective crossover studies;[16] and 3 prospective non-controlled studies.[17–19] All the available individual studies have been limited by small numbers and generally short follow-up times.

Thomas *et al*[7] conducted a randomised, double-blind, placebo-controlled trial of the effect of simvastatin therapy in 30 non-diabetic, hypercholesterolaemic patients with proteinuria greater than 1 g per day. The patients were randomly assigned to treatment with simvastatin or placebo targeted to achieve total cholesterol levels of 5.2 mmol/L or below. Angiotensin converting enzyme (ACE) inhibitors were permitted, but were only prescribed for 5 patients (17%). Allocation concealment was adequate and the two groups were similar at baseline; 23 patients (77%) completed the trial. After 24 weeks' follow-up, total and LDL cholesterol levels fell by a mean of 33% and 31%, respectively, in simvastatin-treated patients, compared with 5% and 1% in patients on placebo ($P < 0.001$ and $P = 0.002$, respectively). No significant differences were seen between the 2 groups with respect to proteinuria, plasma creatinine concentration or decline in inulin clearance. The major limitations of the study were the short follow-up time, small numbers, significant drop-out rate (23%), and the fact that complete inulin clearance data were only obtained in 17 patients (57%).

A one-year, prospective, open-label, randomised controlled study of atorvastatin (titrated up to 40 mg daily) vs. no treatment was conducted in 56 patients with mild-to-moderate CKD (creatinine clearance 50.4 ± 1.3 mL/min, proteinuria >1 g/day) who had already been treated for at least 1 year with angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers.[11] It is uncertain whether allocation was concealed. Total cholesterol fell significantly in the atorvastatin group from 327 ± 8 to 211 ± 5 mg/dL, but remained unchanged in the control group (313 ± 4–305 ± 5 mg/dL). By the end of one year of treatment with atorvastatin, urine protein excretion decreased from 2.2 ± 0.1 to 1.2 ± 1.0 g every 24 h (–45.5%). By contrast, in patients who did not receive atorvastatin, urinary protein excretion decreased only from 2.1 ± 0.1 to 1.86 ± 0.1 g every 24 h (–10%; $P < 0.01$). Creatinine clearance decreased only slightly and not significantly (from 51 ± 1.8 to 49.8 ± 1.7 mL/min [-2.0%]) in patients treated with atorvastatin. By contrast, during the same time, creatinine clearance decreased significantly (from 50 ± 1.9 to 44.2 ± 1.6 mL/min [-11.6%] [$P < 0.01$]) in controls.

Tonelli *et al*[12] reported a post hoc subgroup analysis of the CARE study (a randomised double-blind placebo-controlled trial of pravastatin vs. placebo in 4159 participants with previous myocardial infarction and total plasma cholesterol < 240 mg/dL). A total of 690 patients with an MDRD calculated glomerular filtration rate (GFR) < 60 mL/min were included in the subanalysis. A significant stepwise inverse relation was observed between MDRD-GFR before treatment and slowing of renal function loss with pravastatin use, with more benefit in those with lower MDRD-GFR at baseline ($P = 0.04$). The rate of change in MDRD-GFR in the pravastatin group was 0.6 mL/min per 1.73 m^2/ year slower than placebo (95% CI, –0.1–1.2; $P = 0.07$) in those with MDRD-GFR < 50 mL/min, and 2.5 mL/min per 1.73 m^2/ year slower (95% CI, 1.4–3.6 slower; $P = 0.0001$) in those with MDRD-GFR < 40 mL/min per 1.73 m^2/ year. Pravastatin also reduced rates of renal loss to a greater extent in participants with than without proteinuria at baseline (P-value for interaction = 0.006). The significant limitations of this study were (a) it was a secondary analysis such that the results should be interpreted with caution; and (b) the use of calculated GFR was less optimal than more precise measurements of GFR.

The Simvastatin in Nephrotic Syndrome study by Olbricht *et al*,[9,10] is a randomised, double-blind, placebo-controlled trial investigating the effect of simvastatin on renal failure progression (inulin clearance) in 56 non-diabetic, nephrotic, hypercholesterolaemic patients with creatinine clearances > 40 mL/min/1.73 m^2. The results have only been published in abstract form and suggest a significant slowing of renal failure progression in the simvastatin-treated group at 12 months.[20] A cholesterol-lowering efficacy paper has been published by a group in 1999,[9,10] even though the primary renal outcome data have not appeared in print.

A 2-year, randomised, double-blind, placebo-controlled pilot trial of simvastatin vs. placebo was conducted in 39 Type 1 diabetics without overt nephropathy.[21] Simvastatin significantly reduced total cholesterol (mean on treatment 173.4 vs. 191.4, $P = 0.020$) and LDL cholesterol (mean on treatment 105.0 vs. 127.7, $P < 0.001$) and was associated with a non-significant trend towards a slower rise in albumin excretion rate compared with placebo (median rate of change/month 0.004 vs. 0.029). The study was underpowered, so a type 2 statistical error was possible.

Rayner *et al*[15] reported a prospective, open-label, controlled trial of simvastatin in 17 hypercholesterolaemic (cholesterol > 6.1 mmol/L) nephrotic patients with idiopathic membranous nephropathy whose serum creatinine concentrations were less than 0.15 mmol/L. Patients were 'alternatively assigned' to receive simvastatin and a low cholesterol diet or diet alone, aiming to keep cholesterol levels below 5.1 mmol/L. Over a mean follow-up period of 19.3 months in the simvastatin group and 16.6 months in controls, cholesterol levels were significantly reduced in the simvastatin-treated group, but no differences were seen between the 2 groups with respect to the EDTA clearance decline, plasma albumin or proteinuria in EDTA clearances. The small numbers and inadequate allocation concealment seriously undermined the value of this study.

Imai *et al*[14] reported a 6-month, prospective, randomised controlled trial of pravastatin vs. placebo in 57 hypertensive patients with mild renal dysfunction and hyperlipidaemia. Pravastatin significantly reduced total cholesterol from 251.4 ± 7.3 mg/dL to 218.2 ± 6.5 mg/dL, whilst no significant change was observed in the placebo group. Serum creatinine concentration rose in the placebo group from 1.6 ± 0.07 to 2.1 ± 0.2 mg/dL, but did not change in the pravastatin group (1.3 ± 0.07–1.3 ± 0.09 mg/dL). The difference in serum creatinine change and the slope of change in reciprocal creatinine between the 2 groups was statistically significant.

Two small ($n = 18$ and 34), medium term (0.7 and 2 years), randomised, placebo-controlled trials in hypercholesterolaemic patients with normal plasma creatinine concentrations and either microalbuminuria,[18] or proteinuria[5] complicating Type 2 diabetes mellitus have both demonstrated either no significant decline in GFR with HMGCoA reductase inhibitor treatment, whilst GFR decreases were observed in controls (although the decrease was only significant in the study by Lam *et al*[5]). Neither of the 2 studies found a significant reduction in urinary protein excretion rates.

An underpowered, double-blind, crossover study of 19 normotensive, hypercholesterolaemic patients with diabetic nephropathy[16] also failed to demonstrate a beneficial effect of simvastatin on decline in creatinine clearance over a 1-year period. However, a 25% reduction in albumin excretion rate was noted.

Smulders *et al*[6] conducted a randomised, placebo-controlled trial in 15 normotensive, microalbuminuric Type 2 diabetics with elevated plasma triglyceride levels (>2.5 mmol/L). Patients were randomly allocated to gemfibrozil 600 mg bd ($n = 8$) or placebo ($n = 7$) and were followed for 12 months. Progression of microalbuminuria tended to be lower in gemfibrozil-treated patients (36%) than controls (65%), but the difference was not statistically significant. The result became significant if the one treated patient who did not experience a greater than 20% reduction in triglycerides was excluded. However, the validity of such a *post hoc* analysis is highly questionable. This is the only study to have examined the effect of triglyceride reduction on renal disease progression decline, but is seriously limited by small numbers, short follow-up time and lack of an appropriate measure of renal function.

In patients with nephrotic syndrome complicating a variety of glomerulonephritides, small, prospective, non-controlled studies have found either no effect[22–24] or a slower decline[25–27] of renal functional impairment.

Type 1 diabetics with overt nephropathy (urinary albumin excretion rate > 200 μg/min) showed no changes in their degrees of proteinuria following 12 weeks of treatment with simvastatin,[8] although a beneficial effect on albuminuria was reported for pravastatin after 9 weeks.[28]

Fried *et al*[21] published a meta-analysis of 9 RCTs, 1 quasi-RCT and 2 randomised cross-over trials (384 patients) examining the effects of lipid-lowering agents on change in GFR in hyperlipidaemic patients with renal disease. Ten of the trials studied statins, whilst one assessed gemfibrozil and

one assessed probucol. Sixty-six per cent of patients were diabetic. Lipid-lowering treatment was associated with a lower rate of decline in GFR compared with controls (net difference 0.156 mL/min/month; 95% CI: 0.026–0.285 mL/min/month, $P = 0.008$). There was a tendency for a favourable effect of treatment on protein or albumin excretion. A chi square test for study heterogeneity supported the validity of pooling the results for GFR, but not for proteinuria. However, heterogeneity tests are fairly insensitive, and it seems highly questionable that separate trials of cholesterol- and triglyceride-lowering agents on such diverse patient groups with often very short follow-up times can really be grouped together to provide meaningful results. The other major limitation of the meta-analysis was the inclusion of non-RCTs.

SUMMARY OF THE EVIDENCE

There have been 9 RCTs, 1 meta-analysis, 1 prospective controlled study, 2 prospective crossover studies and 3 prospective non-controlled studies of lipid-lowering agents (primarily statins) mostly (but not exclusively) in hypercholesterolaemic subjects. All of the available individual studies have been limited by small numbers and generally short follow-up times. The bulk of the studies have suggested that lipid-lowering agents exert a propitious effect on renal failure progression, although most have also suffered from significant methodological limitations. These results should therefore be considered preliminary.

WHAT DO THE OTHER GUIDELINES SAY?

Kidney Disease Outcomes Quality Initiative: No recommendation.
UK Renal Association: No recommendation.
Canadian Society of Nephrology: No recommendation.
European Best Practice Guidelines: No recommendation.
International Guidelines: No recommendation.

IMPLEMENTATION AND AUDIT

No recommendation.

SUGGESTIONS FOR FUTURE RESEARCH

Any future trials assessing the benefits of lipid-lowering treatments on cardiovascular outcomes in patients with renal insufficiency (e.g. the SHARP trial) should also assess the effects of such treatments on renal failure progression.

REFERENCES

1. Ravid M, Brosh D, Ravid-Safran D *et al*. Main risk factors for nephropathy in type 2 diabetes mellitus are plasma cholesterol levels, mean blood pressure, and hyperglycemia. *Arch. Intern. Med.* 1998; **158**: 998–1004.
2. Krolewski AS, Warram JH, Christlieb AR. Hypercholesterolemia – a determinant of renal function loss and deaths in IDDM patients with nephropathy. *Kidney Int. Suppl.* 1994; **45**: S125–S131.
3. Yang WQ, Song NG, Ying SS *et al*. Serum lipid concentrations correlate with the progression of chronic renal failure. *Clin. Laboratory Sci.* 1999; **12**: 104–8.
4. Oda H, Keane WF. Lipids in progression of renal disease. *Kidney Int. Suppl.* 1997; **62**: S36–S38.
5. Lam KS, Cheng IK, Janus ED *et al*. Cholesterol-lowering therapy may retard the progression of diabetic nephropathy. *Diabetologia*. 1995; **38**: 604–9.
6. Smulders YM, van Eeden AE, Stehouwer CD *et al*. Can reduction in hypertriglyceridaemia slow progression of microalbuminuria in patients with non-insulin-dependent diabetes mellitus? *Eur J. Clin. Invest.* 1997; **27**: 997–1002.
7. Thomas ME, Harris KP, Ramaswamy C *et al*. Simvastatin therapy for hypercholesterolemic patients with nephrotic syndrome or significant proteinuria. *Kidney Int.* 1993; **44**: 1124–9.
8. Hommel E, Andersen P, Gall MA *et al*. Plasma lipoproteins and renal function during simvastatin treatment in diabetic nephropathy. *Diabetologia*. 1992; **35**: 447–51.
9. Olbricht CJ, Wanner C, Thiery J *et al*. Simvastatin in nephrotic syndrome. Simvastatin in Nephrotic syndrome Study Group. *Kidney Int.* 1999; **56**: S113–S116.
10. Olbricht CJ, Wanner C, Thiery J *et al*. Simvastatin in nephrotic syndrome. Simvastatin Nephrotic Syndrome Study Group. *Kidney Int. Suppl.* 1999; **71**: S113–S116.
11. Bianchi S, Bigazzi R., Caiazza A *et al*. A controlled, prospective study of the effects of atorvastatin on proteinuria and progression of kidney disease. *Am. J. Kidney Dis.* 2003; **41**: 565–70.
12. Tonelli M, Moye L, Sacks FM *et al*. Cholesterol and Recurrent Events Trial Investigators. Effect of pravastatin on loss of renal function in people with moderate chronic renal insufficiency and cardiovascular disease. *J. Am. Soc. Nephrol.* 2003; **14**: 1605–13.
13. Fried LF, Orchard TJ, Kasiske BL. Effect of lipid reduction on the progression of renal disease: a meta-analysis. *Kidney Int.* 2001; **59**: 260–9.
14. Imai Y, Suzuki H, Saito T *et al*. The effect of pravastatin on renal function and lipid metabolism in patients with renal dysfunction with hypertension and hyperlipidemia. Pravastatin and Renal Function Research Group. *Clin. Exp. Hypertens.* 1999; **21**: 1345–55.
15. Rayner BL, Byrne MJ, van Zyl Smit R. A prospective clinical trial comparing the treatment of idiopathic membranous nephropathy and nephrotic syndrome with simvastatin and diet, versus diet alone. *Clin. Nephrol.* 1996; **46**: 219–24.
16. Tonolo G, Ciccarese M, Brizzi P *et al*. Reduction of albumin excretion rate in normotensive microalbuminuric type 2 diabetic patients during long-term simvastatin treatment. *Diabetes Care*. 1997; **20**: 1891–5.
17. Fuiano G, Esposito C, Sepe V *et al*. Effects of hypercholesterolemia of renal hemodynamics: study in patients with nephrotic syndrome. *Nephron*. 1996; **73**: 430–5.
18. Nielsen S, Schmitz O, Moller N *et al*. Renal function and insulin sensitivity during simvastatin treatment in type 2 (non-insulin-dependent) diabetic patients with microalbuminuria. *Diabetologia*. 1993; **36**: 1079–86.
19. Scanferla F, Toffoletto PP, Roncali D *et al*. Associated effect of hepatic hydroxymethylglutaryl coenzyme A reductase + angiotensin converting enzyme inhibitors on the progression of renal failure in hypertensive subjects. *Am. J. Hypertens.* 1991; **4**: 868.
20. Olbricht CJ. Cholesterol in progressive renal disease [abstract]. *Nephrology*. 1997; **3**: S39.

21. Fried LF, Forrest KY, Ellis D *et al*. Lipid modulation in insulin-dependent diabetes mellitus: effect on microvascular outcomes. *J. Diabetes Complications*. 2001; **15**: 113–9.
22. Golper TA, Illingworth DR, Morris CD *et al*. Lovastatin in the treatment of multifactorial hyperlipidemia associated with proteinuria. *Am. J. Kidney Dis*. 1989; **13**: 312–20.
23. Kasiske BL, Velosa JA, Halstenson CE *et al*. The effects of lovastatin in hyperlipidemic patients with the nephrotic syndrome. *Am. J. Kidney Dis*. 1990; **15**: 8–15.
25. Gonzalo A, Pascual J, Mampaso F *et al*. Remission of nephrotic syndrome on lovastatin treatment. *Nephron*. 1994; **66**: 233–4.
26. Chan PC, Robinson JD, Yeung WC *et al*. Lovastatin in glomerulonephritis patients with hyperlipidaemia and heavy proteinuria. *Nephrol. Dial Transplant*. 1992; **7**: 93–9.
27. Rabelink AJ, Hene RJ. Erkelens *et al*. Partial remission of nephrotic syndrome in patient on long-term simvastatin. *Lancet*. 1990; **335**: 1045–6.
28. Sasaki T, Kurata H, Nomura K *et al*. Amelioration of proteinuria with pravastatin in hypercholesterolemic patients with diabetes mellitus. *Jpn J. Med*. 1990; **29**: 156–63.
34. Elisaf M, Dardamanis M, Pappas M *et al*. Treatment of nephrotic hyperlipidemia with lovastatin. *Clin. Nephrol*. 1991; **36**: 50–2.

APPENDICES

Table 1 Characteristics of included studies

Study ID (author, year)	N	Study design	Setting	Participants	Intervention (experimental group)	Intervention (control group)	Follow up (months)	Comments
Bianchi *et al*, 2003[11]	56	Prospective randomised controlled open-label study	Single centre	56 adult patients with mild to moderate chronic kidney disease, proteinuria and hypercholesterolaemia	Atorvastatin (max 40 mg/day until LDL levels reduced to <120 mg/dL or by 40% compared to baseline levels)	No atorvastatin	24	
Fried *et al*, 2001[21]	39	Randomised double-blind placebo-controlled trial	Single centre	39 adult patients who have had insulin-dependent diabetes mellitus for at least 10 years; LDL cholesterol 100–160 mg/dL, AER <200 μg/min	10 mg/day simvastatin	Placebo	24	
Hommel *et al*, 1992[8]	26	Randomised double-blind placebo-controlled trial	Single centre (outpatient clinic)	26 adult hypercholesterolaemic patients with Type 1 diabetes and nephropathy	10 mg/day simvastatin for 12 weeks	Placebo	3	
Imai *et al*, 1999[14]	57	Randomised open-label controlled trial	Multicentre	57 adult patients with hypertension and mild renal dysfunction who were receiving treatment with a dihydropyridine calcium entry blocker	Pravastatin 5 mg or 10 mg per day depending on serum cholesterol level	Placebo	6	
Lam *et al*, 1995[5]	36	Randomised single-blind placebo-controlled trial	Single centre	36 Chinese NIDDM patients with mild to moderate hypercholesterolaemia and proteinuria	Lovastatin 20 mg/day as a single evening dose; increased by 20 mg/day at 6 wk intervals if fasting total cholesterol remained >5.2 mmol/L.	Placebo	24	

Table 1 *Continued*

Study ID (author, year)	N	Study design	Setting	Participants	Intervention (experimental group)	Intervention (control group)	Follow up (months)	Comments
Olbricht *et al*, 1999[9,10]	56	Randomised double-blind placebo-controlled trial	Multicentre	56 adult patients with primary glomerulonephritis, hypercholesterolaemia and a creatinine clearance >40 mL/min/1.73m^2	10 mg/day simvastatin (adjusted in 10 mg or 20 mg increments to a max of 40 mg/day depending on LDL-cholesterol level)	Placebo	24	
Smulders *et al*, 1997[6]	15	Randomised placebo-controlled trial	Single centre	15 normotensive NIDDM patients with hypertriglyceridaemia (>2.5 mmol/L) and microalbuminuria	Gemfibrozil 600 mg b.i.d	Placebo	12	
Thomas *et al*, 1993[7]	30	Randomised double-blind placebo-controlled trial	Multicentre (3 renal centres)	30 adult patients with significant proteinuria (1–3.5 g/day) or nephrotic syndrome and hypercholesterolaemia (= 6.5 mmol/L)	Simvastatin 10 mg/day increasing to 20–40 mg/day if required for 24 weeks	Placebo	6	
Tonelli *et al*, 2003[12]	4159	Randomised double-blind placebo-controlled trial	Multicentre	Adult patients who experienced a myocardial infarction between 3–20 months before randomisation with a total plasma cholesterol level <240 mg/dL and moderate renal insufficiency	Pravastatin 40 mg/day	Placebo	58.9 (median follow up)	

Table 2 Quality of randomised trials

Study ID (author, year)	Method of allocation concealment	Blinding			Intention-to-treat analysis	Loss to follow up (%)
		(participants)	(investigators)	(outcome assessors)		
Bianchi *et al*, 2003[11]	Randomly assigned in a blinded fashion	No	No	No	Unclear	0
Fried *et al*, 2001[21]	Unblinded pharmacist using a randomly generated list	Yes	Yes	No	No	0 (after 6 months) 7.7 after 12 mths 56.4 after 18 mths 94.9 after 24 mths
Hommel *et al*, 1992[8]	Not specified	Yes	Yes	No	No	19.2 (5/26)
Imai *et al*, 1999[14]	Not specified	No	No	No	No	8 (5/62)
Lam *et al*, 1995[5]	Block randomisation	Yes	No	No	No	5.6 (2/36)
Olbricht *et al*, 1999[9,10]	Not specified	Yes	Yes	No	No	23 (13/56) after 24 months
Smulders *et al*, 1997[6]	Not specified	Yes	Unclear	No	Unclear	0
Thomas *et al*, 1993[7]	Not specified	Yes	Yes	No	No	23.3 (7/30)
Tonelli *et al*, 2003[12]	Computerised randomisation	Yes	Yes	No	Time-to-event analyses	Unclear

Table 3 Results for continuous outcomes

Study ID (author, year)	Outcomes	Intervention group (mean [SD])	Control group (mean [SD])	Difference in means [95% CI]
Bianchi *et al.* 2003	Creatinine clearance (mL/min) at 12 mo	49.8 (9.00)	44.2 (7.94)	5.60 (95%CI: 1.15, 10.05)
	Total cholesterol (mg/dL) at 12 mo	211 (26.46)	305 (26.46)	−94.00 (95%CI: −107.86, −80.14)
	LDL cholesterol (mg/dL) at 12 mo	121 (21.17)	206 (21.17)	−85.00 (95%CI: −96.09, −73.91)
	Triglycerides (mg/dL) at 12 mo	132 (26.46)	139 (15.87)	−7.00 (95%CI: −18.43, 4.43)
	SBP (mmHg) at 12 mo	131 (5.29)	130 (5.29)	1.00 (95%CI: −1.77, 3.77)
	DBP (mmHg) at 12 mo	83 (5.29)	83 (5.29)	0.00 (95%CI: −2.77, 2.77)
	Serum albumin (g/dL) at 12 mo	3.50 (2.63)	3.38 (2.65)	0.12 (95%CI: −1.26, 1.50)
	Unrinary protein excretion (g/24 hr) at 12 mo	1.2 (5.29)	1.86 (0.53)	−0.66 (95%CI: −2.63, 1.31)
Fried *et al.* 2001	Total cholesterol at 18 mo	165.1 (36.7)	188.3 (26.8)	−23.20 (95%CI: −56.56, 10.16)
	LDL cholesterol at 18 mo	97.2 (27.4)	123.7 (23.0)	−26.50 (95%CI: −52.30, −0.70)
	HDL cholesterol at 18 mo	53.1 (9.0)	48.5 (11.8)	4.60 (95%CI: −5.42, 14.62)
Hommel *et al.* 1992	Total cholesterol at 12 wk (mmol/L)	4.8 (0.7)	6.8 (1.0)	−2.00 (95%CI: −2.76, −1.24)
	LDL cholesterol at 12 wk (mmol/L)	2.6 (0.5)	4.7 (1.0)	−2.10 (95%CI: −2.81, −1.39)
	VLDL cholesterol at 12 wk (mmol/L)	0.69 (0.3)	0.77 (0.3)	−0.10 (95%CI: −0.36, 0.16)
	HDL cholesterol at 12 wk (mmol/L)	1.53 (0.5)	1.26 (0.3)	0.27 (95%CI: −0.07, 0.61)
	Triglycerides at 12 wk	1.49 (0.6)	2.06 (0.8)	−0.57 (95%CI: −1.19, 0.05)
	Apolipoprotein A-1 at 12 wk	1.77 (0.3)	1.62 (0.2)	0.15 (95%CI: −0.06, 0.36)
	Apolipoprotein B at 12 wk	1.06 (0.2)	1.66 (0.4)	−0.60 (95%CI: −0.88, −0.32)
	GFR (mL/min/1.73 m^2) at 12 wk	63 (29)	74 (23)	−11.00 (95%CI: −33.25, 11.25)
	SBP (mmHg)	135 (21)	138 (18)	−3.00 (95%CI: −19.72, 13.72)
	DBP (mmHg)	82 (10)	86 (11)	−4.00 (95%CI: −13.15, 5.15)
	HbA_{1c}(%)	9.7 (2)	9.6 (1.0)	0.10 (95%CI: −1.21, 1.41)
	Blood glucose (mmol/L)	11 (4)	12 (4)	−1.00 (95%CI: −4.46, 2.46)

Imai *et al.* 1999	Total cholesterol (mg/dL) at 6 mo	218.2 (26.80)	243.8 (41.4)	−25.60 (95%CI: −47.68, −3.52)
	HDL cholesterol (mg/dL) at 6 mo	53.0 (15.49)	51.1 (21.36)	1.90 (95%CI: −6.24, 10.04)
	LDL cholesterol (mg/dL) at 6 mo	128.1 (23.24)	154.6 (43.59)	−26.50 (95%CI: −49.36, −3.64)
	Triglycerides (mg/dL) at 6 mo	180.0 (60.81)	177.5 (101.96)	2.50 (95%CI: −51.76, 56.76)
	Apolipoprotein A-1 (mg/dL) at 6 mo	146.7 (30.18)	146.5 (38.16)	0.20 (95%CI: −26.59, 26.99)
	Apolipoprotein B (mg/dL) at 6 mo	129.5 (23.55)	141.5 (45.27)	−12.00 (95%CI: −39.50, 15.50)
	Apolipoprotein E (mg/dL) at 6 mo	6.3 (1.33)	6.7 (1.50)	−0.40 (95%CI: −1.51, 0.71)
	Fasting blood glucose (mg/dL) at 6 mo	102.5 (20.92)	108.3 (25.50)	−5.80 (95%CI: −15.40, 3.80)
	Haemoglobin A_{1c} (%) at 6 mo	6.0 (0.82)	5.7 (1.0)	0.30 (95%CI: −0.25, 0.85)
	BUN (mg/dL)	21.0 (7.41)	32.4 (14.87)	−11.40 (95%CI: −18.07, −4.73)
	Serum creatinine (mg/dL)	1.3 (0.48)	2.1 (1.15)	−0.80 (95%CI: −1.30, −0.30)
	Creatinine clearance (mg/dL)	63.8 (29.06)	49.8 (27.74)	14.00 (95%CI: −2.22, 30.22)
	Urinary protein excretion (g/day)	1.1 (1.09)	1.7 (1.20)	−0.60 (95%CI: −1.35, 0.15)
Lam *et al.* 1995	MAP (mmHg) at 24 mo	105.9 (12.8)	103.4 (11.88)	2.50 (95%CI: −53.83, 10.83)
	BMI (kg/m^2) at 24 mo	26.3 (4.4)	250 (4.24)	1.30 (95%CI: −1.61, 4.21)
	HbA_{1c} (%) at 24 mo	6.6 (1.6)	6.8 (1.70)	−0.20 (95%CI: −1.31, 0.91)
	Total cholesterol (mmol/L) at 24 mo	4.9 (0.4)	6.4 (0.85)	−1.50 (95%CI: −1.94, −1.06)
	Triglyceride (mmol/L) at 24 mo	2.0 (1.6)	3.7 (2.55)	−1.70 (95%CI: −3.12, −0.28)
	HDL cholesterol (mmol/L) at 24 mo	1.09 (0.24)	0.99 (0.30)	0.09 (95%CI: −0.09, 0.27)
	LDL cholesterol (mmol/L) at 24 mo	3.0 (0.8)	3.8 (0.85)	−0.80 (95%CI: −1.35, −0.25)
	Apolipoprotein A1 (g/L) at 24 mo	1.98 (0.32)	1.90 (0.30)	0.08 (95%CI: −0.13, 0.29)
	Apolipoprotein B (g/L) at 24 mo	1.27 (0.2)	0.50 (0.30)	−0.23 (95%CI: −0.40, −0.06)
Olbricht *et al.* 1999	Mean DBP (mmHg)	86 (5) 20	88 (6) 23	−2.00 (95%CI: −5.29, 1.29)
	Mean SDP (mmHg)	137 (13) 20	138 (7) 23	−1.00 (95%CI: −7.38, 5.38)
Thomas *et al.* 1993	Mean change in inulin clearance ($mL/min/1.73\ m^2$)	−4.1 (25)	−16.7 (21)	12.60 (95%CI: −10.04, 35.24)

Table 4. Results for dichotomous outcomes

Study ID (author, year)	Outcomes	Intervention group (number of patients with events/number of patients exposed)	Control group (number of patients with events/number of patients not exposed)	Relative risk (RR) [95% CI]	Risk difference (RD) [95% CI]
Hommel *et al.* 1992	GI symptoms	1/12	0/9	2.31 (95%CI: 0.10, 50.85)	0.08 (95%CI: –0.14, 0.30)
	Myalgia	1/12	0/9	2.31 (95%CI: 0.10, 50.85)	0.08 (95%CI: –0.14, 0.30)
Smulders *et al.* 1997	Spontaneous reaction in triglyceride levels	0/15	1/15	0.33 (95%CI: 0.01, 7.58)	–0.07 (95%CI: –0.23, 0.10)
Tonelli *et al.* 2003	Mortality	39/345	61/345	0.64 (95%CI: 0.44, 0.93)	–0.06 (95%CI: 0.44, 0.93)
	Asymptomatic elevations in Serum Cr and P levels >3 × upper limit of normal	3/345	2/345	1.50 (95%CI: 0.25, 8.92)	0.00 (95%CI: –0.01, 0.02)
	Rhabdomyolysis	0/345	2/345	0.20 (95%CI: 0.01, 4.15)	–0.01 (95%CI: –0.02, 0.00)
	Depression	6/345	13/345	0.46 (95%CI: 0.18, 1.20)	–0.02 (95%CI: –0.04, 0.00)
	Non-dermatologic malignancy	61/345	75/345	0.81 (95%CI: 0.60, 1.10)	–0.04 (95%CI: –0.10, 0.02)
	Skin cancer	25/345	29/345	0.86 (95%CI: 0.52, 1.44)	–0.01 (95%CI: –0.05, 0.03)

Uric acid

Date written: February 2004
Final submission: July 2004
Author: David Johnson

GUIDELINES

No recommendations possible based on Level I or II evidence.

SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on Level III and IV sources)

- **Treating hyperuricaemia does not retard the progression of renal failure and cannot be recommended for this indication. (Level IV evidence; limited case series; clinically relevant outcomes; consistent effects)**
- **Physicians should be aware that the use of protein-restricted diets in chronic renal patients treated with allopurinol may require further reduction of the dose of allopurinol due to inhibition of urinary excretion of oxypurinol. (Level II evidence; single randomised cross-over study; surrogate outcome; moderate effect)**

BACKGROUND

Hyperuricaemia is an almost invariable feature of renal failure.[1] Long-standing hyperuricaemia has occasionally been associated with the development of chronic kidney disease (CKD),[2–11] although it has been difficult to establish whether the elevated plasma urate levels in these patients reflect a cause, consequence or accelerant of renal dysfunction. The aim of this guideline is to evaluate the available clinical evidence that treatment of hyperuricaemia retards the progression of CKD.

SEARCH STRATEGY

Databases searched: Medline (1999 to November Week 2, 2003). MeSH terms for kidney diseases were combined with MeSH terms and text words for allopurinol and hyperuricaemia. The results were then combined with the Cochrane highly sensitive search strategy for randomised controlled trials and MeSH terms and text words for identifying meta-analyses and systematic reviews. The Cochrane Renal Group Specialized Register of Randomised Controlled Trials was also searched for relevant trials not indexed by Medline.
Date of search: 16 December 2003.

WHAT IS THE EVIDENCE?

There are no randomised or prospective controlled trials addressing the effect of treatment of hyperuricaemia on progression of renal failure.

Occasional renal patients with hyperuricaemia and CKD have demonstrated histologic findings of urate crystals in the renal cortical, medullary or papillary interstitium with surrounding giant cell reaction.[6,12,13] It is uncertain whether this contributes to renal dysfunction, is a consequence of renal injury or is merely an epiphenomenon.

A case-control study by Fessel[14] demonstrated that azotaemia occurred in only 2 of 113 patients with asymptomatic hyperuricaemia compared with 4 of 193 normouricaemic controls over a mean follow-up period of 8 years. Similarly, long-term follow-up studies of 524 gouty patients failed to demonstrate any adverse effect of hyperuricaemia on renal function.[15]

Therapy directed at lowering plasma urate levels (uricosurics or allopurinol) in patients with familial hyperuricaemia has not been successful in preventing the development of renal insufficiency.[10,11]

Case series reports[16] have generally not observed an alteration in the rate of progression of renal disease after correction of hyperuricaemia by allopurinol.

In a retrospective case series, Fairbanks *et al*[17] examined the effects of allopurinol commencement in 32 patients with familial juvenile hyperuricaemic nephropathy. Twenty-seven patients started immediately on allopurinol (serum creatinine <0.2 mmol/L) experienced mild deterioration of renal function compared with five patients who commenced allopurinol with a serum creatinine concentration > 0.2 mmol/L, all of whom progressed to end-stage kidney disease (ESKD) with an average period of 6 years. The study's results were significantly limited by the absence of a control group and lead-time bias.

The unproven benefit of allopurinol in preventing renal failure progression in the setting of asymptomatic hyperuricaemia must be balanced against the documented small incidence of serious adverse reactions to allopurinol, including drug hypersensitivity syndromes. For example, a review of allopurinol hypersensitivity reactions by Lupton and Odom[18] reported that 97% of such reactions occurred in the setting of pre-existing renal failure and that in over 60% of cases, allopurinol was prescribed for the treatment of asymptomatic hyperuricaemia; 10% of the reported patients died from allopurinol hypersensitivity.

The use of protein-restricted diets has been shown in a randomised crossover trial[19] to significantly diminish the excretion of allopurinol and its active metabolite oxypu-

rinol by 28% and 64%, respectively. This results in a 3-fold increase in the half-life of oxypurinol.

SUMMARY OF THE EVIDENCE

There are no randomised or prospective controlled trials addressing the effect of treatment of hyperuricaemia on progression of renal failure. The majority of the small numbers of published case series and anecdotal reports suggest that treatment of hyperuricaemia per se does not appreciably influence renal failure progression.

WHAT DO THE OTHER GUIDELINES SAY?

Kidney Disease Outcomes Quality Initiative: No recommendation.
UK Renal Association: No recommendation.
Canadian Society of Nephrology: No recommendation.
European Best Practice Guidelines: No recommendation.
International Guidelines: No recommendation.

IMPLEMENTATION AND AUDIT

No recommendation.

SUGGESTIONS FOR FUTURE RESEARCH

A multicentre, prospective, randomised controlled trial of allopurinol therapy on the progression of renal failure would help to clarify the issue, although such a study would not be a very high priority. The study would need to be stratified for sex, diabetes and severity of renal dysfunction.

REFERENCES

1. Ifudu O, Tan CC, Dulin AL *et al*. Gouty arthritis in end-stage renal disease: clinical course and rarity of new cases. *Am. J. Kidney Dis* 1994; **23**: 347–51.
2. Foreman JW, Yudkoff M. Familial hyperuricemia and renal insufficiency. *Child Nephrol. Urol.* 1990; **10**: 115–8.
3. Yu TF, Berger L. Renal disease in primary gout. a study of 253 gout patients with proteinuria. *Semin Arthritis Rheum* 1975; **4**: 293–305.
4. Coombs FS, Pecora LJ, Thorogood E. Renal function in patients with gout. *J. Clin. Invest* 1940; **19**: 525–35.
5. Gutman AB, Yu TF. Renal function in gout with a commentary on the renal regulation of urate excretion, and the role of the kidney in the pathogenesis of gout. *Am. J. Med.* 1957; **23**: 600–22.
6. Talbott JH, Terplan KL. The kidney in gout. *Medicine* 1960; **39**: 405–67.
7. Barlow KA, Beilin KJ. Renal disease in primary gout. *Q J. Med.* 1968; **37**: 79–96.
8. Duncan H, Dixon ST. Gout, familial hyperuricaemia and renal failure. *Q J. Med.* 1960; **29**: 127–35.
9. Rosenbloom FM, Kelley WN, Carr AA. Familial nephropathy and gout in a kindred. *Clin. Res.* 1967; **15**: 270–1.
10. Van Goor W, Koorker CJ, Mees CJD. An unusual form of renal disease associated with gout and hypertension. *J. Clin. Pathol* 1971; **24**: 254–9.
11. Massari PU, Hsu CH, Barnes RV *et al*. Familial hyperuricemia and renal disease. *Arch. Intern. Med.* 1980; **140**: 680–4.
12. Sokoloff L. The pathology of gout. *Metabolism* 1957; **6**: 230–43.
13. Brown J, Mallory GK. Renal changes in gout. *N Engl. J. Med.* 1950; **243**: 325–9.
14. Fessel WJ. Renal outcomes of gout and hyperuricemia. *Am. J. Med.* 1979; **67**: 74–82.
15. Berger L, Yu TF. Renal function in gout IV. An analysis of 524 gouty subjects including long-term follow-up studies. *Am. J. Med.* 1979; **59**: 605–13.
16. Emmerson BT. Gout and renal disease. In. Smyth, CJ Holers, VM, eds. *Gout, Hyperuricaemia and Other Crystal-Associated Arthropathies*, 1st edn. New York, Marcel Dekker, 1999: pp. 241–60.
17. Fairbanks LD, Cameron JS, Venkat-Raman G *et al*. Early treatment with allopurinol in familial juvenile hyerpuricaemic nephropathy (FJHN) ameliorates the long-term progression of renal disease. *QJM* 2002; **95**: 597–607.
18. Lupton GP, Odom RB. The allopurinol hypersensitivity syndrome. *J. Am. Acad. Dermatol.* 1979; **1**: 365–74.
19. Berlinger WG, Park GD, Spector R. The effect of dietary protein on the clearance of allopurinol and oxypurinol. *N Engl. J. Med.* 1985; **313**: 771–6.

Phosphate

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Author: David Johnson

GUIDELINES

No recommendations possible based on Level I or II evidence.
There are no randomised controlled trials (RCTs) to date which have assessed the effect of isolated dietary phosphate restriction on renal failure progression.

SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on Level III and IV sources)
• **Isolated phosphate restriction is not recommended for retarding the progression of chronic renal insufficiency. (Level III evidence; single small study; clinically relevant outcome; negative effect)**

BACKGROUND

Hyperphosphataemia is observed in the majority of patients with stage 4 chronic kidney disease (CKD) and has been identified as a risk factor for the progression of chronic renal failure.[1] Dietary phosphorus restriction can prevent the progression of renal failure in subtotally nephrectomized rats or in rats with nephrotoxic serum nephritis, independent of protein and caloric intake. Conversely, diets high in phosphorus content result in a more rapid deterioration of renal function.[2] The objective of this guideline is to review the evidence that correction of hyperphosphataemia retards the progression of renal insufficiency in the clinical setting.

SEARCH STRATEGY

Databases searched: Medline (1999 to November Week 2, 2003). MeSH terms for kidney diseases were combined with MeSH terms and text words for phosphate binders. The results were then combined with the Cochrane highly sensitive search strategy for randomised controlled trials and MeSH terms and text words for identifying meta-analyses and systematic reviews. The Cochrane Renal Group Specialized Register of Randomised Controlled Trials was also searched for relevant trials not indexed by Medline.
Date of search: 16 December 2003.

WHAT IS THE EVIDENCE?

There are no RCTs that have specifically addressed the issue of whether isolated phosphate restriction retards the progression of chronic renal insufficiency.

Many of the protein-restricted diets trialled in progressive renal insufficiency have additionally incorporated dietary phosphate restriction.[3–45] However, the specific role of phosphate restriction remains uncertain due to the conflicting findings of the studies and their often poor experimental design due to small numbers, short follow-up times, variable phosphate binder usage, different degrees of renal insufficiency, concomitant protein and caloric restrictions, and the inappropriate use of plasma creatinine or creatinine clearance as a GFR measure (as these are inaccurate and influenced by diet).

Barsotti *et al*[42] performed a non-randomised study of a very low phosphate, low protein diet (6.5 mg/kg/day phosphate, 0.6 g/kg/day protein) vs. a conventional low-phosphate low-protein diet (12 mg/kg/day phosphate, 0.6 g/kg/day protein) in 55 patients with non-diabetic renal disease. It is not clear from the analysis whether the study was prospective or retrospective and whether the 2 groups were studied in parallel or sequentially. Both groups were followed initially on a free uncontrolled mixed diet for mean durations of 11.5 and 10.0 months, respectively. They were then switched to their special diets for average durations of 20.8 and 16.3 months, respectively. Serum phosphate significantly fell in the first group from 4.39 to 3.99 mg/dL and rose in the second group from 4.25 to 4.96 mg/dL. Urinary phosphate excretion differed between the 2 groups (362.3 vs. 628.8 mg/day), but urinary urea excretion was comparable (7.62 vs. 8.23 g/day) thereby indicating that protein intake was not significantly different. Despite comparable declines in creatinine clearance whilst on the free diet (-0.90 ± 0.67 vs. -0.79 ± 0.53 mL/min/month), the patients who subsequently received a very low-phosphate diet had a slower rate of renal function deterioration compared with the other group (-0.07 ± 0.38 vs. -0.53 ± 0.40 mL/min/month), although no comment was made as to whether the difference was statistically significant (the difference did not appear to be significant based on calculations from the summary data). The limitations of the study are its small size, short follow-up time, inappropriate renal function measure, lack of randomization and inappropriate statistical analysis (*t*-tests in the setting of repeated measures).

SUMMARY OF THE EVIDENCE

There has only been 1 non-randomised study of isolated dietary phosphate restriction vs. a conventional low phos-

phate, low protein diet in 55 patients with non-diabetic renal disease. No significant differences were found between the 2 groups, although the study was limited by a lack of statistical power, inappropriate statistical analysis, inadequate measurement of renal function and a lack of randomization.

WHAT DO THE OTHER GUIDELINES SAY?

Kidney Disease Outcomes Quality Initiative: No recommendation.
UK Renal Association: No recommendation.
Canadian Society of Nephrology: No recommendation.
European Best Practice Guidelines: No recommendation.
International Guidelines: No recommendation.

IMPLEMENTATION AND AUDIT

No recommendation.

SUGGESTIONS FOR FUTURE RESEARCH

No recommendation.

REFERENCES

1. Klahr S, Morrissey J. Progression of chronic renal disease. *Am. J. Kidney Dis.* 2003; **41** (**3** Suppl. 1): S3–7.
2. Loghman-Adham M. Role of phosphate retention in the progression of renal failure. *J. Laboratory Clin. Med.* 1993; **122**: 16–26.
3. Klahr S, Levey AS, Beck GJ *et al.* The effects of dietary protein restriction and blood-pressure control on the progression of chronic renal disease. Modification of Diet in Renal Disease Study Group. *N Engl. J. Med.* 1994; **330**: 877–84.
4. Rosman JB. Dietary protein restriction in chronic renal failure: an update. *Klin Wochenschr.* 1989; **67**: 882–8.
5. Jungers P, Chauveau P, Ployard F *et al.* Comparison of ketoacids and low protein diet on advanced chronic renal failure progression. *Kidney Int. Suppl.* 1987; **22**: S67–S71.
6. Locatelli F, Alberti D, Graziani G *et al.* Prospective, randomised, multicentre trial of effect of protein restriction on progression of chronic renal insufficiency. Northern Italian Cooperative Study Group. *Lancet* 1991; **337**: 1299–304.
7. D'Amico G, Gentile MG, Fellin G *et al.* Effect of dietary protein restriction on the progression of renal failure: a prospective randomized trial. *Nephrol. Dial Transplant.* 1994; **9**: 1590–4.
8. Ihle BU, Becker GJ, Whitworth JA *et al.* The effect of protein restriction on the progression of renal insufficiency. *N Engl. J. Med.* 1989; **321**: 1773–7.
9. Williams PS, Stevens ME, Fass G. *et al.* Failure of dietary protein and phosphate restriction to retard the rate of progression of chronic renal failure: a prospective, randomized, controlled trial. *Q J. Med.* 1991; **81**: 837–55.
10. Bergstrom J, Alvestrand A, Bucht H *et al.* Stockholm clinical study on progression of chronic renal failure – an interim report. *Kidney Int. Suppl.* 1989; **27**: S110–S14.
11. Hecking E, Andrzejewski L, Prellwitz W *et al.* Double-blind crossover study with oral alpha-ketoacids in patients with chronic renal failure. *Am. J. Clin. Nutr.* 1980; **33**: 1678–81.
12. Frohling PT, Schmicker R, Vetter K *et al.* Conservative treatment with ketoacid and amino acid supplemented low-protein diets in chronic renal failure. *Am. J. Clin. Nutr.* 1980; **33**: 1667–72.
13. Maschio G, Oldrizzi L, Tessitore N *et al.* Effects of dietary protein and phosphorus restriction on the progression of early renal failure. *Kidney Int.* 1982; **22**: 371–6.
14. Gretz N, Korb E, Strauch M. Low-protein diet supplemented by keto acids in chronic renal failure: a prospective controlled study. *Kidney Int. Suppl.* 1983; **16**: S263–S267.
15. Oldrizzi L, Rugiu C, Valvo E *et al.* Progression of renal failure in patients with renal disease of diverse etiology on protein-restricted diet. *Kidney Int.* 1985; **27**: 553–7.
16. Di Landro D, Perin N, Bertoli M *et al.* Clinical effects of a low protein diet supplemented with essential amino acids and keto analogues in uremic patients. *Contrib Nephrol.* 1986; **53**: 137–43.
17. Schmicker R. Froehling PT, Goetz KH *et al.* Influence of low protein diet supplemented with amino acids and keto acids on the progression of chronic renal failure. *Contrib Nephrol.* 1986; **53**: 121–7.
18. Frohling PT, Lindenau K, Vetter K *et al.* What can be safely said about predialysis treatment? *Blood Purif.* 1989; **7**: 28–32.
19. Walser M. Ketoacids in the treatment of uremia. *Clin. Nephrol.* 1975; **3**: 180–6.
20. Mallick NP. Dietary protein and progression of chronic renal disease. *BMJ.* 1994; **309**: 1101–2.
21. Burns J, Cresswell E, Ell S *et al.* Comparison of the effects of keto acid analogues and essential amino acids on nitrogen homeostasis in uremic patients on moderately protein-restricted diets. *Am. J. Clin. Nutr.* 1978; **31**: 1767–75.
22. Kampf D, Fischer HC, Kessel M. Efficacy of an unselected protein diet (25 g) with minor oral supply of essential amino acids and keto analogues compared with a selective protein diet (40 g) in chronic renal failure. *Am. J. Clin. Nutr.* 1980; **33**: 1673–7.
23. Attman PO, Bucht H, Larsson O *et al.* Protein-reduced diet in diabetic renal failure. *Clin. Nephrol.* 1983; **19**: 217–20.
24. Frohling PT, Kokot F, Schmicker R *et al.* Influence of keto acids on serum parathyroid hormone levels in patients with chronic renal failure. *Clin. Nephrol.* 1983; **20**: 212–5.
25. El Nahas AM, Masters TA, Brady SA *et al.* Selective effect of low protein diets in chronic renal diseases. *Br. Medical J Clin. Res. Ed.* 1984; **289**: 1337–41.
26. Mitch WE, Walser M, Steinman TI *et al.* The effect of a keto acid-amino acid supplement to a restricted diet on the progression of chronic renal failure. *N Engl. J. Med.* 1984; **311**: 623–9.
27. Lucas PA, Meadows JH, Roberts DE *et al.* The risks and benefits of a low protein-essential amino acid-keto acid diet. *Kidney Int.* 1986; **29**: 995–1003.
28. Walser M, LaFrance N, Ward L *et al.* Progression of chronic renal failure in patients given keto acids following amino acids. *Infusionsther Klin Ernahr.* 1987; **14** (Suppl. 5): S17–S20.
29. Barsotti G, Ciardella F, Morelli E *et al.* Nutritional treatment of renal failure in type 1 diabetic nephropathy. *Clin. Nephrol.* 1988; **29**: 280–7.
30. Levine SE, D'Elia JA, Bistrian B *et al.* Protein-restricted diets in diabetic nephropathy. *Nephron.* 1989; **52**: 55–61.
31. Zeller K, Whittaker E, Sullivan L *et al.* Effect of restricting dietary protein on the progression of renal failure in patients with insulin-dependent diabetes mellitus. *N Engl. J. Med.* 1991; **324**: 78–84.
32. Alvestrand A, Ahlberg M, Furst P *et al.* Clinical experience with amino acid and keto acid diets. *Am. J. Clin. Nutr.* 1980; **33**: 1654–9.
33. Barsotti G, Guiducci A, Ciardella F *et al.* Effects on renal function of a low-nitrogen diet supplemented with essential amino acids and ketoanalogues and of hemodialysis and free protein supply in patients with chronic renal failure. *Nephron.* 1981; **27**: 113–7.
34. Alvestrand A, Ahlberg M, Bergstrom J. Retardation of the progression of renal insufficiency in patients treated with low-protein diets. *Kidney Int. Suppl.* 1983; **16**: S268–S272.

35. Bennett SE, Russell GI, Walls J. Low protein diets in uraemia. *Br. Med. J. Clin. Res. Ed.* 1983; **287**: 1344–5.
36. Attman PO. Long-term treatment with low protein diet in uremia. *Contrib Nephrol.* 1986; **53**: 128–36.
37. Hannedouche T, Chauveau P, Fehrat A *et al.* Effect of moderate protein restriction on the rate of progression of chronic renal failure. *Kidney Int. Suppl.* 1989; **27**: S91–S95.
38. Klahr S. Prevention of progression of nephropathy. *Nephrol. Dial Transplant.* 1997; **12**: 63–6.
39. Simpson IJ, Bailey RR, Robson RA *et al.* Management guidelines for progressive chronic renal failure. New Zealand Nephrologists Consensus Group. *N Z. Med. J.* 1997; **110**: 421–3.
40. Maschio G, Oldrizzi L, Tessitore N *et al.* Early dietary protein and phosphorus restriction is effective in delaying progression of chronic renal failure. *Kidney Int. Suppl.* 1983; **16**: S273–S277.
41. Barsotti G, Morelli E, Giannoni A *et al.* Restricted phosphorus and nitrogen intake to slow the progression of chronic renal failure: a controlled trial. *Kidney Int. Suppl.* 1983; **16**: S278–S284.
42. Barsotti G, Giannoni A, Morelli E *et al.* The decline of renal function slowed by very low phosphorus intake in chronic renal patients following a low nitrogen diet. *Clin. Nephrol.* 1984; **21**: 54–9.
43. Barrientos A, Arteaga J, Rodicio JL *et al.* Role of the control of phosphate in the progression of chronic renal failure. *Miner Electrolyte Metab.* 1982; **7**: 127–33.
44. Ciardella F, Morelli E, Niosi F *et al.* Effects of a low phosphorus, low nitrogen diet supplemented with essential amino acids and ketoanalogues on serum triglycerides of chronic uremic patients. *Nephron.* 1986; **42**: 196–9.
45. Gin H, Aparicio M, Potaux L *et al.* Low protein and low phosphorus diet in patients with chronic renal failure: influence on glucose tolerance and tissue insulin sensitivity. *Metabolism.* 1987; **36**: 1080–5.

Exercise

Date written: February 2004
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Author: David Johnson

GUIDELINES

Exercise training has not been shown to retard the progression of renal insufficiency. (Level II evidence; single, small, underpowered trial; clinically relevant outcome; negative effect)

BACKGROUND

Chronic kidney disease (CKD) is typically associated with sarcopenia and a reduction in exercise tolerance. In rat models of CKD, augmented exercise has been shown to be renoprotective (Kohzuki *et al.*[1]). The objective of this guideline is to assess the available clinical trials of the effects of enhanced physical activity on renal function decline in patients with CKD.

SEARCH STRATEGY

Databases searched: Medline (1999 to November Week 2, 2003). MeSH terms for kidney disease were combined with MeSH terms and text words for exercise training. The results were then combined with the Cochrane highly sensitive search strategy for randomised controlled trials and MeSH terms and text words for identifying meta-analyses and systematic reviews. The Cochrane Renal Group Specialized Register of Randomised Controlled Trials was also searched for relevant trials not indexed by Medline.
Date of search: 16 December 2003.

WHAT IS THE EVIDENCE?

There is one randomised controlled trial (RCT).

Eidemak *et al.*[2] randomised 30 patients with moderate-to-severe CKD (median GFR 25 mL/min/1.73 m^2, range 10–43) to physical training (30 min of bicycling daily or an equal amount of other physical activities) or to maintenance of usual lifestyle. Over a median follow-up time of 20 months, median maximal work capacity increased significantly in the exercise group, but not in the controls. However, no change in GFR decline was observed between the 2 groups. The chief limitation of the study was its lack of statistical power.

A small prospective, non-controlled study of 16 subjects with CKD[3] showed no effect of endurance exercise training (cycle ergometer) on renal function, as determined by plasma creatinine. The major limitations of the study were its small numbers, short follow-up time, high drop-out rate (50%) and inappropriate measure of renal function.

SUMMARY OF THE EVIDENCE

There has only been one small, underpowered RCT of intensive exercise vs. usual lifestyle in 30 patients with stages 3–5 CKD. After a median follow-up of 20 months, no significant change in GFR decline was observed between the 2 groups, although a type 2 statistical error is likely.

WHAT DO THE OTHER GUIDELINES SAY?

Kidney Disease Outcomes Quality Initiative: No recommendation.
UK Renal Association: No recommendation.
Canadian Society of Nephrology: No recommendation.
European Best Practice Guidelines: No recommendation.
International Guidelines: No recommendation.

IMPLEMENTATION AND AUDIT

No recommendation.

SUGGESTIONS FOR FUTURE RESEARCH

A larger, longer-term study of the effects of exercise on renal failure progression is warranted.

REFERENCES

1. Kohzuki M, Kamimoto M, Wu XM *et al*. Renal protective effects of chronic exercise and antihypertensive therapy in hypertensive rats with chronic renal failure. *J. Hypertens* 2001; **19**: 1877–82.
2. Eidemak I, Haaber AB, Feldt-Rasmussen B *et al*. Exercise training and the progression of chronic renal failure. *Nephron* 1997; **75**: 36–40.
3. Castaneda C, Grossi L, Dwyer J. Potential benefits of resistance exercise training on nutritional status in renal failure. *J. Ren Nutr* 1998; **8**: 2–10.

APPENDICES

Table 1 Characteristics of included studies

Study ID (author, year)	N	Study Design	Setting	Participants	Intervention (experimental group)	Intervention (control group)	Follow up (months)	Comments
Eidemak *et al*, 1997[2]	30	Prospective, randomised, controlled trial	Hospital	30 non-diabetic patients aged 22–70 yrs with moderate progressive CKD and a median GFR of 25 mL/min/1.73m^2)	Exercise program designed to match patient's physical capacity. Exercises consisted of bicycle ergometer exercise, running, swimming and walking. Duration and intensity of exercise gradually increased over time.	No exercise program	Minimum of 18	

Table 2 Quality of randomised trials

Study ID (author, year)	Method of allocation concealment	Blinding			Intention-to-treat analysis	Loss to follow up (%)
		(participants)	(investigators)	(outcome assessors)		
Eidemak *et al*, 1997[2]	Central	No	No	No	Unclear	Unclear

Table 3 Results for continuous outcomes

Study ID (author, year)	Outcomes	Intervention group (mean [SD])	Control group (mean [SD])	Difference in means [95% CI]
Eidemak *et al.* 1997	Total cholesterol (mmol/L) at follow up	5.65 (1.05)	5.42 (1.17)	0.23 (95%CI: –0.57, 1.03)
	Triglyceride (mmol/L) at follow up	1.44 (0.8)	1.56 (1.25)	–0.12 (95%CI: –0.87, 0.63)

Table 4 Results for dichotomous outcomes

Study ID (author, year)	Outcomes	Intervention group (number of patients with events/number of patients exposed)	Control group (number of patients with events/number of patients not exposed)	Relative risk (RR) [95% CI]	Risk difference (RD) [95% CI]
Eidemak *et al.* 1997	ESKD	3/15	2/15	1.50 (95%CI: 0.29, 7.73)	0.07 (95%CI: –0.20, 0.33)

Acidosis

Date written: February 2004
Final submission: July 2004
Author: David Johnson

GUIDELINES

There are no human trials with clinically relevant outcomes that have assessed the impact of acidosis correction on renal failure progression.

SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on Level III and IV sources)

- **There are no studies of the effect of alkali therapy on the progression of renal failure in humans. No recommendations can therefore be made regarding the use of alkali treatment specifically for the purposes of renoprotection.**

BACKGROUND

Metabolic acidosis is a common accompaniment of chronic kidney disease (CKD) and has been identified as a risk factor for the progression of renal insufficiency.[1] The objective of this guideline is to assess the available clinical evidence pertaining to the impact of correction of metabolic acidosis on renal function decline.

SEARCH STRATEGY

Databases searched: Medline (1999 to November Week 2, 2003). MeSH terms for kidney disease were combined with MeSH terms and text words for alkali therapy and bicarbonates. The results were then combined with the Cochrane highly sensitive search strategy for randomised controlled trials and MeSH terms and text words for identifying meta-analyses and systematic reviews. The Cochrane Renal Group Specialized Register of Randomised Controlled Trials was also searched for relevant trials not indexed by Medline.
Date of search: 16 December 2003.

WHAT IS THE EVIDENCE?

There are no randomised controlled trials (RCTs).

Although a renal protective effect of alkali therapy is unproven in humans, a brief (26 h) study of oral sodium bicarbonate in 11 patients with mild-to-moderate renal insufficiency[2] found that urinary excretion of N-acetyl-β-D-glucose-aminidase (a marker of tubular injury) was decreased, although proteinuria and ^{51}Cr-EDTA clearance remained unchanged. No longer term studies assessing the influence of alkali therapy on renal failure progression in humans are available.

SUMMARY OF THE EVIDENCE

There are no human trials with clinically relevant outcomes that have assessed the impact of acidosis correction on renal failure progression.

WHAT DO THE OTHER GUIDELINES SAY?

Kidney Disease Outcomes Quality Initiative: No recommendation.
Canadian Society of Nephrology: No recommendation.
UK Renal Association: No recommendation.
European Best Practice Guidelines: No recommendation.
International Guidelines: No recommendation.

IMPLEMENTATION AND AUDIT

No recommendation.

SUGGESTIONS FOR FUTURE RESEARCH

Considering the general benefits of acidosis correction (prevention of muscle breakdown and osteopenia), a study of the effects of alkali therapy on renal function per se would not seem warranted.

REFERENCES

1. Klahr S, Morrissey J. Progression of chronic renal disease. *Am. J. Kidney Dis* 2003; **41** (**3** Suppl. 1): S3–S7.
2. Rustom R., Grime JS, Costigan M *et al.* Oral sodium bicarbonate reduces proximal renal tubular peptide catabolism, ammoniogenesis, and tubular damage in renal patients. *Ren Fail* 1998; **20**: 371–82.

Erythropoietin

Date written: February 2004
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Author: David Johnson

GUIDELINES

The weight of clinical evidence indicates that erythropoietin exerts neither a beneficial nor deleterious effect on the progression of renal impairment in patients with chronic renal insufficiency. (Level II evidence, 6 small randomised controlled trials; clinically relevant outcomes; inconsistent effects)

BACKGROUND

Erythropoietin is routinely used to correct the anaemia associated with chronic kidney disease (CKD). Early experience with this drug (in relatively high doses) in clinical and experimental chronic kidney failure (CKF) suggested that erythropoietin may have been deleterious to renal function, although this effect was not apparent when blood pressure was adequately controlled.[1] More recent experiences with lower dosages of erythropoeitin have not reported adverse effects on renal function. The objective of this guideline was to review the available clinical evidence pertaining to the effect of erythropoietin on renal failure progression.

SEARCH STRATEGY

Databases searched: Medline (1999 to November Week 2, 2003). MeSH terms for kidney disease were combined with MeSH terms and text words for erythropoietin therapy. The results were then combined with the Cochrane highly sensitive search strategy for randomised controlled trials and MeSH terms and text words for identifying meta-analyses and systematic reviews. The Cochrane Renal Group Specialized Register of Randomised Controlled Trials was also searched for relevant trials not indexed by Medline.
Date of search: 16 December 2003.

WHAT IS THE EVIDENCE?

There are 6 randomised controlled trials (RCTs).

Roth *et al*[2] conducted a 48-week, prospective, randomised, open-label, multicentre trial in which 83 anaemic predialysis patients (plasma creatinine 3–8 mg/dL) were randomly assigned to no treatment (n = 43) or treatment with erythropoietin (50 IU/kg subcutaneously three times weekly, n = 43). Allocation concealment was not specified. The dose of erythropoietin was titrated to maintain a haematocrit level of 35%. GFR was evaluated by ^{125}I-iothalamate clearance at weeks 1, 8, 16, 32 and 48 weeks. The two groups were similar at baseline. The overall decline in GFR was identical for the two groups (–0.43 mL/min/month). The major limitation of the study was the very high drop-out rate (42%).

A prospective, single centre, randomised, open-label controlled trial[3] was conducted in 108 Japanese patients over 36 weeks. Anaemic CKD patients with a plasma creatinine concentration between 2 and 4 mg/dL (mean 2.9) and a haematocrit < 30% were randomly assigned to treatment with (n = 42) or without (n = 31) erythropoietin. Untreated non-anaemic (haematocrit > 30%) CKD patients (n = 35) were also recruited. Just over half the patients were diabetic and 60%–68% of patients in each group were receiving ACE inhibitors. All patients were treated with a 0.6 g/kg/day protein diet. Erythropoietin doses were adjusted to maintain haematocrit between 33% and 35% in the treated group. Mean haematocrit increased significantly in the treated group (27.0% to 32.1%), but declined significantly in the other two groups. Cumulative renal survival, derived from the time it took baseline plasma creatinine concentration to double, was significantly better in the treated group than in the untreated anaemic group, but was not different from that in untreated non-anaemic controls. Dialysis was commenced in 33%, 65% and 37% of patients, respectively ($P < 0.05$). The improvement in cumulative renal survival in the erythropoietin-treated group was attributable solely to improved renal survival in non-diabetics. It was concluded that reversal of anaemia by erythropoietin retards the progression of renal failure, especially in non-diabetic patients (they speculated that this was due to prevention of renal tissue hypoxia). However, significant limitations of the study were (a) the use of plasma creatinine as a marker of renal function; (b) the high drop-out rate (17%); (c) the potential for sample bias in view of differences in baseline characteristics of the groups (creatinine clearances tended to be lower and 24-h urinary protein excretion rates tended to be higher in the untreated anaemic patients); and (d) lack of adjustment for these potential confounders in the survival curves (e.g. by a Cox's proportional hazards model). It is also questionable that allocation concealment was adequate.

A prospective, multicentre, randomised, open-label controlled trial evaluated the effects of haemoglobin normaliza-

tion (135–160 g/L) vs. maintenance of subnormal haemoglobin levels (90–120 g/L), with or without erythropoietin therapy, in 416 Scandinavian patients with renal anaemia treated across 62 hospital centres in Sweden, Norway, Finland and Iceland.[4] Of the 416 study subjects, 46 patients were predialysis and had their renal function measured at baseline and at two years by local routine methods (creatinine clearance, iohexol clearance or Cr-EDTA clearance). GFR decline was comparable between the two groups ($P = 0.43$). The major limitation of the study was its small sample size and lack of statistical power.

In a 2-year, prospective, multicentre, randomised, open-label controlled trial conducted in Australia and New Zealand, Roger *et al*[5] randomly allocated 155 patients with CKD (creatinine clearance 15–50 mL/min) to receive erythropoietin as necessary to maintain haemoglobin concentration between 120 and 130 g/L (group A) or between 90 and 100 g/L (group B). This trial was sponsored by Janssen-Cilag. By the end of two years of follow-up, the mean achieved haemoglobin concentrations were 121 ± 14 g/L for Group A and 108 ± 13 g/L for Group B. The decline in renal function over two years, as determined by isotopic measurements of GFR, did not differ significantly between the two groups (8 ± 9 versus 6 ± 8 mL/min/1.73 m^2). Significant limitations of the study included (a) lack of statistical power due to small size and a failure to reach haemoglobin target for many patients in Group B; and (b) a much higher drop-out rate in Group B (25%) compared with Group A (12%), raising the possibility of survivor bias and informative censoring.

Using plasma creatinine, reciprocal plasma creatinine or creatinine clearance to assess progression of renal insufficiency, other prospective studies[6–15] including an additional three randomised, double-blind, placebo-controlled trials,[16,17] have not observed any significant effect of erythropoietin on renal function. The use of plasma creatinine or creatinine clearance as an index of renal function is a major limitation of all of these studies, particularly since erythropoietin may have significant effects on appetite[2] and muscle metabolism.[18]

A recent retrospective cohort study has also suggested that erythropoietin treatment may slow the progression of renal failure.[19] In this study, the authors compared 20 patients with CKD who were treated with erythropoietin with 43 patients who had a similar degree of renal failure but who were less anaemic and thus did not receive erythropoietin. The rate of decline of creatinine clearance did not change over time in the control group, whereas in the treated group, it was significantly slower after epoetin treatment had been started (–0.36 ± 0.16 mL/min per 1.73 m^2 per month vs. –0.26 ± 0.15 mL/min per 1.73 m^2 per month; $P < 0.05$). The significant limitations of this trial were (a) retrospective design (potential for recall bias); (b) selection bias (erythropoietin-treated patients were older, had a higher proportion of females, were less likely to be diabetic and possibly had a longer duration of uraemia); (c) lack of statistical adjustment for differences in characteristics between the two groups; and (d) the use of creatinine clearance as an index of renal function.

SUMMARY OF THE EVIDENCE

Of the 6 RCTs published to date, 5 trials have found no significant effect of erythropoietin administration on the progression of CKD. One trial with significant flaws observed that erythropoietin significantly retarded renal failure progression, primarily in non-diabetics.

WHAT DO THE OTHER GUIDELINES SAY?

Kidney Disease Outcomes Quality Initiative: No recommendation.
UK Renal Association: No recommendation.
Canadian Society of Nephrology: No recommendation.
European Best Practice Guidelines: No recommendation.
International Guidelines: No recommendation.

IMPLEMENTATION AND AUDIT

No recommendation.

SUGGESTIONS FOR FUTURE RESEARCH

A meta-analysis of the 6 RCTs performed to date is recommended.

REFERENCES

1. Abraham PA, Opsahl JA, Rachael KM *et al*. Renal function during erythropoietin therapy for anemia in predialysis chronic renal failure patients. *Am. J. Nephrol.* 1990; **10**: 128–36.
2. Roth D, Smith RD, Schulman G *et al*. Effects of recombinant human erythropoietin on renal function in chronic renal failure predialysis patients. *Am. J. Kidney Dis*. 1994; **24**: 777–84.
3. Kuriyama S, Tomonari H, Yoshida H *et al*. Reversal of anemia by erythropoietin therapy retards the progression of chronic renal failure, especially in nondiabetic patients. *Nephron*. 1997; **77**: 176–85.
4. Furuland H, Linde T, Ahlmen J *et al*. A randomized controlled trial of haemoglobin normalization with epoetin alfa in pre-dialysis and dialysis patients. *Nephrol. Dial Transplant*. 2003; **18**: 353–61.
5. Roger SD, McMahon LP, Clarkson A *et al*. Effects of early and late intervention with epoetin alpha on left ventricular mass among patients with chronic kidney disease (stage 3 or 4): results of a randomized clinical trial. *J. Am. Soc. Nephrol*. 2004; **15**: 148–56.
6. Lim VS, Fangman J, Flanigan MJ *et al*. Effect of recombinant human erythropoietin on renal function in humans. *Kidney Int*. 1990; **37**: 131–6.
7. Eschbach JW, Kelly MR, Haley NR *et al*. Treatment of the anemia of progressive renal failure with recombinant human erythropoietin. *N Engl. J. Med*. 1989; **321**: 158–63.
8. Lim VS, De Gowin RL, Zavala D *et al*. Recombinant human erythropoietin treatment in pre-dialysis patients. A double-blind placebo-controlled trial. *Ann. Intern. Med*. 1989; **110**: 108–14.
9. Frenken LA, Verberckmoes R, Michielsen P *et al*. Efficacy and tolerance of treatment with recombinant-human erythropoietin in chronic renal failure (pre-dialysis) patients. *Nephrol. Dial Transplant*. 1989; **4**: 782–6.

10. Koch KM, Koene RA, Messinger D *et al*. The use of epoetin beta in anemic predialysis patients with chronic renal failure. *Clin. Nephrol*. 1995; **44**: 201–8.
11. Watson AJ, Gimenez LF, Cotton S *et al*. Treatment of the anemia of chronic renal failure with subcutaneous recombinant human erythropoietin. *Am. J. Med*. 1990; **89**: 432–5.
12. Lim VS. Recombinant human erythropoietin in predialysis patients. *Am. J. Kidney Dis*. 1991; **18**: 34–7.
13. Onoyama K, Kumagai H, Takeda K *et al*. Effects of human recombinant erythropoietin on anaemia, systemic haemodynamics and renal function in predialysis renal failure patients. *Nephrol. Dial Transplant*. 1989; **4**: 966–70.
14. Mitwalli A, Abuaisha H, al Wakeel J *et al*. Effectiveness of low-dose erythropoietin in predialysis chronic renal failure patients. *Nephrol. Dial Transplant*. 1993; **8**: 1085–8.
15. Branger B, Vecina F, Zabadani B *et al*. Subcutaneous erythropoietin administration in predialysis patients: a single centre prospective study. *Nephrol. Dial Transplant*. 1995; **10** (Suppl. 6): S36–S39.
16. Lim VS, Kirchner PT, Fangman J *et al*. The safety and the efficacy of maintenance therapy of recombinant human erythropoietin in patients with renal insufficiency. *Am. J. Kidney Dis*. 1989; **14**: 496–506.
17. Kleinman KS, Schweitzer SU, Perdue ST *et al*. The use of recombinant human erythropoietin in the correction of anemia in predialysis patients and its effect on renal function: a double-blind, placebo-controlled trial. *Am. J. Kidney Dis*. 1989; **14**: 486–95.
18. Park JS, Kim SB, Park SK *et al*. Effect of recombinant human erythropoietin on muscle energy metabolism in patients with end-stage renal disease: a 31P-nuclear magnetic resonance spectroscopic study. *Am. J. Kidney Dis*. 1993; **21**: 612–8.
19. Jungers P, Choukroun G, Oualim Z. *et al*. Beneficial influence of recombinant human erythropoietin therapy on the rate of progression of chronic renal failure in predialysis patients. *Nephrol. Dial Transplant*. 2001; **16**: 307–12.

APPENDICES

Table 1 Characteristics of included studies

Study ID (author, year)	N	Study design	Setting	Participants	Intervention (experimental group)	Intervention (control group)	Follow up (months)	Comments
Roger *et al*, 2003[5]	155	Randomised prospective open-label controlled trial	Multicentre trial conducted in Australia and New Zealand	155 adult patients with chronic kidney disease	Epoetin α as necessary to maintain Hb between 120 and 130 g/L	Epoetin α was initiated if Hb was < 90 g/L at clinical visits 2 months apart or was < 80 g/L at any visit.	24	
Furuland *et al*, 2003[4]	416	Randomised prospective open-label controlled trial	62 hospital centres in Sweden, Norway, Finland and Iceland	416 Scandinavian patients with renal anaemia (pre-dialysis, HD or PD)	Normal haemoglobin group: epoetin α to achieve target Hb levels of 135–150 g/L in females and 145–160 g/L in males	Subnormal haemoglobin group: target haemoglobin level of 90–120 g/L with or without epoetin α treatment	11.5–17.5	
Kuriyama *et al*, 1997[3]	108	Randomised prospective open-label controlled trial	Single centre	108 anaemic Japanese patients with chronic renal failure	6000 IU of IV EPO once/week for 36 weeks	No EPO therapy	18–36	
Kleinman *et al*, 1989[17]	14	Randomised double-blind controlled trial	Single centre	14 non-dialysed patients with chronic renal failure and severe anaemia	100 U/kg r-HuEPO 3 times/week for 12 weeks or until 38% to 40% haemocrit target attained	Placebo	3	
Lim *et al*, 1989[8]	14	Four-arm randomised double-blind controlled trial	Single centre	14 adult patients with renal and failure anaemia	50, 100 or 150 U/kg r-HuEPO (IV) 3 times/week	Placebo	2	
Roth *et al*, 1994[2]	83	Randomised parallel-group, open-label controlled trial	11 study centres in the USA	83 adult pre-dialysis patients with anaemia	50 U/kg r-HuEPO 3 times/week	No EPO treatment	11	

Table 2 Quality of randomised trials

Study ID (author, year)	Method of allocation concealment	Blinding			Intention-to-treat analysis	Loss to follow up (%)
		(participants)	(investigators)	(outcome assessors)		
Roger *et al*, 2004[5]	Computer-generated	No	No	Yes	Yes	0
Furuland *et al*, 2003[4]	Not specified	No	No	No	Unclear	Unclear
Kuriyama *et al*, 1997[3]	Not specified	No	No	No	Unclear	Unclear
Kleinman *et al*, 1989[17]	Not specified	Yes	Yes	No	Yes	0
Lim *et al*, 1989[8]	Third party (pharmaceutical company)	Yes	Yes	No	Yes	0
Roth *et al*, 1994[2]	Not specified	No	No	No	Unclear	Unclear

Table 3 Results for continuous outcomes

Study ID (author, year)	Outcomes	Intervention group (mean [SD])	Control group (mean [SD])	Difference in means [95% CI]
Furuland *et al.* 2003	Transferrin saturation at 48 wk (%)	32 (16)	31 (15)	1.00 (95%CI: −1.98, 3.98)
	Serum ferritin at 48 wk (μg/L) at 48 wk	559 (421)	487 (339)	72.00 (95%CI: −1.21, 145.21)
	Hemoglobin (g/L) at 48 wk, predialysis	143 (11)	117 (13)	26.00 (95%CI: 20.44, 31.56)
	Hemoglobin (g/L) at 48 wk, HD	135 (14)	113 (13)	22.00 (95%CI: 18.91, 25.09)
	Hemoglobin (g/L) at 48 wk, PD	134 (15)	115 (12)	19.00 (95%CI: 11.43, 26.57)
	GFR in predialysis at 48 wk (mL/min/1.73 m^2)	13 (10)	16 (7)	−3.00 (95%CI: −8.40, 2.40)
	SBP (mmHg) at 48 wk, predialysis	147 (21)	148 (24)	−1.00 (95%CI: −14.95, 12.95)
	DBP (mmHg) at 48 wk, predialysis	90 (6)	83 (11)	7.00 (95%CI: 1.58, 12.42)
Kleinman *et al.* 1989	Quality of life	68 (22)	33 (21)	35.00 (95%CI: 12.47, 57.53)
Kuriyama *et al.* 1997	Ht (%) after treatment	35.5 (4.4)	25.3 (1.9)	10.20 (95%CI: 8.71, 11.69)
Lim *et al.* 1989	Hematocrit wk 8	0.38 (0.03)	0.24 (0.03)	0.14 (95%CI: 0.09, 0.19)
	Erythrocyte mass (mL/kg) wk 8	19.6 (3.32)	11.8 (3.25)	7.80 (95%CI: 2.89, 12.71)
	Plasma volume mass (mL/kg) wk 8	43.5 (6.30)	43.7 (5.80)	−0.20 (95%CI: −9.06, 8.66)
	Total blood volume (mL/kg) wk 8	63.1 (6.30)	55.4 (9.05)	7.70 (95%CI: −5.38, 20.78)
Roger *et al.* 2004	Mean LVMi (g/m^2) at 2 yrs	105 (22)	102 (22)	−3.00 (95%CI: −4.66, 10.66)
	Mean change in LVMi (g/m^2) at 2 yrs	1.5 (17)	3.5 (16)	−2.00 (95%CI: −21.01, 173.01)
	SBP (mmHg) at 2 yrs	141 (14)	138 (13)	3.00 (95%CI: −1.70, 7.70)
	DBP (mmHg) at 2 yrs	80 (6)	79 (7)	1.00 (95%CI: −1.28, 3.28)
	Hb conc (g/L) at 2 yrs	122 (7)	110 (10)	12.00 (95%CI: 8.98, 15.02)
	GFR (mL/min/1.73 m^2) at 2 yrs	23 (9)	24 (9)	−1.00 (95%CI: −4.13, 2.13)
	Creatinine (mM) at 2 yrs	0.38 (0.19)	0.34 (0.15)	0.04 (95%CI: −0.02, 0.10)
	PTH (pM) at 2 yrs	25 (22)	18 (15)	7.00 (95%CI: 0.49, 13.51)
	Albumin (g/L)	39 (4)	39 (4)	0.00 (95%CI: −1.39, 1.39)
	Ferritin (μg/L)	204 (227)	207 (149)	−3.00 (95%CI: −69.31, 63.31)
	Transferring saturation (%)	26 (6)	28 (7)	−2.00 (95%CI: −4.28, 0.28)
	SF–36 change in physical health score	−2 (14)	−1 (13)	−1.00 (95%CI: −5.70, 3.70)
	Change in mental health score	0 (14)	−3 (11)	3.00 (95%CI: −1.36, 7.36)
	Change in renal QoL profile	7 (17)	5 (14)	2.00 (95%CI: −3.40, 7.40)
Roth *et al.* 1994	Mean change in GFR (mL/min)	−2.1 (3.2)	−2.8 (3.5)	0.70 (95%CI: −0.75, 2.15)
	GFR (mL/min) at wk 48	9.5 (4.4)	8.0 (2.2)	1.50 (95%CI: −1.03, 4.03)
	Mean change in creatinine (mg/dL)	2.4 (2.4)	1.1 (1.6)	1.30 (95%CI: 0.43, 2.17)
	Mean change in potassium (mEq/dL0	0.0 (0.7)	0.0 (0.7)	0.00 (95%CI: −0.30, 0.30)
	Mean change in uric acid (mg/dL)	0.2 (1.6)	0.1 (1.3)	0.10 (95%CI: −0.53, 0.73)
	Mean change in phosphorus (mg/dL)	0.9 (1.7)	−0.2 (1.3)	1.10 (95%CI: 0.23, 1.97)
	Mean change in blood urea nitrogen (mg/dL)	12 (25)	3 (22)	9.00 (95%CI: −1.12, 19.12)
	Mean change in glucose (mg/dL)	12 (70)	15 (38)	−3.00 (95%CI: −27.01, 21.01)
	Mean change in daily protein intake	0.0 (0.22)	−0.1 (0.22)	0.10 (95%CI: 0.01, 0.19)

Table 4 Results for dichotomous outcomes

Study ID (author, year)	Outcomes	Intervention group (number of patients with events/number of patients exposed)	Control group (number of patients with events/number of patients not exposed)	Relative risk (RR) [95% CI]	Risk difference (RD) [95% CI]
Furuland *et al.* 2003	Mortality	29/216	27/200	0.99 (95%CI: 0.61, 1.62)	0.00 (95%CI: –0.07, 0.06)
	Stopped treatment due to adverse event	34/216	15/200	1.48 (95%CI: 0.80, 2.74)	0.08 (95%CI: 0.02, 0.14)
	Sepsis	5/216	7/200	0.66 (95%CI: 0.21, 2.05)	–0.01 (95%CI: –0.04, 0.02)
Kleinman *et al.* 1989	Mortality	0/7	0/7	Not estimable	0.00 (95%CI: –0.24, 0.24)
Kuriyama *et al.* 1997	Mortality (anaemic)	1/42	2/31	0.37 (95%CI: 0.04, 3.89)	0.04 (95%CI: –0.14, 0.06)
	Dialysis (anaemic)	14/42	20/31	0.52 (95%CI: 0.31, 0.85)	–0.31 (95%CI: –0.53, –0.09)
	Doubling of serum Cr (anaemic)	22/42	26/31	0.62 (95%CI: 0.45, 0.87)	–0.31 (95%CI: –0.51, –0.12)
Roth *et al.* 1994	Stopped treatment due to adverse events	1/43	3/40	0.31 (95%CI: 0.03, 2.86)	–0.05 (95%CI: –0.14, 0.04)
	Mortality	0/43	1/40	–0.31 (95%CI: 0.01, 7.41)	–0.03 (95%CI: –0.09, 0.04)
	Increase in hematocrit to at least 36%	34/43	0/40	64.30 (95%CI: 4.07, 1015.06)	0.79 (95%CI: 0.66, 0.92)
	At least 1 RBC transfusion	4/43	9/40	0.41 (95%CI: 0.14, 1.24)	–0.13 (95%CI: –0.29, 0.02)
	Hypertension	11/43	4/40	2.56 (95%CI: 0.89, 7.39)	0.16 (95%CI: 0.00, 0.32)

Pregnancy

Date written: February 2004
Final submission: July 2004
Author: David Johnson

GUIDELINES

No recommendations possible based on Level I or II evidence.

SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on Level III and IV sources)

- **Pregnancy generally does not affect the course of renal disease in women who have normal or near-normal renal function at conception. Such individuals should not be discouraged from conceiving purely on the basis of their renal disease. (Level II–III evidence; retrospective cohort and case-control studies; clinically relevant outcomes; inconsistent effects)**
- **Renal function deterioration is probably accelerated by pregnancy in patients with poorly-controlled hypertension or plasma creatinine concentrations of > 0.20 mmol/L at conception. The magnitude of this increase in risk compared with non-pregnant individuals with renal disease has not been established. (Level II–III evidence; retrospective cohort and case-control studies; clinically relevant outcomes; inconsistent effects)**

BACKGROUND

Opinions vary markedly as to the frequency (or even the existence) of accelerated renal function deterioration during and after pregnancy in women with chronic kidney disease (CKD).[1,2] The objective of this guideline is to review the available clinical evidence pertaining to the effect of pregnancy on the rate of GFR decline in CKD.

SEARCH STRATEGY

Databases searched: Medline (1996 to November Week 2, 2003). MeSH terms for kidney disease were combined with MeSH terms for pregnancy. The results were then limited to cohort and case-control studies.
Date of search: 16 December 2003.

WHAT IS THE EVIDENCE?

There are no randomised controlled trials (RCTs) or prospective controlled studies.

Most of the literature addressing this subject is limited to retrospective studies and case series, which suffered from many of the following serious limitations:

- case selection bias, since retrospective analyses often in tertiary institutions are likely to be biased in terms of selecting more severely diseased cases;
- recall bias;
- small numbers with a low event rate (i.e. progression to end-stage kidney disease [ESKD]);
- short follow-up times;
- collection of data from several decades ago when maternal and obstetric care (particularly with respect to antihypertensive treatment) were not as advanced as presently;
- lack of data prior to the index pregnancy, making it difficult to determine whether the natural history of a patient's kidney disease was actually altered by pregnancy;
- failure to use controls or the selection of inappropriate controls (e.g. unaffected family members where maternal surveillance may have been altered by knowledge of the proband);
- lack of a secure histologic diagnosis in involved patients; and
- infrequent or suboptimal measures of renal function.

Jungers *et al*[3] performed a retrospective analysis of the effect of pregnancy on the occurrence of ESKD in 360 women with various forms of histologically-proven glomerulonephritis, but with plasma creatinine concentrations less than 0.11 mmol/L at presentation. These patients were referred between 1965 and 1994. One hundred and seventy-one patients became pregnant at least once after the clinical onset of the glomerulonephritis, whilst 189 patients did not conceive. Mean follow-up was over 14 years. Survival curves for time to ESKD, defined as plasma creatinine >0.5 mmol/L or need for dialysis, did not differ between the two groups. A case-control study was also performed in which patients who reached ESKD (cases) were matched with those who did not (controls) for age at onset of glomerulonephritis and duration of follow-up with less than 3 years' difference for either. Logistic regression analysis demonstrated that pregnancy was not an independent risk factor for development of ESKD. The authors concluded that pregnancy does not affect the course of renal disease in patients who have normal renal function at conception.

The bulk of other retrospective analyses have also indicated that when renal function is normal or near-normal

and hypertension is well-controlled at conception, the natural course of maternal renal disease due to a variety of causes is usually not adversely affected by pregnancy.[3–20] A small number of authors (mainly from one group in Australia) have not concurred and have suggested that a significant number of such women experience a pregnancy-induced deterioration of renal function.[21–24]

Although the numbers of patients progressing to ESKD in each of the studies are very small, the bulk of reports suggest that the risk of deterioration in maternal renal function is increased mainly when conception has occurred at a plasma creatinine concentration in excess of 0.20 mmol/L or in the setting of poorly-controlled hypertension.[5,25–32] However, determining the magnitude of the increased risk of renal function deterioration is difficult given the often poor documentation of renal failure progression in these patients prior to conception coupled with the fact that many of these patients do not reach ESKD for many years after delivery. Moreover, rapid deterioration of renal function has also been reported in non-pregnant females and males, such that it is almost impossible to gauge the relative risk of renal function deterioration in the absence of prospective data collection and the inclusion of appropriate controls. For example, in the general renal disease population in Australia, a plasma creatinine between 0.30 and 0.40 mmol/L is associated with a risk of progression to ESKD of 11% in one year.[33] Thus, the reported cases of women with pre-pregnancy plasma creatinine concentrations of >0.20 mmol/L who progressed to ESKD within several years of a pregnancy could conceivably have just reflected the natural history of their disease without having to invoke a pregnancy-induced deterioration.

SUMMARY OF THE EVIDENCE

There are no RCTs or prospective controlled studies. Most of the literature addressing this subject is limited to retrospective studies and case series, which have suffered from many limitations (detailed in the 'What is the evidence?' section – vide supra). Data are conflicting, but the bulk of studies have suggested that when renal function is normal or near-normal and hypertension is well-controlled at conception, the natural course of maternal renal disease due to a variety of causes is usually not adversely affected by pregnancy. Although the numbers of patients progressing to ESKD in each of the studies are very small, the bulk of reports also suggest that the risk of deterioration in maternal renal function is increased mainly when conception has occurred at a plasma creatinine concentration in excess of 0.20 mmol/L or in the setting of poorly-controlled hypertension. Whether such deterioration represents an acceleration of renal failure progression or merely the natural history of the underlying CKD has not been conclusively established.

WHAT DO THE OTHER GUIDELINES SAY?

Kidney Disease Outcomes Quality Initiative: No recommendation.

UK Renal Association: No recommendation.
Canadian Society of Nephrology: No recommendation.
European Best Practice Guidelines: No recommendation.
International Guidelines: No recommendation.

IMPLEMENTATION AND AUDIT

No recommendation.

SUGGESTIONS FOR FUTURE RESEARCH

No recommendation.

REFERENCES

1. Hayslett JP. Pregnancy does not exacerbate primary glomerular disease. *Am. J. Kidney Dis.* 1985; **6**: 273–7.
2. Becker GJ, Fairley KF, Whitworth JA. Pregnancy exacerbates glomerular disease. *Am. J. Kidney Dis.* 1985; **6**: 266–72.
3. Jungers P, Houillier P, Forget D *et al.* Influence of pregnancy on the course of primary chronic glomerulonephritis. *Lancet.* 1995; **346**: 1122–4.
4. Jungers P. Reflux nephropathy and pregnancy. *Baillieres Clin. Obstet Gynaecol.* 1994; **8**: 425–42.
5. Chapman AB, Johnson AM, Gabow PA *et al.* Overt proteinuria and microalbuminuria in autosomal dominant polycystic kidney disease. *J. Am. Soc. Nephrol.* 1994; **5**: 1349–54.
6. Chapman AB, Johnson AM, Gabow PA. Pregnancy outcome and its relationship to progression of renal failure in autosomal dominant polycystic kidney disease. *J. Am. Soc. Nephrol.* 1994; **5**: 1178–85.
7. Kaplan AL, Smith JP, Tillman AJ. Healed acute and chronic nephritis in pregnancy. *Am. J. Obstet Gynecol.* 1966; **3**: 21–34.
8. Katz AI, Davison JM, Hayslett JP *et al.* Pregnancy in women with kidney disease. *Kidney Int.* 1980; **18**: 192–206.
9. Imbasciati E, Surian M, Bottino S *et al.* Lupus nephropathy and pregnancy. A study of 26 pregnancies in patients with systemic lupus erythematosus and nephritis. *Nephron.* 1984; **36**: 46–51.
10. Rovati C, Perrino ML, Barbiano di Belgiojoso G *et al.* Pregnancy and course of primary glomerulonephritis. *Contrib Nephrol.* 1984; **37**: 182–9.
11. Surian M, Imbasciati E, Cosci. P *et al.* Glomerular disease and pregnancy. A study of 123 pregnancies in patients with primary and secondary glomerular diseases. *Nephron.* 1984; **36**: 101–5.
12. Abe S, Amagasaki Y, Konishi K *et al.* The influence of antecedent renal disease on pregnancy. *Am. J. Obstet Gynecol.* 1985; **153**: 508–14.
13. Oken DE. Chronic renal diseases and pregnancy: a review. *Am. J. Obstet Gynecol.* 1966; **94**: 1023–43.
14. Felding CF. Obstetric aspects in women with histories of renal disease. *Acta Obstet Gynecol. Scand.* 1969; **48** (Suppl. 2): S1–S43.
15. Schewitz LJ. Hypertension and renal disease in pregnancy. *Med. Clin. North Am.* 1971; **55**: 47–69.
16. Strauch BS, Hayslett JP. Kidney disease and pregnancy. *Br. Med. J.* 1974; **4**: 578–82.
17. Bear RA. Pregnancy in patients with renal disease. A study of 44 cases. *Obstet Gynecol.* 1976; **48**: 13–8.
18. Hara N. The effect of pregnancy on the long-term renal function in lupus nephritis patients. *Nippon Jinzo Gakkai Shi.* 2001; **43**: 369–77.

19. Huong DL, Wechsler B, Vauthier-Brouzes D *et al*. Pregnancy in past or present lupus nephritis: a study of 32 pregnancies from a single centre. *Ann. Rheum Dis*. 2001; **60**: 599–604.
20. Rossing K, Jacobsen P, Hommel E *et al*. Pregnancy and progression of diabetic nephropathy. *Diabetologia* 2002; **45**: 36–41.
21. Mackay EV. Pregnancy and renal disease: a ten year survey. *Aust. N Z. J. Obstet Gynaecol*. 1966; **3**: 21–34.
22. Kincaid-Smith P, Fairley KF, Bullen M. Kidney disease and pregnancy. *Med. J. Aust*. 1967; **2**: 1155–9.
23. Becker GJ, Ihle BU, Fairley KF *et al*. Effect of pregnancy on moderate renal failure in reflux nephropathy. *Br. Med. J. Clin. Res. Ed*. 1986; **292**: 796–8.
24. Fairley KF, Whitworth JA, Kincaid-Smith P. Glomerulonephritis and pregnancy. *Perspect Nephrol. Hypertens*. 1973; **1 Part 2**: 997–1011.
25. Hou SH, Grossman SD, Madias NE. Pregnancy in women with renal disease and moderate renal insufficiency. *Am. J. Med*. 1985; **78**: 185–94.
26. Bobrie G, Liote F, Houillier P *et al*. Pregnancy in lupus nephritis and related disorders. *Am. J. Kidney Dis*. 1987; **9**: 339–43.
27. Jungers P, Houillier P, Forget D. Reflux nephropathy and pregnancy. *Baillieres Clin. Obstet Gynaecol*. 1987; **1**: 955–69.
28. Jungers P, Forget D, Houillier P *et al*. Pregnancy in IgA nephropathy, reflux nephropathy, and focal glomerular sclerosis. *Am. J. Kidney Dis*. 1987; **9**: 334–8.
29. Jungers P, Forget D, Henry-Amar M *et al*. Chronic kidney disease and pregnancy. *Adv. Nephrol. Necker Hosp*. 1986; **15**: 103–41.
30. Taylor J, Novak R, Christiansen R. *et al*. Focal sclerosing glomerulopathy with adverse effects during pregnancy. *Arch. Intern. Med*. 1978; **138**: 1695–6.
31. Hou S. Pregnancy in women with chronic renal disease. *N Engl. J. Med*. 1985; **312**: 836–9.
32. North RA, Taylor RS, Gunn TR. Pregnancy outcome in women with reflux nephropathy and the inheritance of vesico-ureteric reflux. *Aust. NZ. J. Obstet Gynaecol*. 2000; **40**: 280–5.
33. Australian Kidney Foundation. *The Australian kidney: national epidemiological survey of diseases of the kidney and urinary tract*. Adelaide: Australian Kidney Foundation; 1999.

Smoking

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GUIDELINES

No recommendations possible based on Level I or II evidence.

SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on Level III and IV sources)

- **Smoking is associated with more severe proteinuria and renal failure progression in patients with kidney disease. (Level II–III evidence; numerous large retrospective cohort studies; clinically relevant outcomes; consistent strong effects) The clinical evidence for this association is stronger for diabetic patients than for non-diabetic patients.**
- **Cessation of smoking has been associated with retardation of renal failure progression. (Level II–III evidence; several small cohort studies; clinically relevant outcomes; consistent strong effects)**

BACKGROUND

Smoking has been associated with accelerated renal failure progression. The objective of this guideline is to evaluate the available clinical evidence pertaining to the impact of smoking on renal function decline in chronic kidney disease (CKD).

SEARCH STRATEGY

Databases searched: Medline (1996 to November Week 2, 2003). MeSH terms for kidney disease were combined with MeSH terms for smoking. The results were then limited to cohort and case-control studies.
Date of search: 16 December 2003.

WHAT IS THE EVIDENCE?

There are no randomised controlled trials (RCTs).

The evidence for a deleterious effect of smoking is stronger for diabetics than non-diabetics, but is limited to retrospective analysis. In addition to the recall bias and case selection bias inherent in such studies, the association of smoking with the development of renal failure does not establish whether smoking promotes kidney disease or whether smoking is merely associated with other factors that promote kidney disease (such as non-compliance, vascular disease, hypertension, etc.).

A retrospective, case-control study using data obtained from 4142 non-diabetic, elderly (> 65 yrs) participants of the Cardiovascular Health Study Cohort identified that current smoking was a significant, independent risk factor for clinically important changes in renal function (increase in serum creatinine of at least 0.3 mg/dL, odds ratio 2.1, 95% CI: 1.3–3.6). Former smokers were not at increased risk, suggesting that cessation of smoking is associated with a reduction in risk of progressive kidney disease.

Stengel *et al*[1] retrospectively analysed data from a non-concurrent cohort study of 9082 US adults, aged 30–74 years, who participated in the second National Health and Nutrition Examination Survey (NHANES II) from 1976 to 1980. Up until 1992, 189 incident cases of either treated end-stage kidney disease (ESKD) or CKD-related death were identified. The study observed that, compared with never-smokers, the adjusted relative risk of CKD was significantly increased in smokers of more than 20 cigarettes a day (RR 2.3, 95% CI: 1.3–4.2), but not in smokers of 1–20 cigarettes per day (RR 1.2, 95% CI: 0.7–2.3).

In a prospective study of 51 patients with severe essential hypertension followed for a mean period of 35.5 months, smoking was identified by multivariate regression analysis as the most powerful, independent predictor of decreases in both the reciprocal creatinine slope over time and the calculated GFR.[2]

A retrospective cohort study of 160 adults with lupus nephritis[3] followed for a median of 6.4 years demonstrated in a Cox's proportional hazard analysis, that smoking at the onset of nephritis was associated with a hazard ratio of 2.05 (95% CI: 1.07–3.93) for ESKD.

In a retrospective cohort study of patients with polycystic kidney disease, Chapman *et al*[4] observed that individuals with significant proteinuria had a greater number of cigarette pack years than those without proteinuria.

Smoking is a significant independent predictor of significant renal artery stenosis in elderly patients beginning renal replacement therapy.[5]

In retrospective studies of diabetic patients, smoking has been associated with an increased risk of microalbuminuria,[6–11] a shortened time interval between onset of diabetes and onset of albuminuria,[12] an accelerated rate of progression from microalbuminuria to persistent proteinuria[6,10,11] and an accelerated progression of diabetic nephropathy to

ESKD.[12] Improved blood pressure control and angiotensin-converting enzyme inhibition do not appear to abrogate the risk associated with smoking in diabetic nephropathy.[13,14] However, there is some conflicting data in that a prospective observational cohort study of 301 albuminuric Type 1 diabetics followed for at least 3 years at the Steno Diabetes Centre was unable to demonstrate statistically significant differences in GFR decline between non-smokers, former smokers or current smokers.[15] These negative results may reflect a type 2 statistical error.

Smoking cessation has been associated with a reduction in albumin excretion[9] and renal failure progression in diabetics.[16] In 45 patients with progressive non-diabetic nephropathy (chronic glomerulonephritis or tubulointerstitial nephritis) who were encouraged to stop smoking (1–2 packs per day), 16 successfully stopped smoking and demonstrated a significantly slower rate of decline in creatinine clearance over 2 years compared with the 26 patients who continued to smoke.[17] Compliance was assessed by carboxyhaemoglobin measurements performed every 6 months.

SUMMARY OF THE EVIDENCE

There are no RCTs. Numerous retrospective and prospective studies (some of which have included thousands of patients) have suggested that smoking is associated with renal failure progression in both diabetic and non-diabetic kidney disease. Current smoking confers a greater risk than former smoking. Three small cohort studies suggest that cessation of smoking may ameliorate renal failure progression in diabetic and non-diabetic CKD.

WHAT DO THE OTHER GUIDELINES SAY?

Kidney Disease Outcomes Quality Initiative: No recommendation.
UK Renal Association: No recommendation.
Canadian Society of Nephrology: No recommendation.
European Best Practice Guidelines: No recommendation.
International Guidelines: No recommendation.

IMPLEMENTATION AND AUDIT

No recommendation.

SUGGESTIONS FOR FUTURE RESEARCH

No recommendation.

REFERENCES

1. Stengel B, Tarver-Carr ME, Powe NR *et al*. Lifestyle factors, obesity and the risk of chronic kidney disease. *Epidemiology* 2003; **14**: 479–87.
2. Regalado M, Yang S, Wesson DE. Cigarette smoking is associated with augmented progression of renal insufficiency in severe essential hypertension. *Am. J. Kidney Dis* 2000; **35**: 687–94.
3. Ward MM, Studenski S. Clinical prognostic factors in lupus nephritis. The importance of hypertension and smoking. *Arch. Intern. Med.* 1992; **152**: 2082–8.
4. Chapman AB, Johnson AM, Gabow PA *et al*. Overt proteinuria and microalbuminuria in autosomal dominant polycystic kidney disease. *J. Am. Soc. Nephrol.* 1994; **5**: 1349–54.
5. Appel RG, Bleyer AJ, Reavis S *et al*. Renovascular disease in older patients beginning renal replacement therapy. *Kidney Int.* 1995; **48**: 171–6.
6. Muhlhauser I, Sawicki P, Berger M. Cigarette-smoking as a risk factor for macroproteinuria and proliferative retinopathy in type 1 (insulin-dependent) diabetes. *Diabetologia* 1986; **29**: 500–2.
7. Couper JJ, Staples AJ, Cocciolone R *et al*. Relationship of smoking and albuminuria in children with insulin-dependent diabetes. *Diabet Med.* 1994; **11**: 666–9.
8. Almdal T, Norgaard K, Feldt Rasmussen B *et al*. The predictive value of microalbuminuria in IDDM. A five-year follow-up study. *Diabetes Care* 1994; **17**: 120–5.
9. Chase HP, Garg SK, Marshall G *et al*. Cigarette smoking increases the risk of albuminuria among subjects with type I diabetes. *JAMA* 1991; **265**: 614–7.
10. Rossing P, Hougaard P, Parving HH. Risk factors for development of incipient and overt diabetic nephropathy in type 1 diabetic patients: a 10–year prospective observational study. *Diabetes Care* 2002; **25**: 859–64.
11. Gambaro G, Bax G, Fusaro M *et al*. Cigarette smoking is a risk factor for nephropathy and its progression in type 2 diabetes mellitus. *Diabetes Nutr Metab* 2001; **14**: 337–42.
12. Stegmayr B, Lithner F. Tobacco and end stage diabetic nephropathy. *Br. Med. J. Clin. Res. Ed* 1987; **295**: 581–2.
13. Chuahirun T, Wesson DE. Cigarette smoking predicts faster progression of type 2 established diabetic nephropathy despite ACE inhibition. *Am. J. Kidney Dis* 2002; **39**: 376–82.
14. Chuahirun T, Khanna A, Kimball K *et al*. Cigarette smoking and increased urine albumin excretion are interrelated predictors of nephropathy progression in type 2 diabetes. *Am. J. Kidney Dis* 2003; **41**: 13–21.
15. Hovind P, Rossing P, Tarnow L *et al*. Smoking and progression of diabetic nephropathy in type 1 diabetes. *Diabetes Care* 2003; **26**: 911–6.
16. Sawicki PT, Didjurgeit U, Muhlhauser I *et al*. Smoking is associated with progression of diabetic nephropathy. *Diabetes Care* 1994; **17**: 126–31.
17. Schiffl H, Lang SM, Fischer R. Stopping smoking slows accelerated progression of renal failure in primary renal disease. *J. Nephrol.* 2002; **15**: 270–4.

Other agents

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GUIDELINES

There is limited evidence to suggest that the progression of certain forms of renal disease are retarded by ibopamine. (Level II evidence; single RCT with suboptimal design; clinically relevant outcome; moderately strong effect) However, this benefit is outweighed by the serious side-effects of ibopamine (3-fold increased risk of death) and its use cannot be recommended.

SUGGESTIONS FOR CLINICAL CARE

(Suggestions based on level III and IV sources)

- **There is limited evidence to suggest that the progression of certain forms of renal disease is retarded by non-steroidal anti-inflammatory drugs (NSAIDs), (Level III evidence; several retrospective and prospective cohort studies; mostly surrogate outcome measures; consistent weak effect) and by combined ketaconazole and prednisone (Level II–III evidence; single small cross-over study; clinically relevant outcome; weak effect). However, these benefits are outweighed by the serious side-effects of these medications and their use cannot be currently recommended.**

BACKGROUND

Animal studies have suggested renoprotective benefits associated with the administration of ibopamine (an orally active dopamine agonist with renin-angiotensin system blocking activity) and NSAIDs. Moreover, based on earlier case series demonstrating a correlation of renal failure progression with urinary excretion of 17-hydroxycorticosteroid[1] and free cortisol, some investigators have hypothesized that combined therapy with ketaconazole (an inhibitor of cortisol production) and 2.5 mg prednisone (to prevent increased ACTH release but still allowing reduced total steroid activity) may retard renal failure progression. The objectives of this guideline are to evaluate the clinical evidence that ibopamine, NSAIDs and combined ketaconazole and prednisone therapy retard renal failure progression in humans.

SEARCH STRATEGY

Databases searched: Medline (1999 to November Week 2, 2003). MeSH terms for kidney disease were combined with MeSH terms and text words for non-steroidal anti-inflammatory drugs, dopamine agonists and cyclo-oxygenase 2 inhibitors. The results were then combined with the Cochrane highly sensitive search strategy for randomised controlled trials and MeSH terms and text words for identifying meta-analyses and systematic reviews. The Cochrane Renal Group Specialized Register of Randomised Controlled Trials was also searched for relevant trials not indexed by Medline.
Date of search: 16 December 2003.

WHAT IS THE EVIDENCE?

Ibopamine

There have been one randomised controlled trial (RCT)[2] and three prospective, non-controlled trials[3–5] (all but 1 trial was reported by the same group).

Ibopamine is an orally active dopamine agonist which has been shown to activate dopaminergic receptors DA1 and DA2 at daily doses of 100–200 mg, β–adrenergic receptors at 300–400 mg, and α-adrenergic receptors at greater than 400 mg.[6,7] Its pharmacological effect is maintained over prolonged periods.[8,9] Both in normal subjects and in patients with mild renal impairment, ibopamine administration has produced an increase in renal plasma flow, an increase in ^{99m}Tc–DTPA clearance, a reduction in filtration fraction and an increase in sodium excretion and diuresis.[10–12]

Stefoni *et al*[2] conducted a prospective, randomised, open-label, multicentre trial of ibopamine in patients with mild-to-moderate chronic kidney disease CKD (plasma creatinine 1.5–4.0 mg/dL). A total of 189 patients from 11 nephrology centres were randomly allocated to receive ibopamine 100 mg omni die (n = 96) or no treatment (n = 93). Allocation concealment was inadequate. Exclusion criteria included diabetes mellitus, resistant hypertension with diastolic blood pressures of 100 mmHg or more, NYHA class III–IV congestive cardiac failure, nephrotic range proteinuria, pregnancy, rapid renal function deterioration (> 30% in plasma creatinine over preceding 6 months) and patients receiving steroids, cytotoxics or ACE inhibitors. Ibopamine compliance was not formally assessed. Both groups were comparable at baseline. 93% of patients completed the first year of observation and 78% reached the end of the whole 2–year study. Drop-out rates were nearly identical in both groups. Four (4.2%) patients withdrew from the ibopamine group due to drug intolerance (epigastric

pain or tachycardia). Adverse effects were more common in the ibopamine group (40 vs. 20 or 42% vs. 22%), but the statistical significance and breakdown of these events were not reported. Renal function survival curves were significantly improved in the ibopamine-treated group. Mean plasma creatinine rose by 17% in the ibopamine group and by 36% in controls. Creatinine clearance decline was significantly reduced by ibopamine (5% vs. 14%). Ibopamine exerted a significant positive effect on renal function compared with controls in both patients with mild (creatinine 1.5–2.5 mg/dL) and moderate (creatinine 2.6–4.0 mg/dL) renal impairment. Ibopamine-treated patients experienced an initial increase in creatinine clearance (not seen in the controls), raising the possibility that ibopamine exerted an early haemodynamic and/or tubular secretory effect. The main limitations of the study were: (a) the use of plasma creatinine and creatinine clearance to evaluate renal function (the effect of ibopamine on tubular secretion of creatinine has not been studied); (b) inadequate allocation concealment which could have potentially introduced physician bias; (c) high drop-out rates (22%); and (d) the exclusion of ACE inhibitors (thus it is not known whether the effects of ibopamine would be additive with these agents). The latter point may be particularly relevant since ibopamine has been shown to exert an antagonistic effect against angiotensin II at both a glomerular and tubular level.[8,13] It also directly reduces activation of the renin-angiotensin system and inhibits aldosterone secretion.[14–16]

Three prospective, non-controlled, small studies by single centres[3–5] have reported a significant improvement in renal function indices (plasma creatinine, reciprocal plasma creatinine or creatinine clearance) in patients with mild-to-moderate CKD treated with ibopamine 100 mg daily for periods ranging from 6 to 24 months.

Significant concerns regarding the safety of ibopamine have been raised by the PRIME II study, which showed that ibopamine was associated with an increased risk of death in patients with NYHA class III and IV heart failure,[17] particularly in patients with renal impairment. A subsequent nested case-control study in users of ibopamine in the Netherlands[18] demonstrated that patients with a serum creatinine level in the highest quartile had a 3-fold increased risk of death on ibopamine.

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

There are no RCTs or prospective studies. NSAIDs have generally been avoided in the setting of chronic kidney disease (CKD) because of frequent reports of deterioration of renal function following administration of these compounds. However, two retrospective studies have suggested a benefit of NSAIDs on the progression of renal insufficiency.[19,20]

Numerous prospective uncontrolled studies[21–29] and a double-blind, crossover study[30] have reported a significant antiproteinuric effect of NSAIDs (primarily indomethacin) in nephrotic patients. The proportional decrease in proteinuria exceeded the associated 12–36% fall in GFR (e.g. for indomethacin, the fall in proteinuria/GFR was 53%).[19] Suppression of proteinuria can be sustained for up to 3 years of treatment,[19] but tends to reverse to pretreatment levels on discontinuation of the drug.

Vriessendorp *et al*[19] retrospectively studied the influence of indomethacin on renal function decline and renal outcome in 114 patients with nephrotic syndrome due to membranous nephropathy, focal segmental glomerulosclerosis or membranoproliferative glomerulonephritis. Fifty-eight patients received indomethacin (median dose 150 mg, range 75–225 mg) for a median period of 3 years (range 0.5–9 years) during the period between 1968 and 1983. Forty untreated patients were used as controls, although 5 of these had received indomethacin for up to 1 month. Sixteen patients were excluded because follow-up was less than 6 months. None of the patients had received corticosteroids or cytotoxic agents. Compared with controls, indomethacin-treated patients had significantly lower plasma creatinine concentrations, lower mean arterial pressures and higher 24–hour urinary protein excretion rates at baseline. Renal survival was significantly better in the indomethacin-treated patients with only 31% reaching dialysis at 10 years (cf. 66% of controls). However, when the end-point of creatinine doubling time was used in the analysis, no significant difference was observed between the 2 groups. A subsequent analysis suggested that only patients with a creatinine < 0.11 mmol/L benefited significantly from indomethacin treatment. Significant side-effects of treatment (such as azotaemia or gastrointestinal haemorrhage), were not mentioned in the paper. The major limitations of the study include: (a) the likelihood of serious recall bias and case selection bias as a result of the retrospective design; (b) the lack of comparability of the indomethacin-treated and control groups (the former had less severe renal functional impairment and lower blood pressure); (c) the high exclusion rate (14%) due to incomplete follow-up; (d) failure to make appropriate statistical adjustments for the differences in renal function, blood pressure and proteinuria between the 2 groups; and (e) use of a log-rank analysis for renal survival rather than a Cox's proportional hazards model (which could be used to adjust for potentially confounding factors).

Lagrue and associates[20] also reported a retrospective analysis of the effect of indomethacin of renal failure progression in 53 nephrotic patients with membranoproliferative glomerulonephritis. They similarly reported an improvement in renal survival but based this on comparisons with published literature regarding the natural history of untreated disease (obviously inappropriate).

Inhibitors of Endogenous Cortisol Synthesis

There are no RCTs.

Based on earlier case series demonstrating a correlation between renal failure progression and urinary excretion of 17–hydroxycorticosteroid[1] and free cortisol,[31,32] Walser *et al* performed a small, prospective, crossover study of combined administration of 200–600 mg daily of ketaconazole (an inhibitor of cortisol production) and 2.5 mg prednisone (to prevent increased ACTH release but still allowing reduced total steroid activity) in 24 patients with progressive renal

failure. Four patients were withdrawn because of severe ketaconazole side-effects and one patient was withdrawn because of the development of oliguric acute-on-chronic renal failure. A variety of crossover designs were employed in the remaining 19 patients, including AB (n = 10), BA (n = 3), ABA (n = 3) and ABAB (n = 3). 'Randomization' of patients to a particular crossover design was by an 'individual not involved in the study.' To estimate the effect of treatment on GFR, estimated by ^{99,m}Tc–DTPA clearance, a linear spline technique was used. The durations of each study period were quite variable between patients but were of the order of 3–11 months. Significant slowing of GFR decline was observed for patients with chronic glomerular disease, interstitial nephritis and diabetic nephropathy, but the treatment was associated with an acceleration of GFR decline in patients with polycystic kidney disease (n = 5). The study was obviously too small with too short a follow-up time to draw any conclusions regarding the value of this therapy. Moreover, the design and statistical analysis were suboptimal and the serious side-effects of the treatment were disconcerting.

SUMMARY OF THE EVIDENCE

Ibopamine has been shown in one moderately large RCT with inadequate allocation concealment to be associated with a statistically significant and clinically meaningful reduction in GFR decline in mild-to-moderate chronic renal failure. However, Ibopamine administration has also been shown to be associated with significant harm (including an increased risk of death), which outweighs its renoprotective benefits.

There are no RCTs of NSAID therapy in the chronic renal failure. However, limited retrospective and prospective cohort studies involving nephrotic patients suggest a benefit of NSAID, as evidenced by an antiproteinuric response and, in some cases, by a retardation of renal function decline. Significant adverse effects were noted in several studies.

One small, prospective, crossover study of combined administration of ketaconazole and prednisone in 24 patients with chronic renal failure observed a significant slowing of GFR decline (except in polycystic kidney disease where GFR decline was accelerated). These benefits appeared to be outweighed by serious side-effects.

WHAT DO THE OTHER GUIDELINES SAY?

Kidney Disease Outcomes Quality Initiative: No recommendation.
UK Renal Association: No recommendation.
Canadian Society of Nephrology: No recommendation.
European Best Practice Guidelines: No recommendation.
International guidelines: No recommendation.

IMPLEMENTATION AND AUDIT

No recommendation.

SUGGESTIONS FOR FUTURE RESEARCH

No recommendation.

REFERENCES

1. Walser M, Ward L. Progression of chronic renal failure is related to glucocorticoid production. *Kidney Int*. 1988; **34**: 859–66.
2. Stefoni S, Mosconi G, La Manna G *et al*. Low-dosage ibopamine treatment in progressive renal failure: a long-term multicentre trial. *Am. J. Nephrol*. 1996; **16**: 489–99.
3. Docci D, Pistocchi E, Turci F *et al*. Effect of ibopamine on the progression of chronic renal failure. *Clin. Nephrol*. 1986; **26**: 121–4.
4. Russo GE, Scarpellini MG, Spaziani M. The effects of ibopamine on chronic renal insufficiency: a long-term trial. *Curr. Ther Res*. 1990; **48**: 912–24.
5. Stefoni S, Docci D, Vangelista A *et al*. Long-term treatment of chronic renal insufficiency with Ibopamine (SB 7505), a new orally active dopamine-related drug. *Clin. Nephrol*. 1982; **18**: 168–73.
6. Itoh H. Clinical pharmacology of ibopamine. *Am. J. Med*. 1991; **90**: 36S–42S.
7. Dei Cas L, Metra M, Visioli O. Clinical pharmacology of inodilators. *J. Cardiovasc Pharmacol*. 1989; **14** (Suppl. 8): S60–S71.
8. Itoh H, Taniguchi K, Tsujibayashi T *et al*. Hemodynamic effects and pharmacokinetics of long-term therapy with ibopamine in patients with chronic heart failure. *Cardiology*. 1992; **80**: 356–66.
9. Dei Cas L, Metra M, Nodari S *et al*. Lack of tolerance development during chronic ibopamine administration to patients with congestive heart failure. *Cardiovasc Drugs Ther*. 1988; **2**: 221–9.
10. Kasmer RJ, Cutler RE, Munger MA *et al*. Single-dose effects of ibopamine hydrochloride on renal function in patients with congestive heart failure. *Br. J. Clin. Pharmacol*. 1990; **30**: 485–9.
11. Stefoni S, Coli L, Mosconi G *et al*. Ibopamine (SB 7505) in normal subjects and in chronic renal failure: a preliminary report. *Br. J. Clin. Pharmacol*. 1981; **11**: 69–72.
12. Melloni GF, Minoja GM, Scorazzati G *et al*. Renal effect of SB 7505: a double-blind study. *Eur J. Clin. Pharmacol*. 1981; **19**: 177–80.
13. Felder RA, Felder CC, Eisner GM *et al*. The dopamine receptor in adult and maturing kidney. *Am. J. Physiol*. 1989; **257**: F315–27.
14. Lopez Sendon J. Hemodynamic and neurohumoral effects of ibopamine in patients with chronic congestive heart failure. *Cardiology*. 1990; **77** (Suppl. 5): S9–S21.
15. Girbes AR, van Veldhuisen DJ, Smit AJ *et al*. Renal and neurohumoral effects of ibopamine and metoclopramide in normal man. *Br. J. Clin. Pharmacol*. 1991; **31**: 701–4.
16. Missale C, Metra M, Sigala S *et al*. Inhibition of aldosterone secretion by dopamine, ibopamine, and dihydroergotoxine in patients with congestive heart failure. *J. Cardiovasc Pharmacol*. 1989; **14** (Suppl. 8): S72–S76.
17. Hampton JR, van Veldhuisen DJ, Kleber FX *et al*. Randomised study of effect of ibopamine on survival in patients with advanced severe heart failure. Second Prospective Randomised Study of Ibopamine on Mortality and Efficacy (PRIME II) Investigators. *Lancet*. 1997; **349**: 971–7.
18. Stricker BH, Feenstra J, Ottervanger JP *et al*. A nested case-control study on mortality in users of ibopamine. *Neth. J. Med*. 1997; **51**: 163–8.
19. Vriesendorp R, Donker AJ, de Zeeuw D *et al*. Effects of nonsteroidal anti-inflammatory drugs on proteinuria. *Am. J. Med. B*, 1986; **81**: 84–94.
20. Lagrue G, Laurent J, Belghiti D. Renal survival in membranoproliferative glomerulonephritis (MPGN): role of long-term treat-

ment with non-steroid anti-inflammatory drugs (NSAID). *Int. Urol. Nephrol.* 1988; **20**: 669–77.
21. Fieschi A, Bianchi B. Phenylbutazone. Un farmaco attivo sulla albuminuria. *Prog. Med. Napoli.* 1955; **9**: 257–63.
22. de Vries LA, ten Holt SP, van Daatselaar JJ *et al.* Characteristic renal excretion patterns in response to physiological, pathological and pharmacological stimuli. *Clin. Chim Acta.* 1960; **5**: 915–37.
23. Michielsen P, Lambert PP. Effects of corticosteroid and indomethacin treatment on proteinuria. *Bull. Mem Soc. Med. Hop Paris*; 1967; **118**: 217–32.
24. Michielsen P, Lambert PP. Effects of treatment with corticosteroids and indomethacin on proteinuria. *J. Urol. Nephrol. (Paris).* 1967; **73**: 340–55.
25. Conte J, Suc JM, Mignon Conte M. Anti-proteinuric effect of indomethacin in glomerulopathies (nephrotic syndrome, acute glomerulonephritis and chronic glomerulonephritis). Preliminary note. *J. Urol. Nephrol. (Paris)* 1967; **73**: 850–6.
26. Vercellone A, Piccoli G, Ragni R *et al.* Perspectives of indomethacin therapy in glomerular nephropathies. *Minerva Nefrol.* 1969; **16**: 163–74.
27. Wijdeveld PG. Some clinical and therapeutic aspects of the nephrotic syndrome in the adult (with special emphasis on the effects of indomethacin and related substances). *Folia Med. Neerl.* 1971; **14**: 4–31.
28. Donker AJ, Brentjens JR, van der Hem GK *et al.* Treatment of the nephrotic syndrome with indomethacin. *Nephron.* 1978; **22**: 374–81.
29. Vriesendorp R, de Zeeuw D, de Jong PE *et al.* Reduction of urinary protein and prostaglandin E2 excretion in the nephrotic syndrome by non-steroidal anti-inflammatory drugs. *Clin. Nephrol.* 1986; **25**: 105–10.
30. Vriesendorp R, Donker AJ, de Zeeuw D *et al.* Antiproteinuric effect of naproxen and indomethacin. A double-blind crossover study. *Am. J. Nephrol.* 1985; **5**: 236–42.
31. Walser M. Progression of chronic renal failure in man. *Kidney Int.* 1990; **37**: 1195–210.
32. Walser M, Hill S. Effect of ketoconazole plus low-dose prednisone on progression of chronic renal failure. *Am. J. Kidney Dis.* 1997; **29**: 503–13.

APPENDICES

Table 1 Characteristics of included studies

Study ID (author, year)	N	Study design	Setting	Participants	Intervention (experimental group)	Intervention (control group)	Follow up (months)	Comments
Stefoni *et al*, 1996[2]	189	Randomised controlled clinical trial	11 nephrology centres in Italy	Patients aged 18–70 yrs with mild or moderate chronic renal failure	Ibopamine supplement of 100 mg/day in addition to routine medical treatment n = 96	No ibopamine therapy n = 93	24	

Table 2 Quality of randomised trials

Study ID (author, year)	Method of allocation concealment	Blinding			Intention-to-treat analysis	Loss to follow up (%)
		(participants)	(investigators)	(outcome assessors)		
Stefoni *et al*, 1996[2]	Statistical software package	No	No	No	Unclear	7% (after 12 months) 22% (after 24 months)

Table 3 Results for continuous outcomes

Study ID (author, year)	Outcomes	Intervention group (mean [SD])	Control group (mean [SD])	Difference in means [95% CI]
Stefoni *et al*, 1996	Mean BP (mmHg) at 12 mo	107 (17.20)	105 (17.09)	2.00 (95%CI: –3.54, 7.54)
	Diuresis (mL/d) at 12 mo	2250 (765.61)	2031 (538.27)	219.00 (95%CI: 5.28, 432.72)
	Proteinuria (g/d) at 12 mo	1.2 (2.58)	1.1 (2.56)	0.10 (95%CI: –0.73, 0.93)
	Creatinine clearance at end of study (mL/min)	38.1 (17.20)	36.2 (20.51)	1.90 (95%CI: –4.22, 8.02)

Other forms of dietary intervention

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Author: David Johnson

GUIDELINES

A carbohydrate-restricted, low-iron-available, polyphenol-enriched (CR-LIPE) diet may slow the progression of diabetic nephropathy. (Level II evidence; one small randomised controlled trial (RCT); clinically relevant outcome; large effect)

BACKGROUND

Animal models of chronic kidney disease (CKD) have suggested possible renoprotective roles for carbohydrate restriction, augmentation of polyphenol intake and restriction of dietary iron. Caloric restriction (principally achieved by carbohydrate restriction) has been shown in animal models to prevent renal failure progression independently of dietary protein intake[1]). Polyphenols inhibit the digestion and absorption of protein, energy and iron, and significantly prolong renal survival in experimental models of glomerulosclerosis[2]). Finally, iron has been identified as an important factor in the progression of experimental nephropathy after the inciting injury was removed[3]). The objective of this guideline was to assess the potential effectiveness of any of these dietary interventions on renal failure progression.

SEARCH STRATEGY

Databases searched: Medline (1999 to November Week 2, 2003). MeSH terms for kidney diseases were combined with MeSH terms and text words for dietary restriction, CR-LIPE and iron. The results were then combined with the Cochrane highly sensitive search strategy for randomised controlled trials and MeSH terms and text words for identifying meta-analyses and systematic reviews. The Cochrane Renal Group Specialized Register of Randomised Controlled Trials was also search for relevant trials not indexed by Medline.
Date of search: 16 December 2003.

WHAT IS THE EVIDENCE?

1 There is one RCT.
2 Facchini and Saylor[4] conducted a prospective, open-label, RCT of a low-iron-available, polyphenol-enriched, 50% CR-LIPE diet vs. a standard, protein-restricted (0.8 g/kg/day) diet in 191 type 2 diabetic patients with various degrees of CKD (GFR 15–75 mL/min) or proteinuria (350–12000 mg/day). Over a mean follow-up period of 3.9 ± 1.8 years, serum creatinine concentration doubled in 19 (21%) patients on CR-LIPE compared with 31 (39%) patients on the control diet ($P < 0.01$). Renal death occurred in 18 (20%) patients on CR-LIPE and 31 (39%) of controls ($P < 0.01$). The observed differences between the groups were independent of follow-up interval, sex, mean arterial blood pressure, glycated haemoglobin, initial renal dysfunction and angiotensin system inhibition. Drop-out rates were low in each group (CR-LIPE 9%, controls 13%). Dietary compliance was not assessed, but serum ferritin concentration did fall significantly in the CR-LIPE group (from 301 ± 162 to 36 ± 31 μg/L), while it was unchanged in control subjects. Despite the development of iron deficiency in a number of subjects in the CR-LIPE group, haemoglobin levels did not fall (141 ± 21 vs. 140 ± 20 g/L). Body weight and serum albumin concentration also did not fall in the CR-LIPE patients. The principal limitations of the study were: (a) its small size (potentially limiting the generalisability of these findings); (b) the lack of monitoring of dietary compliance; and (c) the uncertainty regarding adequate concealment of randomisation allocation.

SUMMARY OF THE EVIDENCE

One small RCT has demonstrated that a CR-LIPE diet is markedly more effective at retarding the progression of diabetic nephropathy than standard dietary protein restriction. These findings should be considered preliminary.

WHAT DO THE OTHER GUIDELINES SAY?

Kidney Disease Outcomes Quality Initiative: No recommendation.
UK Renal Association: No recommendation.
Canadian Society of Nephrology: No recommendation.
European Best Practice Guidelines: No recommendation.
British Dietetic Association Renal Nutrition Group: No recommendation.
European Dialysis and Transplant Nurses Association – European Renal Care Association: No recommendation.
European Society of Parenteral and Enteral Nutrition: No recommendation.

IMPLEMENTATION AND AUDIT

No recommendation.

SUGGESTIONS FOR FUTURE RESEARCH

A large, multicentre, RCT of CR-LIPE diet in patients with diabetic and non-diabetic renal failure is recommended.

REFERENCES

1. Tapp DC, Wortham WG, Addison JF *et al*. Food restriction retards body growth and prevents end-stage renal pathology in remnant kidneys of rats regardless of protein intake. *Lab. Invest* 1989; **60**: 184–95.
2. Yokozawa T, Chung HY, He LQ *et al*. Effectiveness of green tea tannin on rats with chronic renal failure. *Biosci. Biotechnol Biochem*. 1996; **60**: 1000–5.
3. Alfrey AC. Role of iron and oxygen radicals in the progression of chronic renal failure. *Am. J. Kidney Dis* 1994; **23**: 183–7.
4. Facchini FS, Saylor KL. A low-iron-available, polyphenol-enriched, carbohydrate-restricted diet to slow progression of diabetic nephropathy. *Diabetes* 2003; **52**: 1204–9.

APPENDICES

Table 1 Characteristics of included studies

Study ID (author, year)	N	Study design	Setting	Participants	Intervention (experimental group)	Intervention (control group)	Follow up (months)	Comments
Facchini *et al*, 2003[4]	191	Prospective randomised controlled trial	Nephrology clinics (multicentre trial)	Patients with Type 2 diabetes with various degrees of renal failure and proteinuria	Carbohydrate-restricted, low iron-available, polyphenol-enriched diet (CR-LIPE) n = 100	Conventional standard protein-restricted diet n = 91	8–64	

Table 2 Quality of randomised trials

Study ID (author, year)	Method of allocation concealment	Blinding			Intention-to-treat analysis	Loss to follow up
		(participants)	(investigators)	(outcome assessors)		
Facchini *et al*, 2003[4]	Central	No	No	No	Yes	21/191 (11%)

Table 3 Results for continuous outcomes

Study ID (author, year)	Outcomes	Intervention group (mean [SD])	Control group (mean [SD])	Difference in means [95% CI]
Facchini *et al*, 2003	Weight (kg) at follow up	76 (14)	78 (14)	–2.00 (95%CI: –0.37, –0.09)
	Albumin (g/L) at follow up	41 (6)	41 (7)	0.00 (95%CI: –2.04, 2.04)
	Hb (g/L) at follow up	140 (20)	140 (26)	0.00 (95%CI: –7.31, 7.31)
	TC (mmol/L) at follow up	5.8 (1.4)	5.5 (1.5)	0.30 (95%CI: –0.15, 0.75)
	LDL-C (mmol/L) at follow up	3.68 (1.01)	3.47 (1.99)	0.21 (95%CI: –0.30, 0.72)
	HDL-C (mmol/L) at follow up	1.22 (0.50)	0.92 (0.41)	0.30 (95%CI: 0.16, 0.44)
	TC/HDL-C at follow up	4.7 (0.7)	5.8 (1.1)	–1.10 (95%CI: –1.39, –0.81)

Hb, haemoglobin; TC, total cholesterol; LDL-C, LDL cholesterol; HDL-C, HDL cholesterol.

Table 4 Results for dichotomous outcomes

Study ID (author, year)	Outcomes	Intervention group (number of patients with events/number of patients exposed)	Control group (number of patients with events/number of patients not exposed)	Relative risk (RR) [95% CI]	Risk difference (RD) [95% CI]
Facchini *et al*, 2003	Renal replacement therapy or death	18/100	31/91	0.53 (95%CI: 0.32, 0.88)	–0.16 (95%CI: –0.28, –0.04)
	Doubling of serum Cr	19/91	31/71	0.48 (95%CI: 0.30, 0.77)	–0.23 (95%CI: –0.37, –0.09)

Blood pressure control: targets

Date written: May 2005
Final submission: October 2005
Author: Adrian Gillin

GUIDELINES

a. Lower systolic blood pressure (SBP) minimizes the risk of progression to end-stage kidney disease (ESKD), especially with proteinuria. (Level II evidence)

b. A target blood pressure (BP) of < 125/75 mmHg (or mean BP < 92 mmHg) if proteinuria > 1 g/24 h, may be beneficial. (Level II evidence)

c. A target BP of < 130/80 mmHg (or mean BP < 97 mmHg) if proteinuria is 0.25–1 g/24 h, may be beneficial. (Level II evidence)

d. Target BP should be < 130/85 mmHg (or mean BP < 100 mmHg) if proteinuria < 0.25 g/24 h. (Level II evidence) However, there may be other potential benefits of achieving lower BP than a mean of 100 mmHg with respect to reduced cardiovascular risk.

There is no evidence concerning target BP for paediatric patients with progressive kidney disease.

SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on Level III and IV evidence)

- **There is evidence for a lower BP target with greater degrees of proteinuria (> 1 g/day). A precise goal below 130/80 mmHg is not clear. These patients should be carefully monitored.**

BACKGROUND

Most forms of chronic kidney disease (CKD) are associated with hypertension. Uncontrolled hypertension not only increases the risk of serious cardiovascular morbidity or mortality but is also associated with a more rapid progression of CKD. Studies have suggested that a lower BP target is more beneficial for slowing progression of CKD than reducing cardiovascular disease risk. The objective of this set of guidelines is to evaluate the evidence regarding differing BP targets for differing severity/causes of CKD in preventing progression.

SEARCH STRATEGY

Databases searched: MeSH terms and text words for chronic kidney disease were combined with MeSH terms and text words for angiotensin II antagonists, ACE inhibitors and blood pressure. These were then combined with MeSH terms and text words for locating randomised controlled trials. The search was carried out in Medline (1966 – November Week 1, 2004). The Cochrane Renal Group Register of randomised controlled trials was also searched for any additional relevant trials not indexed in Medline.
Date of searches: 12 November 2004.

WHAT IS THE EVIDENCE?

REIN-2 Study[1]: This was a multicentre randomised controlled trial (RCT) assessing blood-pressure control for renoprotection in 338 patients with non-diabetic CKD. Participants were randomly allocated to conventional (diastolic < 90 mmHg) or intensified (130/80 mmHg) blood pressure control. Patients with a BP target of 130/80 mmHg by addition of felodipine had the same rate of kidney failure progression as did patients with a higher BP target on ramipril. A total of 38 of 167 patients in the intensified BP control group and 34 of 168 patients allocated to the control group progressed to ESKD. However, follow-up was only for 36 months.

MDRD Study[2]: A total of 840 patients were enrolled in 2 studies. Study 1 (n = 585): GFR 25–55 mL/min/1.73 m^2 BSA; Study 2 (n = 255): GFR 13–24 mL/min/1.73 m^2 BSA, with two interventions: (a) usual protein diet or low protein diet (1.3 or 0.58 g/kg/d) and (b) usual or low BP group (MAP 107 or 92 mmHg). At baseline: serum creatinine 106–619 μmol/L for females or 124–619 μmol/L for men, age 18–70 yrs, excluded if < 80% or > 160% of standard body weight, diabetic on insulin, > 10g/d proteinuria or renal transplant. The primary outcome was rate of change of GFR (^{125}Iothalamate clearance). The mean follow up was 2.2 yrs with 60% being men, 85% white, average age 52 yrs, 25% glomerular disease, 24% ADPKD, and 3% NIDDM. Results showed no significant overall benefit of low protein diet or low blood pressure interventions over the full course of the study. However, secondary analyses showed benefit of lower blood pressure after a more rapid phase of decline in GFR in the first 4 months with both studies. The average rate of decline in GFR was 3.3 mL/min/year in all groups combined. It was a mean 29% lower in the low BP group than the usual BP group. GFR declined more rapidly in

patients with a higher degree of proteinuria, in those with ADPKD and in blacks. The benefit of low blood pressure was greatest with > 3 g/day proteinuria, of moderate benefit with 1–3 g/day and there was no benefit if proteinuria was < 1 g/day. This study was not designed to show which antihypertensive agent affected renal function decline. A mean BP of 92 mmHg or less was safe and well tolerated up to the 3 years duration of the study. (Level II evidence)

Observational studies and clinical trials of dietary protein restriction (Marcantoni *et al*[3] Brazy *et al*,[4] 86 patients with mean diastolic BP < 90 mmHg had a slower rate of decline in 1/serum creatinine. Oldrizzi *et al*[5] enrolled 423 patients in a long-term low-protein diet study. Survival at 10 years was 96% with mean BP < 100 mHg, 74% with mean BP < 100–110 mmHg and 48% with mean BP > 110 mmHg. The Northern Italian Cooperative Study, showed 456 patients on a low protein diet, had a worse renal survival with mean BP > 107 mmHg. (Level III evidence)

He and Whelton[6] performed a meta-analysis which showed systolic BP was associated with a greater risk for ESKD than diastolic BP. (Level II evidence).

Wright *et al*.[7] studied 1094 African-Americans with nondiabetic, hypertensive renal disease. It compared 2 levels of BP control and 2 antihypertensive drug classes on GFR decline (3 × 2 factorial design). The BP goals were MAP of (i) 102–107 mmHg or (ii) ≤ 92 mmHg. The drugs were ramipril (2.5–10 mg/day, n = 436), metoprolol (50–200 mg/day, n = 441) and amlodipine (5–10 mg/day, n = 217). It was an open label study. Outcomes were GFR slope alone or GFR slope combined with reduction in GFR by 50% or more, ESKD or death. The lower blood pressure group achieved a mean BP of 128/78 mmHg, which was 12/8 mmHg lower than the other BP group (mean achieved BP 141/85 mmHg). There was no significant outcome difference between groups. The ramipril group manifested risk reductions in the clinical composite outcome of 22% (95%CI: 1–38%, P = 0.04) compared with the metoprolol group and 38% (95%CI: 14–56%, P = 0.004) compared with the amlodipine group. (Level II evidence)[7]

There was no evidence from AASK to support a target BP that is lower than current treatment guidelines for cardiovascular disease. This may be peculiar to African-Americans or to the underlying disease of hypertensive nephro-sclerosis and not be true for other renal diseases.

SUMMARY OF THE EVIDENCE

A meta-analysis has shown that lowering SBP is associated with slowing progression to ESKD. Results from an RCT suggest a target BP of < 125/75 mmHg if proteinuria > 1 g/24 h and a target BP of < 130/80 mmHg if proteinuria is 0.25–1 g/24 h.

WHAT DO THE OTHER GUIDELINES SAY?

JNC VI: Recommends mean BP 100 mmHg (130/85 mmHg) in patients with chronic renal disease. If < 0.25 g/d of proteinuria, no benefit of a lower BP than above.[8] JNC VII recommends less than 130/80 in patients with CKD and proteinuria (> 300 mg/d).

Hypertension Management for Doctors (2004). NHF of Australia: Goal is < 130/85 mmHg with chronic renal disease or < 125/75 mmHg if > 1 g/day of proteinuria.

Kidney Disease Outcomes Quality Initiative: Target BP in non-diabetic kidney disease should be < 130/80 mmHg.[9] (see Fig. 1)

UK Renal Association: The previous edition of this document suggested a higher standard, 160/90 mmHg, for patients over 60 years of age than for younger patients (140/90 mmHg). In the general population, systolic hypertension is more common in the elderly, probably due to decreased large vessel compliance. Recent studies have shown that increased pulse pressure, a result of decreased conduit artery compliance, is a much more powerful risk factor for death in the general population than systolic or diastolic blood pressure. It has been shown recently that the absolute benefits of blood pressure reduction are greater in the elderly than in younger patients, due to the former having higher baseline risk, and that isolated systolic hypertension or combined systolic and diastolic hypertension in patients up to the age of 80 can be safely treated with good results. However, many of the elderly patients in these trials had marked systolic hypertension, and the question of whether there is benefit from reducing systolic blood pressure from 160 mmHg to, say, 130 mmHg, has not been specifically examined in this patient group, or even in the general population. Setting a more liberal standard for blood pressure in the elderly risks giving the message that control of hypertension is less

Clinical Assessment	Target Blood Pressure		Preferred Agents for CKD		Additional Agents to Reduce CVD Risk and Reach Target Blood Pressure	
Blood pressure ≥130/80 mm Hg and spot urine total protein-to-creatinine ratio ≥200 mg/g	<130/80 mm Hg	A	ACE inhibitor or ARB	A	Diuretic preferred, then beta-blocker or calcium-channel blocker	A
Blood pressure ≥130/80 mm Hg and spot urine total protein-to-creatinine ratio <200 mg/g	<130/80 mm Hg	B	None preferred		Diuretic preferred, then ACE inhibitor, ARB, beta-blocker or calcium-channel blocker	A
Blood pressure <130/80 mm Hg and spot urine total protein-to-creatinine ratio ≥200 mg/g			ACE inhibitor or ARB	C	Diuretic preferred, then beta-blocker or calcium-channel blocker	A
Blood pressure <130/80 mm Hg and spot urine total protein-to-creatinine ratio <200 mg/g			None preferred			

Letters in shaded areas represent strength of recommendations.

Fig. 1 Hypertension and antihypertensive agents in nondiabetic kidney disease
Source: NKF K/DOQI Guidelines, 2002.

important in these patients, when the reverse is probably the case. For these reasons, the targets set here are independent of age.[10]

Canadian Society of Nephrology: No recommendation.

European Best Practice Guidelines: No recommendation.

VA Primary Care Guidelines: In patients with chronic kidney disease . . . Vigorous control of hypertension reduces the glomerular capillary pressure and slows the progression of glomerulosclerosis. The goal blood pressure should be < 125/75 or mean arterial pressure less then 92 for patients with proteinuria and 130/85 in patients without proteinuria. ACEI or ARB is the preferred antihypertensive agents.[11]

IMPLEMENTATION AND AUDIT

No recommendation.

SUGGESTIONS FOR FUTURE RESEARCH

No recommendation.

REFERENCES

1. Ruggenenti P, Perna A, Loriga G *et al*. Blood pressure control for renoprotection in patients with non-diabetic chronic renal disease (REIN-2): multicentre, randomised controlled trial. *Lancet* 2005; **365**: 939–46.
2. MDRD Study Group. Effects of diet and antihypertensive therapy on creatinine clearance and serum creatinine concentration in the Modification of Diet in Renal Disease Study. *J. Am. Soc. Nephrol.* 1996; **7**: 556–66.
3. Marcantoni C, Jafar TH, Oldrizzi L *et al*. The role of systemic hypertension in the progression of non diabetic renal disease. *Kidney Int. Suppl* 2000; **75**: S44–S48.
4. Brazy PC, Stead WW, Fitzwilliam JF. Progression of renal insufficiency: role of blood pressure. *Kidney Int.* 1989; **35**: 670–4.
5. Oldrizzi L, Rugiu C, De Biase V *et al*. Factors influencing dietary compliance in patients with chronic renal failure on unsupplemented low-protein diet. *Contrib Nephrol.* 1990; **81**: 9–15.
6. He J, Whelton PK. Elevated systolic blood pressure as a risk factor for cardiovascular and renal disease. *J. Hypertens Suppl* 1999; **17**: S7–S13.
7. Wright JT Jr, Bakris G, Greene T *et al*. Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: results from the AASK trial. *JAMA* 2002; **288**: 2421–31.
8. Chobanian AV, Bakris GL, Black HR *et al*. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA* 2003; **289**: 2560–72.
9. National Kidney Foundation. K/DOQI Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease. Guideline 9, Pharmacological Therapy: Nondiabetic Kidney Disease. Available from: http://www.kidney.org/Professionals/Kdoqi/Guidelines_Bp/Guide_9.Htm.
10. The Renal Association and the Royal College of Physicians of London. Treatment of adults and children with renal failure: standards and audit measures. 3rd edn. Suffolk: The Lavenham Press Ltd; 2002: pp. 75–6.
11. Veterans Health Administration, Department of Defense. VHA/DoD clinical practice guideline for the management of chronic kidney disease and pre-ESRD in the primary care setting. Washington (DC): Dept of Veterans Affairs (US), Veterans Health Administration; 2001 May. Available from: http://www.guideline.gov/summary/summary.aspx?ss=15&doc_id=3099&nbr=2325/.

APPENDICES

Table 1 Characteristics of included studies

Study ID (author, year)	N	Study design	Setting	Participants	Intervention (experimental group)	Intervention (control group)	Follow up (years)	Comments
MDRD Study, 1996	840	Two randomised two-by-two factorial clinical controlled trials	Multicentre	840 patients with various chronic renal diseases	Restriction of dietary protein and phosphorus; reducing blood pressure to below usual recommended level (MAP 92 mmHg)	Blood pressure (MAP 107 mmHg)	2.2	Study A compared usual vs low-protein. Study B compared low protein vs very low protein. Both compared usual vs low MAP.
Ruggenenti *et al*, 2005	338	Randomised controlled clinical trial	Multicentre	228 non-diabetic patients with proteinuric nephropathy	Intensified blood pressure control (< 130/80 mmHg)	Conventional blood pressure control (diastolic < 90 mmHg)	3	
Wright *et al*, 2002	1094	Randomised controlled clinical trial	21 clinical centres in the US	1094 African-Americans with hypertensive renal disease, 18–70 yrs	Low MAP < 92 mmHg	Usual MAP 102–107 mmHg	3–6.4	3 × 2 factorial trial (2 levels of MAP, 3 anti-hypertensive drug classes)

MAP, mean arterial pressure.

Table 2 Quality of randomised trials

Study ID (author, year)	Method of allocation concealment	Blinding			Intention-to-treat analysis	Loss to follow up (%)
		(participants)	(investigators)	(outcome assessors)		
MDRD Study, 1996	Not specified	No	No	No	Yes	1.7
Ruggenenti *et al*, 2005	Central	No	No	No	Yes	1.8
Wright *et al*, 2002	Not specified	No	No	No	Yes	0.8

Table 3 Results for continuous outcomes

Study ID (author, year)	Outcomes	Intervention group (mean [SD])	Control group (mean [SD])	Difference in means [95% CI]
MDRD Study, 1996	Rate of change in GFR at 4 mo in study A (mL/min/month)	–0.32 (0.3)	–0.23 (0.3)	0.09 (95%CI: 0.04, 0.14)
Ruggenenti *et al*, 2005	Mean SBP (mmHg)	129.6 (10.9)	133.7 (12.6)	–4.10 (95%CI: –6.62, –1.58)
	Mean DBP (mmHg)	79.5 (5.3)	82.3 (7.1)	–2.80 (95%CI: –4.14, –1.46)
Wright *et al*, 2002	Mean GFR decline (mL/min/1.73 m^2 per year)	2.21 (4.0)	1.95 (4.0)	0.26 (95%CI: –0.21, 0.73)

Table 4 Results for dichotomous outcomes

Study ID (author, year)	Outcomes	Intervention group (number of patients with events/number of patients exposed)	Control group (number of patients with events/number of patients not exposed)	Relative risk (RR) [95% CI]	Risk difference (RD) [95% CI]
Ruggenenti et al, 2005	Death	2/169	3/169	0.67 (95%CI: 0.11, 3.96)	–0.01 (95%CI: –0.03, 0.02)
	ESKD	34/169	38/169	0.90 (95%CI: 0.60, 1.36)	–0.02 (95%CI: –0.11, 0.07)

Blood pressure control: role of specific antihypertensives

Date written: May 2005
Final submission: October 2005
Author: Adrian Gillin

GUIDELINES

a. Regimens that include angiotensin-converting enzyme inhibitors (ACEIs) are more effective than regimens that do not include ACEIs in slowing progression of non-diabetic kidney disease. (Level I evidence)

b. Combination therapy of ACEI and angiotensin receptor blocker (ARB) slows progression of non-diabetic kidney disease more effectively than either single agent. (Level II evidence)

c. ACEIs appear to be more effective than beta-blockers and dihydropyridine calcium channel blockers in slowing progressive kidney disease. (Level II evidence)

d. Beta-blockers may be more effective in slowing progression than dihydropyridine calcium channel blockers, especially in the presence of proteinuria. (Level II evidence)

SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on Level III and IV evidence)

- **Use ACEIs cautiously in patients with renal impairment. A safe level of renal impairment has not been clearly defined; therefore, one should monitor plasma electrolytes and renal function closely during therapy.**

BACKGROUND

In general, different classes of antihypertensive agents reduce BP to a similar degree. Some antihypertensive class agents have specific benefits to patients with other comorbidities, e.g. diuretics in oedematous patients due to nephrotic syndrome. ACEIs have been shown to have greater beneficial effects on slowing the rate of diabetic CKD than other antihypertensive agents, when similar BP control is achieved. This set of guidelines evaluates the evidence for the various classes of antihypertensive agent in slowing the rate of progression of non-diabetic CKD.

SEARCH STRATEGY

Databases searched: MeSH terms and text words for chronic kidney disease were combined with MeSH terms and text words for angiotensin II antagonists, ACE inhibitors and blood pressure. These were then combined with MeSH terms and text words for locating randomised controlled trials. The search was carried out in Medline (1966 – November Week 1, 2004). The Cochrane Renal Group Register of randomised controlled trials was also searched for any additional relevant trials not indexed in Medline.
Date of searches: 12 November 2004.

WHAT IS THE EVIDENCE?

Effect of angiotensin-converting enzyme inhibitors on the progression of nondiabetic renal disease: A meta-analysis of randomised trials by Giatras *et al.*[1] included 10 studies (6 blinded), with 1594 patients aged 44–66 years. ACEIs were found to be more effective than other antihypertensive agents in reducing the development of non-diabetic end-stage kidney disease (ESKD); they also do not increase mortality. Pooled relative risk for ESKD was 0.70 (95% CI: 0.51–0.97) indicating a significantly lower risk for developing ESKD in the ACEI group. However, risk of death was not improved [pooled relative risk, 1.24 (95% CI: 0.55–2.83)]. No significant association between BP reduction and ACEI benefit was found. (Level II evidence)

REIN Study[2]: The R/DB/PC trial included 352 patients (18–70 years) with non-diabetic nephropathy (Creatinine clearance of 20–70 mL/min ± 30%). Participants were stratified by degree of proteinuria (1: 1–3 g/d, II: > 3 g/d), ramipril or placebo plus conventional antihypertensives to achieve a target < 90 mmHg diastolic. The endpoint was rate of decline of GFR (iohexol clearance method). Patients included were normotensive (140/90 mmHg) and hypertensive. Other ACEIs and ARBs were prohibited as BP controlling agents.

This study reported a significantly ($P = 0.001$) slower rate of decline in GFR/month in patients with < 3 g/d proteinuria on ramipril ($n = 38$) compared with the placebo-treated patients ($n = 49$) [0.39 ± 0.10 vs. 0.89 ± 0.11 mL/min]. Ramipril decreased protein excretion by 55% at 36 months treatment while it did not change in the placebo group ($P = 0.002$). Risk reduction was significantly predicted by the percentage reduction from baseline in urinary protein excretion during treatment. Improvement was not related to baseline or follow-up blood pressure. In stratum I,

there was no significantly different decline in GFR in either group. (Level II evidence)

AIPRI Trial[3]: This multicentre, randomised, placebo-controlled trial entailed 583 patients with mild to moderate renal insufficiency (Creatinine clearance 30–60 mL/min) due to a variety of causes, target BP – diastolic < 90 mmHg. The outcome measure was a twofold increase in baseline serum creatinine. Results showed a lower rate of decline of renal function with benazepril. There was a small final difference in serum creatinine (0.1–0.2 mg/dL). No effect was shown on progression to ESKD. There was a higher death rate in the ACEI-treated group (1/94/ year vs. 1/657/ year). Target BP was attained in 82% on benazepril and 68% of control group, ACEI attained mean DBP < 85 mmHg and controls attained < 90 mmHg DBP. This study did not conclusively establish the magnitude of the beneficial effect or the safety of the ACEI therapy. (Level I evidence)

Early Randomised ACEI studies: Small sample size usually. Results not uniform – some beneficial effect of ACEI while others not beneficial.

Zuchelli et al.[4] 121 patients were studied to compare captopril vs. nifedipine. Conventional antihypertensives for 1 year then randomised for 2 years on treatment. Similar BP reduction was seen in both groups. Urinary protein fell more with ACEI, but GFR decline was similar for both groups. If mean BP < 100 mmHg, it was associated with slower rate of decline in renal function. (Level III evidence)

Himmelmann et al[5]: Cilazapril vs. atenolol was studied in 260 patients with presumed diagnosis of hypertensive nephrosclerosis and near-normal renal function (GFR 82 mL/min). During 2 years follow-up, ACEI significantly slowed decline in renal function. (Level III evidence)

The COOPERATE Trial: Enrolled 366 patients with non-diabetic CKD in Japan. A total of 263 patients were treated with losartan (100 mg/day), trandolapril (3 mg/day) or a combination of both drugs at equivalent doses and followed for a median of 2.9 years. Survival analysis of the endpoints of doubling of serum creatinine or ESKD showed that combination treatment safely retards progression of non-diabetic kidney disease compared to monotherapy. Of the combination treatment group, 11% reached the combined primary endpoint compared to 23% (95% CI: 0.18–0.63, P = 0.018) on trandolapril and 23% (95% CI: 0.17–0.69, P = 0.016) on losartan.[6] (Level II evidence)

The Jafar *et al.*[7] meta-analysis sourced individual patient data from 11 RCTs that compared efficacy of antihypertensive regimens including ACEIs to the efficacy of regimens without ACEIs in predominantly non-diabetic kidney disease. Data from 1860 patients were analysed and mean follow-up was 2.2 years. All patients were hypertensive. The ACEI group achieved a lower BP (mean 4.5/2.3 mmHg) and had greater proteinuria reduction (mean 0.46 g/day). Regimens that include an ACEI are more effective than regimens without an ACEI in slowing progression of non-diabetic renal disease. It is mediated by factors in addition to decreasing BP and urinary protein excretion and is greater in patients with proteinuria. The data were inconclusive as to whether the benefit extended to those with baseline proteinuria less than 0.5 g/day. (Level I evidence)

The AASK Trial[8] studied 1094 African-Americans with non-diabetic, hypertensive renal disease. It compared 2 levels of BP control and 2 antihypertensive drug classes on GFR decline (3 × 2 factorial design). The BP goals were MAP of (i) 102–107 mmHg or (ii) ≤ 92 mmHg. The drugs were ramipril (2.5–10 mg/day, $n = 436$), metoprolol (50–200 mg/day, $n = 441$) and amlodipine (5–10 mg/day, $n = 217$). It was open label. Outcomes were GFR slope alone or GFR slope combined with reduction in GFR by 50% or more, ESKD or death. The lower blood pressure group achieved a mean BP of 128/78 mmHg, which was 12/8 lower than the other BP group (mean achieved BP 141/85 mmHg). There was no significant outcome difference between groups. The ramipril group manifest risk reductions in the clinical composite outcome of 22% (95% CI: 1–38%, P = 0.04) compared to the metoprolol group and 38% (95% CI: 14–56%, P = 0.004) compared to the amlodipine group. (Level II evidence)

SUMMARY OF THE EVIDENCE

Results from a meta-analysis of RCTs showed treatments which included ACEIs are more effective than treatment regimens without ACEIs in slowing the progression of kidney disease. The data were inconclusive about the benefit for patients with baseline proteinuria < 0.5 g/day. Evidence from RCTs suggest that combination therapy of ACEI and ARB slows the progression of non-diabetic kidney disease more effectively than other agents and ACEIs are more effective in slowing progressive kidney disease compared with beta-blockers and dihydropyridine calcium channel blockers. However, there are limitations to the COOPERATE study, as it is unclear whether ACEI or ARB at maximal doses are the same, or less efficacious than combined therapy. RCTs have also shown that dihydropyridine calcium channel blockers are less effective in slowing progression of kidney disease compared with beta-blockers, particularly when proteinuria is present.

WHAT DO THE OTHER GUIDELINES SAY?

Kidney Disease Outcomes Quality Initiative: See Guideline 11 of Pharmacological therapy: Nondiabetic Kidney Disease – 'Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease.' ACEIs and ARBs can be used safely in most patients with CKD. They . . . "should be used at moderate to high doses, as used in clinical trials. (A)" They should be used as alternatives to each other, if the preferred class cannot be used (B).

Also see Guideline 9 – 'Patients with non-diabetic kidney disease and spot urine protein to creatinine ratio > 200 mg/g, with or without hypertension, should be treated with an ACE inhibitor or ARB.

UK Renal Association: No recommendation.

Canadian Society of Nephrology: No recommendation.

European Best Practice Guidelines: No recommendation.

International Guidelines:

VA Primary Care Guidelines: 'ACEI has beneficial effects in patients with diabetic nephropathy and other kidney diseases. These drugs slow progression independent of their effect on blood pressure. ARBs are a new class of drugs which may be used in patients who are intolerant of ACEI.[10] Studies on their effect are in progress.

Consensus statement ISN 2004: Workshop on Prevention of Progressive Renal Disease. Hong Kong, June 29, 2004. Suggested target BP < 130/80 mmHg. They suggested that BP control was more important than the choice of BP lowering agent.[11]

IMPLEMENTATION AND AUDIT

No recommendation.

SUGGESTIONS FOR FUTURE RESEARCH

Evaluate more precise BP targets for differing degrees of protein excretion.

REFERENCES

1. Giatras I, Lau J, Levey AS. Effect of angiotensin-converting enzyme inhibitors on the progression of nondiabetic renal disease: a meta-analysis of randomised trials. Angiotensin-Converting-Enzyme Inhibition and Progressive Renal Disease Study Group. *Ann. Intern. Med.* 1997; **127**: 337–45.
2. Ruggenenti P, Perna A, Loriga G *et al.* Blood pressure control for renoprotection in patients with non-diabetic chronic renal disease (REIN-2): multicentre, randomised controlled trial. *Lancet* 2005; **365**: 939–46.
3. Locatelli F, Carbarns IR, Maschio G *et al.* Long-term progression of chronic renal insufficiency in the AIPRI Extension Study. The Angiotensin-Converting-Enzyme Inhibition in Progressive Renal Insufficiency Study Group. *Kidney Int. Suppl.* 1997; **63**: S63–S66.
4. Zucchelli P, Zuccala A, Borghi M *et al.* Long-term comparison between captopril and nifedipine in the progression of renal insufficiency. *Kidney Int.* 1992; **42**: 452–8.
5. Himmelmann A, Hansson L, Hansson BG *et al.* ACE inhibition preserves renal function better than beta-blockade in the treatment of essential hypertension. *Blood Press* 1995; **4**: 85–90.
6. Nakao N, Yoshimura A, Morita H *et al.* Combination treatment of angiotensin-II receptor blocker and angiotensin-converting-enzyme inhibitor in non-diabetic renal disease (COOPERATE): a randomised controlled trial. *Lancet* 2003; **361**: 117–24.
7. Jafar TH, Schmid CH, Landa M *et al.* Angiotensin-converting enzyme inhibitors and progression of nondiabetic renal disease. A meta-analysis of patient-level data. *Ann. Intern. Med.* 2001; **135**: 73–87.
8. Wright JT Jr, Bakris G, Greene T *et al.* Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: results from the AASK trial. *JAMA* 2002; **288**: 2421–31.
9. National Kidney Foundation. K/DOQI. Guideline 11, Pharmacological therapy: Nondiabetic Kidney Disease. Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease. Available from: http://www.kidney.org/professionals/kdoqi/guidelines_bp/.
10. Pitt B. ACE inhibitors in heart failure: prospects and limitations. *Cardiovasc Drugs Ther* 1997; **11** (Suppl 1): S285–S90.
11. ISN. Consensus Statements ISN 2004 – Workshop on Prevention of Progressive Renal Disease. Hong Kong; June 29, 2004. *Kidney Int* 2005; **67** (Suppl 94): S2–S27.

APPENDICES

Table 1 Characteristics of included studies

Study ID (author, year)	N	Study design	Setting	Participants	Intervention (experimental group)	Intervention (control group)	Follow up (years)	Comments
Locatelli *et al*, 1997	583	Randomised controlled clinical trial	49 centres in Italy, France, Germany	Patients with chronic renal insufficiency	Benazepril	Placebo	6.6	Core trial with extended follow up, post hoc data included when treatment was not randomised
Nakao *et al*, 2003	336	Randomised controlled clinical trial	1 renal department in Japan	336 patients with non-diabetic renal disease	Angiotensin-II receptor blocker, Iosartan 100 mg/d	Angiotension-converting-enzyme inhibitor, trandolapril 3 mg/d	3	3-arm trial with a third arm receiving combination of both drugs at equivalent doses
Ruggenenti *et al*, 2005	338	Randomised controlled clinical trial	Multicentre in Italy	Patients with non-diabetic nephropathy and persistent proteinuria	Intensified blood-pressure control, dihydropyridine calcium-channel blocker felodipine (5–10 mg/d)	Conventional blood pressure control	3	
Wright *et al*, 2002	1094	Randomised controlled clinical trial	21 clinical centres in the US	1094 African-Americans with hypertensive renal disease, 18–70 yrs	Low MAP < 92 mmHg	Usual MAP 102–107 mmHg	3–6.4	3 × 2 factorial trial (2 levels of MAP, 3 anti-hypertensive drug classes)

Table 2 Quality of randomised trials

Study ID (author, year)	Method of allocation concealment	Blinding			Intention-to-treat analysis	Loss to follow up (%)
		(participants)	(investigators)	(outcome assessors)		
Locatelli *et al*, 1997	Not specified	Yes	Yes	Yes	Yes	13.6
Nakao *et al*, 2003	Permuted blocks of 6, independent, computer-generated	Yes	Yes	Yes	Yes	2.1
Ruggenenti *et al*, 2005	Central	No	No	No	Yes	38.2
Wright *et al*, 2002	Not specified	No	No	No	Yes	0.8

Table 3 Results for continuous outcomes

Study ID (author, year)	Outcomes	Intervention group (mean [SD])	Control group (mean [SD])	Difference in means [95% CI]
Nakao *et al*, 2003	Decrease in mean systolic pressure from baseline (mmHg)	5.1 (1.6) losartan	5.2 (1.3)	–0.10 (95%CI: –0.53, 0.33)
	Decrease in mean systolic pressure from baseline (mmHg)	5.3 (1.4) Combination	5.2 (1.3)	0.10 (95%CI: 0.30, 0.50)
	Decrease in mean diastolic pressure (mmHg)	2.9 (0.9) losartan	2.9 (0.8)	0.00 (95%CI: –0.25, 0.25)
	Decrease in mean diastolic pressure (mmHg)	3.0 (0.7) Combination	2.9 (0.8)	0.10 (95%CI: –0.12, 0.32)
Ruggenenti *et al*, 2005	Mean systolic blood pressure throughout follow up (mmHg)	129.6 (10.9)	133.7 (12.6)	–4.10 (95%CI: –6.62, –1.58)
	Mean diastolic blood pressure throughout follow up (mmHg)	79.5 (5.3)	82.3 (7.1)	–2.80 (95%CI: –4.14, –1.46)
Wright *et al*, 2002	Mean GFR decline (mL/min/1.73 m^2 per year)	2.21 (4.0)	1.95 (4.0)	0.26 (95%CI: –0.21, 0.73)

Table 4 Results for dichotomous outcomes

Study ID (author, year)	Outcomes	Intervention group (number of patients with events/number of patients exposed)	Control group (number of patients with events/number of patients not exposed)	Relative risk (RR) [95% CI]	Risk difference (RD) [95% CI]
Locatelli *et al*, 1997	Mortality	25/300	23/283	1.03 (95%CI: 0.60, 1.76)	0.00 (95%CI: –0.04, 0.05)
	Doubling of baseline serum creatinine at 3 yrs follow up, core study	31/300	57/283	0.51 (95%CI: 0.34, 0.77)	–0.10 (95%CI: –0.16, –0.04)
Nakao *et al*, 2003	Primary endpoint	20/86 (losartan)	20/85	0.99 (95%CI: 0.57, 1.70)	0.00 (95%CI: –0.13, 0.12)
		10/85 (Combination)	20/85	0.50 (95%CI: 0.25, 1.00)	–0.12 (95%CI: –0.23, 0.00)
	Mortality	1/89 (losartan)	0/86	2.90 (95%CI: 0.12, 70.23)	0.01 (95%CI: –0.02, 0.04)
		0/88 (Combination)	0/86	Not estimable	0.00 (95%CI: –0.02, 0.02)
	Non-fatal stroke	0/89 (losartan)	1/86	0.32 (95%CI: 0.01, 7.80)	–0.01 (95%CI: –0.04, 0.02)
		1/88 (Combination)	1/86	0.98 (95%CI: 0.06, 15.38)	0.00 (95%CI: –0.03, 0.03)
	Non-fatal angina	1/89 (losartan)	1/86	0.97 (95%CI: 0.06, 15.21)	0.00 (95%CI: –0.03, 0.03)
		1/88 (Combination)	1/86	0.98 (95%CI: 0.06, 15.38)	0.00 (95%CI: –0.03, 0.03)
	Myocardial infarction	1/89 (losartan)	0/86	2.90 (95%CI: –0.02, 0.04)	0.01 (95%CI: –0.02, 0.04)
		0/88 (Combination)	0/86	Not estimable	0.00 (95%CI: –0.02, 0.02)
	Hypotension	0/89 (losartan)	1/86	0.32 (95%CI: 0.01, 7.80)	–0.01 (95%CI: –0.04, 0.02)
		1/88 (Combination)	1/86	0.98 (95%CI: 0.06, 15.38)	0.00 (95%CI: –0.03, 0.03)
	Total adverse reactions	11/89 (losartan)	19/86	0.56 (95%CI: 0.28, 1.11)	–0.10 (95%CI: –0.21, 0.01)
		18/88 (Combination)	19/86	0.93 (95%CI: 0.52, 1.64)	–0.02 (95%CI: –0.14, 0.11)
Ruggenenti *et al*, 2005	Mortality	2/167	3/168	0.67 (95%CI: 0.11, 3.96)	–0.01 (95%CI: –0.03, 0.02)
	Progression to ESRD	38/167	64/168	0.60 (95%CI: 0.43, 0.84)	–0.15 (95%CI: –0.25, –0.06)
	Non-fatal serious adverse events	37/167	25/168	1.49 (95%CI: 0.94, 2.36)	0.07 (95%CI: –0.01, 0.16)

Reducing proteinuria

Date written: May 2005
Final submission: October 2005
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GUIDELINES

a. The beneficial effect of treatment regimens that include angiotensin-converting enzyme inhibitors (ACEIs) in slowing progression of kidney disease, is greater in patients with greater degrees of proteinuria. (Level I evidence)

b. There may be a proteinuria threshold for beneficial effect of ACEIs, of approximately 0.5 g/day. (Level I evidence)

c. Combined therapy with an ACEI and an angiotensin receptor blocker (ARB) does result in significantly greater antiproteinuric effect than with either agent alone and without further hypotensive effect. (Level II evidence)

d. Dihydropyridine calcium channel blocker-based treatment regimens are less effective than beta-blocker and ACEI-based regimens in slowing progression in non-diabetic kidney disease. (Level II evidence)

BACKGROUND

Proteinuria is an important prognostic feature of chronic kidney disease (CKD). The degree of proteinuria relates to the severity of the kidney disease and with a greater likelihood of progression to end-stages of CKD. Studies primarily using ACEIs to slow progression to CKD indicate that responsiveness differs depending on the baseline (pretreatment) degree of proteinuria and the degree of reduction in proteinuria. Other antihypertensive classes have been evaluated in a similar fashion. Thus, the aim of this set of guidelines is to explore the pharmacological reduction in proteinuria leading to a slowing in the rate of progression of various types of CKD.

SEARCH STRATEGY

Databases searched: MeSH terms and text words for chronic kidney disease were combined with MeSH terms and text words for angiotensin II antagonists, ACE inhibitors and blood pressure. These were then combined with MeSH terms and text words for locating randomised controlled trials. The search was carried out in Medline (1966 – November Week 1, 2004). The Cochrane Renal Group Register of randomised controlled trials was also searched for any additional relevant trials not indexed in Medline.
Date of searches: 12 November 2004.

WHAT IS THE EVIDENCE?

Russo *et al.*[1] carried out an observational study in 8 selected normotensive patients with biopsy-proven IgA nephropathy and mild proteinuria (1–3 g/d) and normal to mildly impaired renal function (Creatinine clearance 69–119 mL/min). Subjects were given a maximum tolerated dose of a variety of ACEIs for 12 weeks, followed by addition of losartan (LOS) 50 mg/d for 4 weeks, then LOS alone for 12 weeks and then combined therapy again. ACEI and LOS reduced protein excretion by the same extent (−39 ± 2.5% and −27 ± 20.8%). Combined therapy reduced proteinuria by a significantly ($P < 0.05$) greater extent than ACEI alone or LOS alone (−69.8 ± 5.5% − ACEI + LOS or −63.0 ± 9.3% – LOS +ACEI). The reduction in urinary protein was independent of the degree of BP decrease. LOS was as effective as ACEIs in reducing proteinuria. Larger trials are needed for definitive information. (Level IV evidence)

Perico *et al.*[2] ran a randomised placebo-controlled trial in 20 patients with biopsy-proven IgA nephropathy, persistent proteinuria (0.5–4.0 g/day), and mildly reduced renal function (serum Creatinine < 0.22 mmol/L); 12 patients had hypertension. There were 3 phases in the study, with washout of 4 weeks. (Level II evidence)

Both MDRD[3] and REIN[4] suggest that proteinuria is a significant independent predictor of CKD progression. Both report a strong association of greater baseline proteinuria with a more rapid decline in GFR. MDRD found that a reduction in proteinuria independent of BP was associated with a further decrease in the rate of decline in GFR, also degree of renoprotection achieved by lowering BP below the usual targets was dependent on the level of proteinuria. Proteinuria is an independent predictor of CV mortality in nondiabetic subjects.

Ramipril Efficacy in Nephropathy (REIN) study (*see above also*): Patients with baseline proteinuria (< 3 g/d) have a slower ($P = 0.001$) rate of decline in GFR compared with those with baseline proteinuria (> 3 g/d) [0.53 ± 0.08 vs 0.88 ± 0.13 mL/min/month]. The degree of ramipril-induced reduction in proteinuria correlated with GFR decline and not with the degree of renal impairment. In both strata, all variables of benefit (e.g. rate of decline of renal function) could be explained by decline in pro-

teinuria. Antihypertensive effect only explains part of the benefit. Ramipril was safe. The benefit of ramipril was greater with higher levels of proteinuria. (Level II evidence)

MDRD Study: In secondary analyses, reducing proteinuria was associated with lowering the rate of decline in renal function. (Level II evidence)

The beneficial effect of ACEIs on slowing progression of CKD is greater in those with higher baseline proteinuria (includes non-nephrotic and nephrotic syndromes) with questionable effect in those with minimal or no proteinuria (< 0.5g/d).[5]

The COOPERATE Trial: enrolled 366 patients with nondiabetic CKD in Japan.[5] A total of 263 patients were treated with losartan (100 mg/day), trandolapril (3 mg/day) or a combination of both drugs at equivalent doses and followed for a median of 2.9 years. Survival analysis of the endpoints of doubling of serum creatinine or end-stage kidney disease showed that combination treatment safely retards progression of non-diabetic renal disease compared with monotherapy. "The benefit of combination treatment in retardation of renal progression was shown not only for patients with a great rate of (*baseline*) urine protein excretion but also for those with a small amount of proteinuria." However, the greater the baseline proteinuria excretion, the more significant a reduction in proteinuria excretion after treatment was seen.[6] (Level II evidence)

The meta-analysis by Jafar *et al*.[7] showed a stronger beneficial effect of ACEIs in slowing progression when baseline proteinuria was > 0.5 g/day. The benefit was inconclusive below this level. (Level I evidence)

In the AASK study, proteinuria increased by 58% in the amlodipine group and declined by 20% in the ramipril group, during the first 6 months of the study. This difference persisted throughout the study and was significant ($P < 0.001$). In addition, even though patients with proteinuria >2.5 g/day were excluded, proteinuria was still a strong predictor of GFR decline. Ramipril did not significantly slow GFR decline in those patients without proteinuria.[8] (Level II evidence)

Ruggenenti *et al*.[9] examined 273 patients randomised to ramipril or conventional therapy. Short term changes in proteinuria and residual levels of proteinuria predicted long term disease progression. Thus any treatment that reduces proteinuria may have a possible long term benefit on progression. The suggested goal was to lower proteinuria to < 0.5 g/day. (Level II to Level III evidence)

SUMMARY OF THE EVIDENCE

Results from MDRD and REIN show that CKD progression is associated with higher baseline proteinuria. In nondiabetic patients, proteinuria is an independent predictor of cardiovascular mortality. Data from meta-analyses of RCTs show that treatment regimens which include ACEIs are effective in slowing the progression of kidney disease, this effect being stronger in patients with more severe proteinuria. A proteinuria threshold of approximately 0.5 g/day was also suggested for the beneficial effect of AECIs in reducing progression of CKD. A greater antiproteinuric effect was seen with combined therapy of ACEI and ARB compared to either administered alone, however, there are limitations to the COOPERATE study. It is unclear whether ACEI or ARB at maximal doses are the same, or less efficacious than combined therapy. Evidence from RCTs suggests that beta-blockers and ACEI-based regimens in non-diabetic kidney disease are more effective in slowing progression of disease.

WHAT DO THE OTHER GUIDELINES SAY?

Kidney Disease Outcomes Quality Initiative: See Guideline 11 of 'Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease.' ACEIs and ARBs can be used in combination to lower blood pressure or reduce proteinuria (C).[10]
UK Renal Association: No recommendation.
Canadian Society of Nephrology: No recommendation.
European Best Practice Guidelines: No recommendation.
International Guidelines:
VA Primary Care Guidelines: 'ACEI reduces proteinuria, an effect that may – in itself – be renoprotective. These agents reduce proteinuria at any given level of blood pressure reduction more than other antihypertensive drugs. Risks associated with use of these drugs include dangerous hyperkalemia and acute kidney failure when they are used in situations associated with decreased glomerular filtration pressure such as dehydration or kidney artery stenosis.[11] Careful monitoring of potassium levels and serum creatinine is warranted.
Consensus statement ISN 2004: Workshop on Prevention of Progressive Renal Disease. Hong Kong, June 29, 2004. Suggested use ACEI and/or ARB to reduce proteinuria. The optimal dose was not determined. The role of combined therapy was still uncertain due to insufficient data.[12]

IMPLEMENTATION AND AUDIT

No recommendation.

SUGGESTIONS FOR FUTURE RESEARCH

More studies on the combination of ARB and ACEI are required to confirm the benefits in slowing progression.

REFERENCES

1. Russo D, Pisani A, Balletta MM *et al*. Additive antiproteinuric effect of converting enzyme inhibitor and losartan in normotensive patients with IgA nephropathy. *Am. J. Kidney Dis* 1999; **33**: 851–6.
2. Perico N, Remuzzi A, Sangalli F *et al*. The antiproteinuric effect of angiotensin antagonism in human IgA nephropathy is potentiated by indomethacin. *J. Am. Soc. Nephrol*. 1998; **9**: 2308–17.
3. MDRD Study Group. Effects of diet and antihypertensive therapy on creatinine clearance and serum creatinine concentration in the Modification of Diet in Renal Disease Study. *J. Am. Soc. Nephrol*. 1996; **7**: 556–66.

4. Remuzzi G, Chiurchiu C, Ruggenenti P. Proteinuria predicting outcome in renal disease: nondiabetic nephropathies (REIN). *Kidney Int. Suppl.* 2004; **92**: S90–S96.
5. Marcantoni C, Jafar TH, Oldrizzi L *et al*. The role of systemic hypertension in the progression of nondiabetic renal disease. *Kidney Int. Suppl.* 2000; **75**: S44–S48.
6. Nakao N, Yoshimura A, Morita H *et al*. Combination treatment of angiotensin-II receptor blocker and angiotensin-converting-enzyme inhibitor in non-diabetic renal disease (COOPERATE): a randomised controlled trial. *Lancet* 2003; **361**: 117–24.
7. Jafar TH, Schmid CH, Landa M *et al*. Angiotensin-converting enzyme inhibitors and progression of nondiabetic renal disease. A meta-analysis of patient-level data. *Ann. Intern. Med.* 2001; **135**: 73–87.
8. Agodoa LY, Appel L, Bakris GL *et al*. Effect of ramipril vs amlodipine on renal outcomes in hypertensive nephrosclerosis: a randomised controlled trial. *JAMA* 2001; **285**: 2719–28.
9. Ruggenenti P, Perna A, Loriga G *et al*. Blood pressure control for renoprotection in patients with non-diabetic chronic renal disease (REIN-2): multicentre, randomised controlled trial. *Lancet* 2005; **365**: 939–46.
10. National Kidney Foundation. K/DOQI Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease. Guideline 11. Use of Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers in Chronic Kidney Disease. Available from: http://www.kidney-org/Professionals/Kdoqi/Guidelines_Bp/guide_11.htm/.
11. Wynckel A, Ebikili B, Melin JP *et al*. Long-term follow-up of acute renal failure caused by angiotensin converting enzyme inhibitors. *Am. J. Hypertens* 1998; **11**: 1080–6.
12. ISN. Consensus Statements ISN 2004 – Workshop on Prevention of Progressive Renal Disease. Hong Kong; June 29, 2004. *Kidney Int* 2005; **67** (Suppl 94): S2–S27.

APPENDICES

Table 1 Characteristics of included studies

Study ID (author, year)	N	Study design	Setting	Participants	Intervention (experimental group)	Intervention (control group)	Follow up (years)	Comments
Agodoa *et al*, 2001	1094	Randomised controlled clinical trial	Multicentre, US	1094 African-Americans with hypertensive renal disease	Ramipril	Amlodipine	3	3 × 2 factorial trial with third intervention metoprolol, with other agents to achieve 1 of 2 BP goals
Nakao *et al*, 2003	336	Randomised controlled clinical trial	1 renal department, Japan	336 patients with non-diabetic renal disease	Angiotensin-II receptor blocker, Iosartan 100 mg/d	Angiotensin-converting-enzyme inhibitor, trandolapril 3 mg/d	3	3-arm trial with a third arm receiving combination of both drugs at equivalent doses
Perico *et al*, 1998	20	Randomised controlled clinical trial	1 outpatient clinic, Italy	20 patients with IgA glomerulo-nephritis	Enalapril 20 mg/d	Irbesartan 100 mg/d	1 mo	Study also evaluated addition of indomethacin 75 mg 2 × /d
Ruggenenti *et al*, 2005	338	Randomised controlled clinical trial	Multicentre, Italy	Patients with non-diabetic nephropathy and persistent proteinuria	Intensified blood-pressure control, dihydropyridine calcium-channel blocker, felodipine (5–10 mg/d)	Conventional blood pressure control	3	

Table 2 Quality of randomised trials

Study ID (author, year)	Method of allocation concealment	Blinding			Intention-to-treat analysis	Loss to follow up (%)
		(participants)	(investigators)	(outcome assessors)		
Agodoa *et al*, 2001	Central	Yes	Yes	Yes	Yes	
Nakao *et al*, 2003	Permuted blocks of 6, independent, computer-generated	Yes	Yes	Yes	Yes	2.1
Perico *et al*, 1998	Not specified	Yes	Yes	Yes	Yes	0.0
Ruggenenti *et al*, 2005	Central	No	No	No	Yes	38.2

Table 3 Results for continuous outcomes

Study ID (author, year)	Outcomes	Intervention group (mean [SD])	Control group (mean [SD])	Difference in means [95% CI]
Agodoa *et al*, 2001	Acute phase: mean total decline in GFR to 3 yrs (mL/min/1.73 m^2/yr); UP/Cr ≤ 0.22	–1.02 (5.22) Ramipril	0.20 (2.95) Amlodipine	–1.22 (95%CI: –1.85, –0.59)
	Acute phase: mean total decline in GFR to 3 yrs (mL/min/1.73 m^2/yr); UP/Cr > 0.22	–3.60 (7.10) Ramipril	–5.62 (9.58) Amlodipine	2.02 (95%CI: 0.58, 3.46)
	Chronic phase: mean GFR decline (mL/min per 1.73 m^2/yr); UP/Cr > 0.22	3.55 (8.56) Ramipril	5.92 (10.16) Amlodipine	–2.37 (95%CI: –3.94, –0.80)
	Chronic phase: mean GFR decline (mL/min/1.73 m^2/yr); UP/Cr ≤ 0.22	1.22 (5.22) Ramipril	2.02 (5.60) Amlodipine	–0.80 (95%CI: –1.69, 0.09)
Nakao *et al*, 2003	Decrease in mean systolic pressure from baseline (mmHg)	5.1 (1.6) Losartan	5.2 (1.3)	–0.10 (95%CI: –0.53, 0.33)
	Decrease in mean systolic pressure from baseline (mmHg)	5.3 (1.4) Combination	5.2 (1.3)	0.10 (95%CI: 0.30, 0.50)
	Decrease in mean diastolic pressure (mmHg)	2.9 (0.9) Losartan	2.9 (0.8)	0.00 (95%CI: –0.25, 0.25)
	Decrease in mean diastolic pressure (mmHg)	3.0 (0.7) Combination	2.9 (0.8)	0.10 (95%CI: –0.12, 0.32)
Perico *et al*, 1998	Systolic BP at end of study, trough value	133 (9)	149 (14)	–16.00 (95%CI: –26.58, –5.42)
	Systolic BP at end of study with indomethacin, trough value	132 (11)	149 (13)	–17.00 (95%CI: –27.70, –6.30)
	Diastolic BP at end of study, trough value	77 (10)	91 (7)	–14.00 (95%CI: –21.47, –6.53)
	Diastolic BP at end of study with indomethacin, trough value	80 (12)	89 (8)	–9.00 (95%CI: –17.81, –0.19)
	Urinary protein excretion rate at end of study (g/24 h)	0.72 (0.39)	1.54 (1.46)	–0.82 (95%CI: –1.80, 0.16)
	Urinary protein excretion rate at end of study (g/24 h) with indomethacin	0.29 (0.13)	0.57 (0.43)	–0.28 (95%CI: –0.57, 0.01)
	GFR (mL/min/1.73 m^2) at end of study	65 (25)	55 (11)	10.00 (95%CI: –6.43, 26.43)
	GFR (mL/min/1.73 m^2) at end of study with indomethacin	67 (25)	54 (11)	13.00 (95%CI: –3.43, 29.43)
Ruggenenti *et al*, 2005	Mean systolic blood pressure throughout follow up (mmHg)	129.6 (10.9)	133.7 (12.6)	–4.10 (95%CI: –6.62, –1.58)
	Mean diastolic blood pressure throughout follow up (mmHg)	79.5 (5.3)	82.3 (7.1)	–2.80 (95%CI: –4.14, –1.46)

Table 4 Results for dichotomous outcomes

Study ID (author, year)	Outcomes	Intervention group (number of patients with events/number of patients exposed)	Control group (number of patients with events/number of patients not exposed)	Relative risk (RR) [95% CI]	Risk difference (RD) [95% CI]
Agodoa *et al*, 2001	Mortality	18/436 (Ramipril)	13/217 (Amlodipine)	0.69 (95%CI: 0.34, 1.38)	–0.02 (95%CI: –0.06, 0.02)
Nakao *et al*, 2003	Primary endpoint	20/86 (Losartan)	20/85	0.99 (95%CI: 0.57, 1.70)	0.00 (95%CI: –0.13, 0.12)
		10/85 (Combination)	20/85	0.50 (95%CI: 0.25, 1.00)	–0.12 (95%CI: –0.23, 0.00)
	Mortality	1/89 (Losartan)	0/86	2.90 (95%CI: 0.12, 70.23)	0.01 (95%CI: –0.02, 0.04)
		0/88 (Combination)	0/86	Not estimable	0.00 (95%CI: –0.02, 0.02)
	Non-fatal stroke	0/89 (Losartan)	1/86	0.32 (95%CI: 0.01, 7.80)	–0.01 (95%CI: –0.04, 0.02)
		1/88 (Combination)	1/86	0.98 (95%CI: 0.06, 15.38)	0.00 (95%CI: –0.03, 0.03)
	Non-fatal angina	1/89 (Losartan)	1/86	0.97 (95%CI: 0.06, 15.21)	0.00 (95%CI: –0.03, 0.03)
		1/88 (Combination)	1/86	0.98 (95%CI: 0.06, 15.38)	0.00 (95%CI: –0.03, 0.03)
	Myocardial infarction	1/89 (Losartan)	0/86	2.90 (95%CI: –0.02, 0.04)	0.01 (95%CI: –0.02, 0.04)
		0/88 (Combination)	0/86	Not estimable	0.00 (95%CI: –0.02, 0.02)
	Hypotension	0/89 (Losartan)	1/86	0.32 (95%CI: 0.01, 7.80)	–0.01 (95%CI: –0.04, 0.02)
		1/88 (Combination)	1/86	0.98 (95%CI: 0.06, 15.38)	0.00 (95%CI: –0.03, 0.03)
	Total adverse reactions	11/89 (Losartan)	19/86	0.56 (95%CI: 0.28, 1.11)	–0.10 (95%CI: –0.21, 0.01)
		18/88 (Combination)	19/86	0.93 (95%CI: 0.52, 1.64)	–0.02 (95%CI: –0.14, 0.11)
Ruggenenti *et al*, 2005	Mortality	2/167	3/168	0.67 (95%CI: 0.11, 3.96)	–0.01 (95%CI: –0.03, 0.02)
	Progression to ESRD	38/167	64/168	0.60 (95%CI: 0.43, 0.84)	–0.15 (95%CI: –0.25, –0.06)
	Non-fatal serious adverse events	37/167	25/168	1.49 (95%CI: 0.94, 2.36)	0.07 (95%CI: –0.01, 0.16)

Antihypertensive therapy in diabetic nephropathy

Date written: September 2004
Final submission: September 2005
Author: Kathy Nicholls

GUIDELINES

a. Adequate control of blood pressure (BP) slows progression in diabetic nephropathy. (Level I evidence)

b. Goal blood pressures in diabetic nephropathy should be < 130/85 mmHg in patients over 50 years of age and <120/70–75 mmHg for those under 50 years.* (Level I evidence). Multiple antihypertensives are usually required to achieve target BP.

c. Protection against both nephropathy progression and cardiovascular events is provided by good BP control.

*The recommendation of target BP to vary with age is based on clinical caution in a population at risk of cerebrovascular disease, rather than any evidence for a J-curve effect in the diabetic population.

SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on Level III and IV sources)

- **Effective BP control is the single most important factor in limiting rate of progression of diabetic nephropathy.**
- **Most hypertensive diabetic patients will require treatment with two or more antihypertensives to achieve optimal BP control.**
- **The recommendation of target BP to vary with age is based on clinical caution in a population at risk of cerebrovascular disease, rather than any evidence for a J-curve effect in the diabetic population.**
- **Elderly patients with Type 2 diabetes commonly have high systolic blood pressure (SBP) and pulse pressure, but normal diastolic pressure. Therapy in this group needs to target SBP.**

BACKGROUND

Hypertension is the major accelerant of progressive kidney failure in diabetic nephropathy. This section reviews the large body of evidence demonstrating that BP control slows progression, and discusses target BP goals.

SEARCH STRATEGY

Databases searched: The Cochrane Renal Group Specialized Register was searched for randomised controlled trials (RCTs) relating to the prevention of progression of kidney disease in people with diabetes mellitus Type 1 and Type 2. Specific interventions included antihypertensive therapies, ACE inhibitors, A2 receptor antagonists, calcium channel blockers, dietary protein restriction and glucose control, and interventions to control hypercholesterolemia and hyperlipidemia.
Date of search: 16 December 2003.

WHAT IS THE EVIDENCE?

Adequate control of blood pressure slows progression in diabetic nephropathy

Multiple studies have been done over the past 25 years, but many were underpowered and short-term. Included here are major RCTs, meta-analyses, and long-term landmark cohort studies.

Type 1 diabetes mellitus

Kasiske *et al*[1] – this meta-analysis of 100 studies providing data on BP, renal function, and/or proteinuria before and after treatment with an antihypertensive agent, included 12 RCTs. Total patient number was 2494. Most studies were short-term, the study duration exceeded 6 months for only 27% of experimental groups, and exceeded 12 months in only 13%.

Studies included both Type 1 and Type 2 diabetics – 49% of groups were comprised solely of Type 1 patients, 32% solely of Type 2, 11% of groups were mixed, and in 9% type of diabetes was unspecified. While there are excellent reasons for separating Type 1 from Type 2 patients in studies, many studies done before 1995 failed to do so, but can no longer be ethically repeated. Both Type 1 and Type 2 patients benefit from BP control.

Thirty-five per cent of groups had clinical nephropathy, 17% had microalbuminuria, but stage of nephropathy was not clearly indicated for 39% of groups. Patients in 78% of groups were hypertensive. An angiotensin-converting enzyme inhibitor (ACEI) was investigated in 46% of experimental groups.

Also reported was a separate meta-analysis of the 11 included RCTs involving treatment with ACEI.

Blood pressure reduction in itself resulted in benefit in GFR preservation of 3.7 ± 0.92 mL/min/year for each 10 mmHg reduction in mean arterial pressure (MAP).

Specific ACEI effect was additional to this (see CARI 'ACE inhibitor treatment in diabetic nephropathy' guideline).

Deferrari *et al.*[2] performed a meta-analysis of 9 studies of proteinuric patients with overt nephropathy, and demonstrated a fourfold reduction in the decline of GFR when MAP < 100 mmHg.

Parving *et al*[3] – this was a prospective, self-controlled, 6-year cohort study of 29 Type 1 diabetics with proteinuria. Patients were followed before (for mean of 29 months, range 23–38 months) and after (for mean of 39 months, range 28–48 months) instigation of antihypertensive treatment with metoprolol, hydralazine and diuretic. BP fell from 144/97 mmHg to 128/84 mmHg. The rate of GFR decline decreased from 0.91 mL/min/month pre-treatment to 0.39 mL/min/month during treatment, and albumin excretion rate (AER) also fell. Crepaldi *et al*[4] randomised 92 normotensive Type 1 diabetics with microalbuminuria to lisinopril, nifedipine or placebo. Both antihypertensives effectively prevented progression to macroalbuminuria over 3 years. Ten patients discontinued the study before completion.

Patient Group	n	Number progressing to AER > 200 μg/min
Placebo	34	7
Lisinopril*	32	2
Nifedipine*	26	2

*$P < 0.02$

However, this study was not controlled for BP, which was significantly lower in the lisinopril group; AER increase was also less in the lisinopril group.

Type 2 diabetes mellitus

In the meta-analysis of Kasiske *et al*[1] discussed above, there was no difference in benefit of antihypertensive treatment between Type 1 and Type 2 diabetes*.

Studies of antihypertensive therapy in Type 2 diabetes show effective protection against the endpoints of proteinuria and/or loss of GFR. The most significant reductions in albuminuria occurred in studies with the largest BP reductions.[5,6] (see CARI 'Angiotensin II antagonists' guideline).

Bjorck[5] used an endpoint of loss of 40% of initial GFR to examine the effect of diastolic blood pressure (DBP) in 158 patients: those with DBP less than 86 mmHg had a 5-year incidence of nephropathy development of 20%, compared with 60% incidence if DBP was above 85 mmHg.

Biesenbach *et al*[7] documented more rapid decline in GFR in hypertensive Type 2 diabetes (SBP > 160 mmHg). This study followed a cohort of 16 Type 1 and 16 Type 2 diabetics with overt nephropathy, from near-normal renal function to end-stage kidney disease (ESKD), over 77 months (44–133 months). The mean rate of creatinine clearance decrease was 1.38 ± 0.40 mL/min/month in patients with SBP > 160 mmHg, and 0.78 ± 0.15 mL/min/month in patients with SBP < 160 mmHg.

The meta-analyses of Weidmann *et al*,[8,9] (see CARI 'ACE inhibitor treatment in diabetic nephropathy' guideline) further support the importance of adequate antihypertensive management for both Type 1 and Type 2 diabetics.

The United Kingdom Prospective Diabetes Study (UKPDS) provided strong evidence that control of BP can reduce the development of nephropathy.

Goal BP in antihypertensive treatment in diabetes

Evidence that lower BP provides better protection against cardiovascular endpoints aligns very well with protection against diabetic nephropathy. Actual BP targets are better defined for cardiovascular than for renal endpoints.

SUMMARY OF THE EVIDENCE

Bjorck[5] documented significantly fewer renal endpoints when DBP was < 85 mmHg.

The meta-analyses of Kasiske *et al*[1] and Weidmann *et al*[8] also support renal functional benefit from lower BP.

Lewis *et al*[10] in the extension of the captopril study of Type 1 diabetics, randomised participants to either intensive (MAP ≤ 92 mmHg) or standard (MAP 102–107 mmHg) antihypertensive treatment with ramipril and showed a better outcome (endpoints were proteinuria and GFR) in the intensively-treated group.

Schmitz *et al*[11] followed a cohort of 278 Type 2 diabetics for 6 years. Initially, 74% had normal AER, 19% had microalbuminuria and 7% had overt proteinuria. A total of 80 patients died over the time of follow-up; older age and higher albuminuria levels were risk factors for mortality. Multiple regression analysis identified SBP as a risk factor for increase in albuminuria. In a previous report of a subgroup of 24 normoalbuminuric and 13 microalbuminuric patients,[12] initial SBP was identified as a significant correlate of GFR fall rate over 3.4 years.

The Appropriate Blood Pressure Control in Diabetes (ABCD) study[13] randomised 470 hypertensive Type 2 diabetics to intensive (goal DBP < 75 mmHg, achieved BP 132/78) vs. standard BP control (goal DBP 80–89 mmHg, achieved BP 138/86), with second randomization to either enalapril or nifedipine. They followed incidence and progression of diabetic complications over 5.3 years. In both groups, patients with normo- or microalbuminuria stabilized their renal function, but those with overt nephropathy showed steady decline in GFR. The most important finding in this study was that mortality was significantly less in the intensively-treated group (5.5% vs. 10.7%, P = 0.037).

The data dovetails with evidence that cardiovascular endpoints in diabetic patients are reduced when diastolic BP is lower (e.g. the diabetic subgroup in the HOT Study had fewer CV events when DBP was reduced from 85 to 81 mmHg).

Bakris *et al*[14] performed multivariate analysis on data from the RENAAL Study[15] to document in Type 2 diabetics with nephropathy, that baseline SBP is a stronger predictor of renal outcomes than is DBP. Goal BP in this study was < 140/90 mmHg pre-dose. Patients with highest baseline pulse pressure had both the highest risk of progression and the greatest risk reduction when SBP was lowered below 140 mmHg. Losartan patients with baseline pulse pressure

> 90 mmHg had a 54% risk reduction of ESKD compared with placebo patients, over the 3.4 year mean follow-up.

In older non-diabetic patients with hypertension, a J-curve effect has been detected, i.e. excessive lowering of DBP increases risk of coronary events, presumably by decreasing coronary perfusion pressure.[16] To date, clinical trials in hypertensive diabetics have not detected a J-curve effect for BP reduction.

WHAT DO THE OTHER GUIDELINES SAY?

Kidney Disease Outcomes Quality Initiative[17]: Target BP in diabetic kidney disease should be < 130/80 mmHg. Preferred agents are ACE inhibitors or ARBs.
Canadian Diabetes Association (2003): <130/80 mmHg.
UK Renal Association: No recommendation.
European Best Practice Guidelines: No recommendation.
International Guidelines:

JNC VI (1997)[18]: Target blood pressure for diabetics with hypertension (and for any patient with renal impairment and hypertension) is 130/85 mmHg. In hypertensives with proteinuria > 1 g/day, recommend goal BP 125/75 mmHg.

JNC VII(2003)[16]: In patients with hypertension and diabetes or renal disease, BP goal is < 130/80 mmHg. Most patients will require 2 or more antihypertensive drugs to achieve goal BP. Lifestyle modifications recommended for all patients.

National Heart Lung & Blood Institute Working Party on Hypertension in Diabetes (1998): Goal BP 130/85 mmHg.

WHO-ISH (1999): Hypertensive diabetics – aim for < 130/85 mmHg.

American Diabetes Association (2004)[19]: Hypertensive adult diabetics – aim for SBP < 130 and DBP < 80 (B). Drug therapy in addition to lifestyle/behavioural modification is required if BP is 140/90 or above (A). Two or more drugs are usually required to achieve targets (B). Initial drug should be a drug class demonstrated to reduce CVD events in diabetes (ACEI, ARBs, β-blockers, diuretics, CCBs (A). If albuminuria is present, ACEI for Type1 and either ACEI or ARB for Type 2 are supported by evidence (A), acknowledging that there are no adequate head-to-head comparisons of ACEIs and ARBs.

Children – aim at or below age-adjusted 90th percentile levels.

In elderly hypertensive patients, blood pressure should be lowered gradually to avoid complications. (E)

NHF (1999): Hypertensive diabetics – aim < 130/85 mmHg.
Australian Diabetes Society Position Statement 1996[20]: aim < 130/85 mmHg.
Australian Diabetes Association (2001)[21]: Hypertensive diabetics with urinary protein above 1 g/day should aim for BP < 125/75 mmHg. Uncomplicated diabetics – aim < 130/85 mmHg.

Scottish Intercollegiate Guideline Network (2001): Target BP in all diabetics < 140/80 mmHg.

AACE (2000): <130/85 mmHg.

APEG (2005): Target BP < 95th centile for age, gender and height normative data.

IMPLEMENTATION AND AUDIT

No recommendation.

SUGGESTIONS FOR FUTURE RESEARCH

Optimal BP targets need to be refined for subgroups of patients, especially the elderly with isolated systolic hypertension and diabetes.

REFERENCES

1. Kasiske BL, Kalil RS, Ma JZ *et al*. Effect of antihypertensive therapy on the kidney in patients with diabetes; a meta-regression analysis. 1993; 118: 129–38.
2. Deferrari G, Ravera M, Beruti V *et al*. Optimizing therapy in the diabetic patient with renal disease: antihypertensive treatment. *J. Am. Soc. Nephrol*. 2004; **15** (Suppl. 1): S6–S11.
3. Parving HH, Andersen AR, Smidt UM *et al*. Early aggressive antihypertensive treatment reduces rate of decline in kidney function in diabetic nephropathy. *Lancet*. 1983; **1**: 1175–9.
4. Crepaldi G, Carta Q, Deferrari G *et al*. Effects of lisinopril and nifedipine on the progression to overt albuminuria in IDDM patients with incipient nephropathy and normal blood pressure. The Italian Microalbuminuria Study Group in IDDM. *Diabetes Care*. 1998; **21**: 104–10.
5. Bjorck S. Clinical trials in overt diabetic nephropathy. In: Mogensen CE, ed. *The Kidney and Hypertension in Diabetes Mellitus*. London: Kluwer Academic Publishers, 1997.
6. Ferder L, Daccordi H, Martello M *et al*. Angiotensin converting enzyme inhibitors versus calcium antagonists in the treatment of diabetic hypertensive patients. *Hypertension* 1992; **19** (Suppl. 2): S237–S242.
7. Biesenbach G, Janko O, Zazgornik J. Similar rate of progression in the predialysis phase in Type 1 and Type 2 diabetes mellitus. *Nephrol. Dial Transplant*. 1994; **9**: 1097–102.
8. Weidmann P, Boehlen LM, De Courten M. Effects of different antihypertensive drugs on human diabetic proteinuria. *Nephrol. Dial Transplant*. 1993; **8**: 582–4.
9. Weidmann P, Schneider M, Bohlen L. Therapeutic efficiency of different antihypertensive drugs in human diabetic nephropathy: an updated meta-analysis. *Nephrol. Dial Transpl*. 1995; **10** (Suppl. 9): S39–S45.
10. Lewis JB, Berl T, Bain RP *et al*. Effect of intensive blood pressure control on the course of type 1 diabetic nephropathy. Collaborative Study Group. *Am. J. Kidney Dis*. 1999; **34**: 809–17.
11. Schmitz A, Vaeth M, Mogensen CE. Systoloic blood pressure relates to the rate of progression of albuminuria in NIDDM. *Diabetologia*. 1994; **37**: 1251–8.
12. Nielsen S, Schmitz A, Rehling M *et al*. Systolic blood pressure relates to the rate of decline of glomerular filtration rate in Type 2 diabetes. *Diabetes Care* 1993; **16**: 1427–32.
13. Estacio RO, Jeffers BW, Gifford N *et al*. Effect of blood pressure control on diabetic microvascular complications in patients with

hypertension and type 2 diabetes. *Diabetes Care*. 2000; **23** (Suppl. 2): B54–B64.
14. Bakris GL, Weir MR, Shanifar S *et al*. RENAAL Study Group. Effects of blood pressure level on progression of diabetic nephropathy: results from the RENAAL study. *Arch. Intern. Med*. 2003; **163**: 1555–65.
15. Brenner BM, Cooper ME, de Zeeuw D *et al*. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl. J. Med*. 2001; **345**: 861–9.
16. Chobanian AV, Bakris GL, Black HR *et al*. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA* 2003; **289**: 2560–72.
17. National Kidney Foundation. K/DOQI Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification, and Stratification. *Am. J. Kidney Dis*. 2002; **39** (2 Suppl. 1): SI–S266.
18. JNC VI. The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure. *Arch. Intern. Med*. 1997; **157**: 2413–46.
19. American Diabetes Association. Standards of Medical Care in Diabetes. *Diabetes Care*. 2004; **27** (Suppl. 1): S15–S35.
20. Australian Paediatric Endocrinology Group 2005 Sydney. Available from: http://www.chw.edu.au/prof/services/endocrinology/apeg/apeg_handbook_final.pdf.
21. Gilbert RE, Jasik M, DeLuise M *et al*. Diabetes and hypertension. Australian Diabetes Society position statement. *Med. J. Aust*. 1995; **163**: 372–5.

APPENDICES

Table 1 Characteristics of included studies

Study ID (author, year)	N	Study Design	Setting	Participants	Intervention (experimental group)	Intervention (control group)	Follow up	Comments
Bakris *et al*, 2003	1513	Randomised controlled clinical trial	Multicentre	1531 patients with NIDDM	Losartan potassium	Placebo	3.4 yrs	
Crepaldi *et al*, 1998	137	Randomised controlled clinical trial	14 hospital-based and diabetes outpatient centres	92 normotensive IDDM patients	Lisinopril	Placebo	3 yrs	With third arm intervention of slow release nifedipine
Estacio *et al*, 2000	470	Randomised controlled clinical trial	Identified from health care systems in Denver, US	470 hypertensive patients	Intensive blood pressure control (75 mmHg)	Moderate blood pressure control (80–90 mmHg)	5.3 yrs	
Ferder *et al*, 1992	30	Randomised controlled clinical trial	Hospital	30 Type 2 diabetic patients with proteinuria	Enalapril	Nifedipine	12 months	
Lewis *et al*, 1999	129	Randomised controlled clinical trial	17 centres of the Collaborative Study Group	129 Type 1 diabetes mellitus patients	≤ 94 mmHg	100–107 mmHg	2 yrs	

NIDDM, non-insulin dependent diabetes mellitus; IDDM, insulin-dependent diabetes mellitus.

Table 2 Quality of randomised trials

Study ID (author, year)	Method of allocation concealment	Blinding			Intention-to-treat analysis	Loss to follow up (%)
		(participants)	(investigators)	(outcome assessors)		
Bakris *et al*, 2003	Not specified	Yes	Yes	Unclear	Yes	Unclear
Crepaldi *et al*, 1998	Balanced blocks	Yes	Yes	Unclear	No	10.9
Estacio *et al*, 2000	Not specified	No	No	Yes	Unclear	39.4
Ferder *et al*, 1992	Not specifed	Yes	Yes	Unclear	Unclear	0.0
Lewis *et al*, 1999	Standard urn design	No	No	Unclear	Yes	28.7

Table 3 Results for dichotomous outcomes

Study ID (author, year)	Outcomes	Intervention group (number of patients with events/number of patients exposed)	Control group (number of patients with events/number of patients not exposed)	Relative risk (RR) [95% CI]	Risk difference (RD) [95% CI]
Crepaldi *et al*, 1998	Albuminuria (lisinopril))	2/32	7/34	0.30 (95%CI: 0.07, 1.35)	–0.14 (95%CI: –0.30, 0.02
	Albuminuria (nifedipine)	2/26	7/34	0.37 (95%CI: 0.08, 1.65)	–0.13 (95%CI: –0.30, 0.04)
Estacio *et al*, 2000	Retinopathy ≥ 3 steps	45/151	45/134	0.89 (95%CI: 0.63, 1.25)	–0.04 (95%CI: –0.15, 0.07)
	Neuropathy	60/151	42/134	1.27 (95%CI: 0.92, 1.74)	0.08 (95%CI: –0.03, 0.19)
Lewis *et al*, 1999	Remission of proteinuria	12/43	5/46	2.57 (95%CI: 0.99, 6.68)	0.17 (95%CI: 0.01, 0.33)
	Postural hypotension	11/63	4/66	2.88 (95%CI: 0.97, 8.58)	0.11 (95%CI: 0.00, 0.22)
	Oedema	4/63	10/66	0.42 (95%CI: 0.14, 1.27)	–0.09 (95%CI: –0.19, 0.02)
	Bronchitis	2/63	7/66	0.30 (95%CI: 0.06, 1.39)	–0.07 (95%CI: –0.16, 0.01)
	Sinusitis	3/63	3/66	1.05 (95%CI: 0.22, 5.00)	0.00 (95%CI: –0.07, 0.07)

Table 4 Results for continuous outcomes

Study ID (author, year)	Outcomes	Intervention group (mean [SD])	Control group (mean [SD])	Difference in means [95% CI]
Crepaldi *et al*, 1998	**Lisinopril treatment group:**			
	Serum creatinine at end of study (μmol/L)	77 (16)	95 (19)	–18.00 (95%CI: –26.46, –9.54)
	Creatinine clearances (mL/min/1.73m^2)	109 (19)	105 (15)	4.00 (95%CI: –4.29, 12.29)
	Serum potassium (mmol/L)	4.5 (0.4)	4.4 (0.4)	0.10 (95%CI: –0.09, 0.29)
	Albumin (g/dL)	4.3 (0.3)	44 (0.3)	–39.70 (95%CI: –39.84, –39.56)
	SBP (mmHg)	117 (11)	126 (12)	–9.00 (95%CI: –14.55, –3.45)
	DBP (mmHg)	73 (7)	76 (7)	–3.00 (95%CI: –6.38, 0.38)
	Nifedipine treatment group:			
	Serum creatinine at end of study (μmol/L)	86 (10)	95 (19)	–9.00 (95%CI: –15.97, –2.03)
	Creatinine clearances (mL/min/1.73m^2)	101 (15)	105 (15)	–4.00 (95%CI: –10.56, 2.56)
	Serum potassium (mmol/L)	4.4 (0.3)	4.4 (0.4)	0.00 (95%CI: –0.16, 0.16)

ACE inhibitor treatment in diabetic nephropathy

Date written: September 2004
Final submission: September 2005
Author: Kathy Nicholls

GUIDELINES

a. All patients with Type 1 or Type 2 diabetes mellitus complicated by microalbuminuria or overt nephropathy should be treated with an angiotensin-converting enzyme inhibitor (ACEI), independent of blood pressure and GFR. (Level I evidence, greater for Type 1 than Type 2). There is no evidence that any specific ACEI offers any advantage over the class effect.

b. Hypertensive diabetics without albuminuria should be treated with ACEI as first-line antihypertensive therapy. (Level I evidence)

c. There is currently insufficient evidence to recommend universal ACEI treatment for all diabetic patients with normal blood pressure (BP) and albumin excretion rate (AER).

SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on level III and IV sources)

- **A strong association between acute increases (up to 30%) in serum creatinine on initiation of ACEI treatment, stabilizing within the first 2 months of therapy, and long-term preservation of renal function is shown in the meta-analysis of Bakris and Weir.[1] ACEI therapy should be withdrawn only if creatinine increases > 30% above baseline within the first 2 months of therapy.**
- **Use of ACE inhibitors may exacerbate hyperkalaemia in patients with kidney failure and/or hyporeninaemic hypoaldosteronism.**

BACKGROUND

Type 2 diabetes with its increased vascular risks is expected to affect 370 million people by 2030 (http://www.who.int/diabetes/en/). The onset of nephropathy trebles the risks of fatal vascular events. Renin-angiotensin system blockade is known to be vasculoprotective in diabetes.

This section reviews the evidence that ACEI in diabetes protects against the onset and progression of diabetic nephropathy.

SEARCH STRATEGY

Databases searched: The Cochrane Renal Group Specialised Register was searched for randomised controlled trials (RCTs) relating to the prevention of progression of kidney disease in people with diabetes mellitus Type 1 and Type 2. Specific interventions included antihypertensive therapies, ACE inhibitors, A2 receptor antagonists, calcium channel blockers, dietary protein restriction and glucose control, and interventions to control hypercholesterolemia and hyperlipidemia.
Date of search: 16 December 2003.

WHAT IS THE EVIDENCE?

ACEI in overt diabetic nephropathy

Type 1 diabetes
Lewis *et al*[2] provided the first RCT evidence that ACEI delays progression of kidney failure in overt diabetic nephropathy. This RCT studied captopril vs. placebo in 409 Type 1 diabetics with overt proteinuria (> 0.5 g/day) and BP < 140/90 mmHg. Endpoints were doubling of serum creatinine and end-stage kidney disease (ESKD)/death.

Further follow-up of the nephrotic subgroup (n = 108) of the total 409 patients randomised to captopril revealed long-term remission of nephrotic syndrome in 8 patients.[3]

Weidmann *et al*[4,5] performed two meta-analyses, including 93 studies in the 1993 analysis, and added a further 11 studies for the updated analysis. Both Type 1 and Type 2 diabetic studies were included, and findings were similar for both groups. In overt nephropathy, GFR was better preserved in ACEI-treated patients than in those treated with beta-blockers, diuretics or nifedipine.

Type 2 diabetes
Evidence in Type 2 diabetic patients with overt nephropathy has taken longer to emerge.

Two studies[6,7] in Type 2 diabetes with overt nephropathy concluded that ACEI may not affect GFR reduction rate beyond their antihypertensive effect. However, subsequent evidence (including the meta-analysis of Weidmann *et al.*[5]) documented that in overt nephropathy in both Type 1 and Type 2 diabetics, GFR was better preserved in ACEI-treated patients than in those treated with beta-blockers, diuretics or nifedipine.

Ferder *et al*[8] randomised 30 Type 2 diabetics with overt nephropathy to either enalapril (40 mg/day) or nifedipine (40 mg/day) for 12 months. Mean arterial pressure (MAP) in the two groups was equivalent, but urine protein dropped significantly only in the ACEI group (4.4–0.56 g/day) and creatinine clearance decreased only in the nifedipine group.

ACEI in microalbuminuria

Meta-analyses (predominantly Type 1)
Type 1 and Type 2 diabetes with microalbuminuria
The meta-analysis of Kasiske *et al*,[9] (see CARI 'Antihypertensive therapy in diabetic nephropathy' guideline), showed ACEI to be better both at decreasing AER and in preserving GFR, in microalbuminuric diabetic patients, than were β-blockers and/or calcium channel blocker. Reducing blood pressure reduced proteinuria, but ACEI produced significant further reduction beyond their antihypertensive effect.

Analysis quantified GFR preservation to be 3.7 ± 0.92 mL/min for each 10 mmHg reduction in MAP, plus a specific ACEI effect of 3.4 ± 1.7 mL/min.

In the meta-analyses of Weidmann *et al*[4,5] (discussed above) initially normotensive, microalbuminuric diabetics who received ACEI showed a fall in AER greater than that in non-ACE inhibitor- or placebo- treated patients.

Type 2 diabetes with hypertension and microalbuminuria
Agardh *et al*[10] studied 300 hypertensive Type 2 diabetics with microalbuminuria in a double-blind, parallel group, multicentre RCT of lisinopril (10–20 mg daily) vs. nifedipine (40–80 mg/day), with target diastolic blood pressure (DBP) < 90 mmHg at the time of trough drug level. Lisinopril but not equipotent-for-BP doses of nifedipine reduced AER over the 12-month study (AER fell from 65 to 39 μg/min in the ACEI group, and from 63 to 58 μg/min in the nifedipine group). Creatinine clearance did not change in either group.

Lebovitz *et al*[11] studied renal function in 121 hypertensive Type 2 diabetics with microalbuminuria over 36 months following randomisation either to an antihypertensive regimen including enalapril or to 'conventional' (non-ACEI) antihypertensives. ACEI specifically prevented progression to overt proteinuria (7% vs. 21% progressing) and prevented fall in GFR.

In a small, longitudinal, parallel group study of 13 hypertensive Type 2 diabetics with biopsy-proven nephropathy and mild-moderate hypertension, Mosconi *et al*[12] randomised patients to either enalapril or nifedipine. Both antihypertensives produced comparable reduction in BP and in AER, and GFR increased in both groups at 15 and 27 months.

Retrospective analysis of annual serum creatinine levels from the diabetic subset within the HOPE study[13] (Microalbuminuria and Renal Outcomes in the Heart Outcomes and Prevention Evaluation study) compared ramipril with placebo over 4.5 years in 3577 diabetics, including 1139 with microalbuminuria and 333 with renal insufficiency. Participants with dipstick-positive proteinuria (> 1 +) or serum creatinine > 0.2 mmol/L were excluded. Serum creatinine levels did not increase significantly during the study in the overall group, or in the microalbuminuric or renal insufficiency subgroups. There were no differences between serum creatinine in the placebo and ramipril-treated groups. However, ramipril decreased the risk of overt nephropathy by 24% (95% CI: 3–40, P = 0.027), even after adjustment for the small (2.4/1.0 mmHg) difference in BP (25%, 95% CI: 12–36, P = 0.0004).

The smaller study of Chan *et al*[14] confirmed the efficacy of ACEIs compared with other drugs in the hypertensive, microalbuminuric, Type 2 diabetic patient group (RRR 23%–68% for progression to overt proteinuria).

In hypertensive microalbuminuric Type 2 diabetics ACE inhibitors diminish AER, or at least prevent an increase in AER. ACE inhibitors progressively lose their antiproteinuric advantage over other antihypertensives as blood pressure control increases. However, there remains a specific advantage for ACEI.

Type 1 diabetes with normotension and microalbuminuria
The studies of Marre *et al*,[15] Bilo *et al*,[16] Chase *et al*,[17] Hallab *et al*,[18] Mathieson *et al*,[19] Viberti *et al*[20] and Parving *et al*[21] are included in the Cochrane Group meta-analysis of Lovell[22] asking the question 'Are ACEI useful for normotensive diabetic patients with microalbuminuria?'. This analysis concluded that ACEI decrease AER in both Type 1 and Type 2 diabetes, but that evidence for a direct link to postponement of ESKD requires further evidence and longer follow-up.

Laffel *et al*[23] reported on a double-blind, placebo-controlled RCT of captopril (50 mg b.d.) in 26 North American centres, of 143 normotensive microalbuminuric patients with Type 1 diabetes. Within 24 months, 6% of captopril-treated subjects and 19% of placebo-treated subjects progressed to clinical proteinuria (RRR = 67.8%, P = 0.037). AER increased at an annual rate of 11.8% (95% CI: −3.3% to 29.1%) in the placebo group, while it declined by 17.9% (95% CI: −29.6% to −4.3%) in the captopril group (P = 0.004). Creatinine clearance decreased by 4.9 mL/min per 1.73 m^2 per year in the placebo group, but remained stable in the captopril group (0.9 mL/min per 1.73 m^2 per year, P = 0.039 between groups). Ten subjects required treatment for hypertension; 8 in the placebo group and 2 in the captopril group. There was little correlation between the 24-month changes in mean arterial blood pressure and AER in either group. Glycohemoglobin and urinary urea excretion did not differ between groups.

Jerums *et al*[24] prospectively randomised 42 normotensive microalbuminuric Type 1 diabetics to perindopril 2–8 mg/day, nifedipine 20–80 mg/day or placebo, and followed 33 patients for at least 24 (mean = 67) months. AER decreased, and GFR was stable in the perindopril group, while AER increased and GFR fell in the nifedipine group, despite no statistical difference in BP.

Type 2 diabetes with normotension and microalbuminuria
Ravid *et al*[25] studied 94 normotensive microalbuminuric Type 2 diabetics, and followed them over 7 years. Enalapril at 10 mg/day protected against rise in AER (AER increased in the placebo group by 41% per year, but remained stable in the enalapril group), protected against an increase in serum creatinine (Cr increased by 3.3% per year in the placebo group but was stable in the enalapril group), and protected against progression to macroalbuminuria (seen in 18% of enalapril patients vs. 60% of placebo patients).

Ravid *et al*[26] extended the above to show that ACEI slowed renal functional decline in Type 2 diabetes.

Trevison and Tiengo[27] documented a decrease in AER with ACEI in normotensive Type 2 diabetes with microalbuminuria.

Ahmad *et al*[28] enrolled 103 normotensive Type 2 diabetics with microalbuminuria, treated them with enalapril or placebo, and followed them for 5 years. AER decreased in the enalapril group (55–20 microg/min), increased in the placebo group (53–85 microg/min) and progressed to overt proteinuria in 7.7% of enalapril- and 23.5% of placebo-treated patients.

Included in the meta-analysis of Lovell *et al*[22] for the Cochrane Diabetes Group, as well as the Type 1 studies as discussed above, were the following studies in Type 2 diabetics – Marre *et al*,[15] Ravid *et al*,[29] Sano *et al*,[30] and Stornello *et al*.[31] Again, there is strong evidence that ACEIs decrease AER in Type 2 as well as Type 1 diabetes, but an extrapolation to postponement of ESKD requires further follow-up.

ACEI in normoalbuminuria

Recent evidence verifies earlier suggestions that ACE inhibition may prevent the onset of microalbuminuria. Some studies have included only hypertensive patients, some only normotensives, and some are mixed.

Type 1 diabetes with normotension and normoalbuminuria

The EUCLID Study[32] followed 530 normotensive Type 1 diabetics with normal urine or microalbuminuria, and documented decrease of AER on lisinopril.

Type 2 diabetes with hypertension or normotension and normoalbuminuria

Lacourciere *et al*[33] studied hypertensive Type 2 diabetics without albuminuria, documenting that captopril protected against development of microalbuminuria, but did not provide long-term renal functional data.

Ravid *et al*[34] reported a RCT of 156 Type 2 diabetics with normal BP and albumin excretion, randomised to enalapril 10 mg or placebo, and followed for a mean of 6 years. This study documented protection from microalbuminuria onset and minor GFR protection, although function was normal in both groups. Follow-up in this group needs to be longer.

The Benedict trial[35] studied 1204 hypertensive (defined as BP > 130/80 mmHg or on antihypertensive therapy) Type 2 diabetics without albuminuria, to assess whether ACEIs and non-dihydropyridine calcium channel blockers, alone or in combination, prevent microalbuminuria in subjects with hypertension, Type 2 diabetes mellitus, and normal urinary albumin excretion. Patients were randomised to trandalopril 2 mg (T), trandalopril 2 mg plus verapamil 180 SR (T + V), verapamil alone 240 SR (V) or placebo (P) for 3 years. The primary endpoint was the development of persistent microalbuminuria (≥ 20 μg/min at 2 consecutive visits), and target BP was 120/80 mmHg, achieved if required via prescribed stepwise addition of drugs without RAS blockade action or non-dihydropyridine calcium channel blockers. Progression to microalbuminuria occurred in 12% of Group V, and 10% of placebo patients (NS), and in 6% of each of the T alone and T + V groups (P = 0.01, T + V vs. P). Serious adverse events were comparable in all groups. Comparable numbers of patients in each group were on statin therapy.

SUMMARY OF THE EVIDENCE

A large body of Level 1 evidence, larger for Type 1 than Type 2 diabetes, supports the recommendations to treat all diabetic patients with microalbuminuria or overt nephropathy with ACEI. There is no evidence that any specific ACEI offers any advantage over the class effect.

Hypertensive diabetics without albuminuria should be treated with ACEI as first-line antihypertensive therapy (Level I evidence), and one RCT in Type 2 diabetes documents protection against development of microalbuminuria in this group.

There is currently insufficient evidence to recommend universal ACEI treatment for all diabetic patients with normal BP and AER.

There is a gap in the clinical trial evidence between decreasing AER and preventing progression to ESKD.

WHAT DO THE OTHER GUIDELINES SAY?

Kidney Disease Outcomes Quality Initiative: Patients with diabetic kidney disease, with or without hypertension, should be treated with an ACE inhibitor or an ARB.[36]
UK Renal Association: No recommendation.
Canadian Society of Nephrology: No recommendation.
European Best Practice Guidelines: No recommendation.
International Guidelines:

JNCVII (2003): ACE inhibitors and ARBs have demonstrated favourable effects on the progression of diabetic kidney disease. An increase in serum creatinine ≤ 35% above is acceptable and not a reason to withhold treatment unless hyperkalemia develops. If glomerular filtration rate < 30 mL/min per 1.73 m^2, increasing doses of loop diuretics are usually needed in combination with other drug classes.[37]

American Diabetic Association (2001): recommends ACEI as first-line antihypertensive agent in all hypertensive diabetic patients, and in normotensive diabetics with microalbuminuria.[38]

American Diabetes Association (2004): In hypertensive Type 1 diabetic patients with any degree of albuminuria, ACE inhibitors have been shown to delay the progression of nephropathy. (A)[39]

In hypertensive Type 2 diabetic patients with microalbuminuria, ACE inhibitors and ARBs have been shown to delay the progression to macroalbuminuria. (A)

If ACE inhibitors or ARBs are used, monitor serum potassium levels for the development of hyperkalemia. (B)

Canadian Diabetes Association (2003): In Type 1 diabetes and albuminuria, an ACE inhibitor should be given, to reduce urinary albumin and prevent progression of nephropathy (Grade A, Level 1 A).[40]

In people with Type 2 diabetes, albuminuria, and Ccr > 60 mL/min, an ACE inhibitor (Grade A, Level 1 A)

or an ARB (Grade A, Level 1 A) should be given, to reduce urinary albumin and prevent progression of nephropathy (Grade A, Level 1 A).

In people with Type 2 diabetes, albuminuria, and Ccr < 60 mL/min, an ARB (Grade A, Level 1 A) should be given, to reduce urinary albumin and prevent progression of nephropathy (Grade A, Level 1 A).

Patients placed on an ACE inhibitor or an ARB should have their Se, Sr and K levels checked within 2 weeks of initiation of therapy and periodically thereafter (Grade D, consensus).

SUGGESTIONS FOR FUTURE RESEARCH

Studies to determine optimal dosage of ACEI for protection against proteinuria progression and GFR reduction could be considered.

REFERENCES

1. Bakris GL, Weir MR. Angiotensin-converting enzyme inhibitor-associated elevations in serum creatinine: is this a cause for concern? *Arch. Intern. Med.* 2000; **160**: 685–93.
2. Lewis EJ, Hunsicker LG, Bain RP *et al.* for the Collaborative Study Group. The effect of angiotension-converting-enzyme inhibition on diabetic nephropathy. The Collaborative Study Group. *N Engl. J. Med.* 1993; **329**: 1456–62.
3. Wilmer WA, Hebert LA, Lewis EJ *et al.* Remission of nephrotic syndrome in type 1 diabetes: long-term follow-up of patients in the Captopril Study. *Am. J. Kidney Dis.* 1999; **34**: 308–14.
4. Weidmann P, Boehlen LM, De Courten M. Effects of different antihypertensive drugs on human diabetic proteinuria. *Nephrol. Dial Transplant.* 1993; **8**: 582–4.
5. Weidmann P, Schneider M, Bohlen L. Therapeutic efficacy of different antihypertensive drugs in human diabetic nephropathy: an updated meta-analysis. *Nephrol. Dial Transplant* 1995; **10** (Suppl. 9): 39–45.
6. Nielsen S, Nielsen FS, Rossing P *et al.* Long term effect of lisinopril compared with atenolol on kidney function in hypertensive NIDDM subjects with diabetic nephropathy. Diabetes. 1997; 46: 1182–8.
7. Parving HH, Rossing P. The use of anti-hypertensive agents in prevention and treatment of diabetic nephropathy. *Curr. Opin. Nephrol. Hypertens.* 1994; **3**: 292–300.
8. Ferder L, Daccordi H, Martello M *et al.* Angiotensin converting enzyme inhibitors versus calcium antagonists in the treatment of diabetic hypertensive patients. *Hypertension* 1992; **19** (Suppl. 2): II237–II242.
9. Kasiske BL, Kalil RS, Ma J *et al.* Effect of antihypertensive therapy on the kidney in patients with diabetes: a meta-regression analysis. *Ann. Intern. Med.* 1993; **118**: 129–38.
10. Agardh CD, Garcia-Puig J, Charbonnel B *et al.* Greater reduction of urinary albumin excretion in hypertensive type 2 diabetic patients with incipient nephropathy by lisinopril than by nifedipine. *J. Hum Hypertens.* 1996; **10**: 185–92.
11. Lebovitz HE, Wiegmann TB, Cnaan A *et al.* Renal protective effects of enalapril in hypertensive NIDDM: role of baseline albuminuria. *Kidney Int. Suppl.* 1994; **45**: S150–S155.
12. Mosconi L, Ruggenenti P, Perna A *et al.* Nitrendipine and enalapril improve albuminuria and glomerular filtration rate in non-insulin dependent diabetes. *Kidney Int. Suppl.* 1996; **55**: S91–S93.
13. Mann JF, Gerstein HC, Yi QL *et al.* HOPE Investigators. Progression of renal insufficiency in type 2 diabetes with and without microalbuminuria: results of the Heart Outcomes and Prevention Evaluation (HOPE) randomized study. *Am. J. Kidney Dis* 2003; **42**: 936–42.
14. Chan JC, Ko GT, Leung DH *et al.* Long-term effects of angiotensin-converting enzyme inhibition and metabolic control in hypertensive type 2 diabetic patients. *Kidney Int.* 2000; **57**: 590–600.
15. Marre M, Chatellier G, Leblanc H *et al.* Prevention of diabetic nephropathy with enalapril in normotensive diabetics with microalbuminuria. *BMJ.* 1988; **297**: 1092–5.
16. Bilo H, Kluitman E, van Ballegooie E *et al.* Long term use of captopril or nifedipine in normotensive microalbuminuric patients with insulin-dependent diabetes mellitus. *Diabetes Res.* 1993; **23**: 115–22.
17. Chase HP, Garg SK, Harris S *et al.* Angiotensin-converting enzyme inhibitor treatment for young normotensive diabetic subjects: a two-year trial. *Ann. Ophthamol.* 1993; **25**: 284–9.
18. Hallab M, Gallois Y, Chatellier G *et al.* Comparison of reduction in microalbuminuria by enalapril and hydrochlorothiazide in normotensive patients with insulin dependent diabetes. *BMJ* 1993; **306**: 175–82.
19. Mathiesen ER, Hommel E, Giese J *et al.* Efficacy of captopril in postponing nephropathy in normotensive insulin dependent diabetics with microalbuminuria. *BMJ.* 1991; **303**: 81–7.
20. Viberti G, Mogensen CE, Groop LC *et al.* Effect of captopril on progression to clinical proteinuria in patients with insulin-dependent diabetes mellitus and microalbuminuria. European Microalbuminuria Captopril Study Group. *JAMA* 1994; **271**: 275–9.
21. Parving HH, Hommel E, Nielsen MD *et al.* Effect of captopril on blood pressure and kidney function in normotensive insulin dependent diabetics with nephropathy. *BMJ.* 1989; **299**: 533–6.
22. Lovell HG. Angiotensin converting enzyme inhibitors in normotensive diabetic patients with microalbuminuria. The Cochrane Database of Systematic Reviews. 1999, Issue 3. Art No.: CD002183. DOI: 10.1002/14651858.CD002183.pub2.
23. Laffel LM, McGill JB, Gans DJ. The beneficial effect of angiotensin-converting enzyme inhibition with captopril on diabetic nephropathy in normotensive IDDM patients with microalbuminuria. North American Microalbuminuria Study Group. *Am. J. Med.* 1995; **99**: 497–504.
24. Jerums G, Allen TJ, Campbell DJ *et al.* Long-term comparison between perindopril and nifedipine in normotensive patients with Type 1 diabetes and microalbuminuria. *Am. J. Kidney Dis.* 2001; **37**: 890–9.
25. Ravid M, Savin H, Jutrin I *et al.* Long-term stablizing effect of angiotensive-converting enzyme inhibition on plasma creatinine and on proteinuria in normotensive Type II diabetic patients. *Ann. Intern. Med.* 1993; **118**: 577–81.
26. Ravid M, Lang R, Rachmani R *et al.* Long-term renoprotective effect of angiotensin-converting enzyme inhibition in non-insulin dependent diabetes mellitus. A 7-year follow-up study. *Arch. Intern. Med.* 1996; **156**: 286–9.
27. Trevison R, Tiengo A. Effect of low dose ramipril on microalbuminuria in normotensive or mild hypertensive non-insulin dependent diabetic patients. *Am. J. Hypertens.* 1995; **8**: 876–83.
28. Ahmad J, Siddiqui MA, Ahmad H. Effective postponement of diabetic nephropathy with enalapril in normotensive Type 2 diabetic patients with microalbuminuria. *Diabetes Care* 1997; **20**: 1576–81.
29. Ravid M, Savin H, Jutrin I *et al.* Long term effect of ACE inhibition on development of nephropathy in diabetes mellitus type II. *Kidney Int. Suppl.* 1994; **45**: S161–S164.

30. Sano T, Hara T, Kawamura T *et al*. Effects of long-term enalapril treatment on persistent microalbuminuria in well-controlled hypertensive and normotensive NIDDM patients. *Diabetes Care* 1994; **17**: 420–4.
31. Stornello M, Valvo EV, Scapellato L. Angiotensin converting enzyme inhibition in normotensive Type II diabetics with persistent mild proteinuria. *J. Hypertens*. 1989; **7** (Suppl. 6): S314–S315.
32. The EUCLID Study Group. Randomised placebo-controlled trial of lisinopril in normotensive patients with insulin-dependent diabetes and normoalbuminuria or microalbuminuria. *Lancet* 1997; **349**: 1787–92.
33. Lacourciere Y, Nadeau A, Poirier L *et al*. Captopril or conventional therapy in hypertensive type II diabetics. Three-year analysis. *Hypertension* 1993; **21**: 786–94.
34. Ravid M, Brosh D, Levi Z *et al*. Use of enalapril to attenuate decline in renal function in normotensive, normoalbuminuric patients with type 2 diabetes mellitus. A randomized, controlled trial. *Ann. Intern. Med*. 1998; **128**: 982–8.
35. Ruggenenti P, Fassi A, Ilieva AP *et al*. Preventing microalbuminuria in type 2 diabetes. The Bergamo Nephrologic Diabetes Complications Trial (BENEDICT). *N Engl. J. Med*. 2004; **351**: 1941–51.
36. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am. J. Kidney Dis*. 2002; **39** (2 Suppl. 1): SI–S266.
37. Chobanian AV, Bakris GL, Black HR *et al*. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA* 2003; **289**: 2560–72.
38. Molitch ME, De Fronzo RA, Franz MJ *et al*. Diabetic nephropathy. *Diabetes Care* 2003; **26** (Suppl. 1): S94–S98.
39. American Diabetes Association. Standards of medical care in diabetes. *Diabetes Care* 2004; **27** (Suppl. 1): S15–S35.
40. Canadian Diabetes Association. 2003 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada. Available from: http://www.diabetes.ca/cpg2003/default.aspx/.

APPENDICES

Table 1 Characteristics of included studies

Study ID (author, year)	*N*	Study Design	Setting	Participants	Intervention (experimental group)	Intervention (control group)	Follow up (years)	Comments
Agardh *et al*, 1996	335	Randomised controlled clinical trial	Multicentre, multinational	314 Type 2 diabetic patients with microalbuminuria and early diabetic nephropathy	Lisinopril	Nifedipine	1	
Ahmad *et al*, 1997	120	Randomised controlled clinical trial	Outpatient clinic	103 non-obese normotensive patients with Type 2 diabetes	Enalapril	Placebo	5	
Bilo *et al*, 1993	24	Randomised controlled clinical trial	5 hospitals	24 normotensive IDDM patients with albuminuria	Captopril 50 mg	Placebo	1	Third arm intervention 20 mg nifedipine retard
Chan *et al*, 2000	102	Randomised controlled clinical trial	University hospital	102 hypertensive Type 2 diabetes patients	Enalapril	Nifedipine	5.5	
Chase *et al*, 1993		Randomised controlled clinical trial	University hospital	16 Type 1 diabetics with diabetic nephropathy and normal BP	Captopril bid	Placebo	2	
EUCLID 1997	530	Randomised controlled clinical trial	18 European centres	530 IDDM with normo- or micro-albuminuria	Lisinopril	Placebo	2	
Ferder *et al*, 1992	30	Randomised controlled clinical trial	Hospital	30 Type 2 diabetic patients with proteinuria	Enalapril	Nifedipine	1	
Hallab *et al*, 1993	25	Randomised controlled clinical trial	Diabetic clinic in a tertiary referral centre	21 diabetic patients with low/high albuminuria	Enalapril 20 mg	Hydrochlorothiazaide	1	
Jerums *et al*, 2001	42	Randomised controlled clinical trial	5 hospitals	42 normotensive patients with Type 1 diabetes and microalbuminuria	Perindopril	Placebo	2	Third arm intervention nifedipine
Laffel *et al*, 1995	143	Randomised controlled clinical trial	26 centres; US and Canada	143 normotensive patients with IDDM	Captopril 50 mg	Placebo	2	
Lebovitz *et al*, 1994	165	Randomised controlled clinical trial	Multicentre	121 NIDDM patients with hypertension	Enalapril	Placebo	3	

Lewis *et al*, 1993	409	Randomised controlled clinical trial	30 clinical centres	409 IDDM patients with urinary protein excretion ≥ 55 mg/d; serum Cr ≤ 2.5 mg/dL	Captopril	Placebo	3	
Mosconi *et al*, 1996	13	Randomised controlled clinical trial	Hospital, Italy	13 microalbuminuric NIDDM patients with mild hypertension and diabetic glomerulopathy	Nitrendipine	Enalapril	2.25	
Mathiesen *et al*, 1991	44	Randomised controlled clinical trial	Outpatient clinic	44 normotensive IDDM patients with persistent microalbuminuria	Captopril	No treatment	4	
Nielsen *et al*, 1997	43	Randomised controlled clinical trial	Hospital	36 hypertensive NIDDM patients with diabetic nephropathy	Lisinopril	Atenolol	3.5	
Ravid *et al*, 1998	156	Randomised controlled clinical trial	8 outpatient clinics	94 normotensive Type 2 diabetics with microalbuminuria	Enalapril	Placebo	6	
Ruggenenti *et al*, 2004	1204	Randomised controlled clinical trial	Multicentre	1204 Type 2 diabetics, hypertension with normal urinary albumin excretion	Trandolapril and verapamil	Placebo	3	Third arm intervention = trandolapril; Fourth arm intervention = verapamil
Sano *et al*, 1994	52	Randomised controlled clinical trial	Hospital	52 normotensive non-IDDM patients with normal renal function, persistent microalbuminuria	Enalapril	No treatment	4	
Stornello *et al*, 1989	16	Randomised controlled clinical trial	Diabetic clinic	16 normotensive Type 2 diabetics with persistent proteinuria	Enalapril	Placebo	1	
Viberti *et al*, 1994	92	Randomised controlled clinical trial	12 hospital-based diabetes centres	92 normotensive IDDM patients with albuminuria	Captopril	Placebo	2	

Table 2 Quality of randomised trials

Study ID (author, year)	Method of allocation concealment	Blinding			Intention-to-treat analysis	Loss to follow up (%)
		(participants)	(investigators)	(outcome assessors)		
Agardh *et al*, 1996	Central	Yes	Yes	Unclear	No	Unclear
Ahmad *et al*, 1997	Not specified	Yes	No	No	Unclear	12.6
Bilo *et al*, 1993	Not specified	Yes	Yes	Unclear	No	25.0
Chan *et al*, 2000	Not specified	Yes	Yes	Unclear	Yes	0.0
Chase *et al*, 1993	Not specified	Yes	Yes	Unclear	Unclear	0.0
EUCLID 1997	Central	Yes	Yes	Yes	Yes	7.5
Ferder *et al*, 1992	Not specifed	Yes	Yes	Unclear	Unclear	0.0
Hallab *et al*, 1993	Computer-generated	Yes	Yes	Unclear	Yes	16.0
Jerums *et al*, 2001	Third party (pharmacy)	No	Yes	No	Yes	9.5
Laffel *et al*, 1995	Block randomisation	Yes	Yes	Unclear	Yes	13.3
Lebovitz *et al*, 1994	Not specified	Yes	Yes	Unclear	No	18.9
Lewis *et al*, 1993	Standard urn design	Yes	Yes	Yes	Yes	14.2
Mosconi *et al*, 1996	Not specified	Yes	Yes	Unclear	No	18.8
Mathiesen *et al*, 1991	Not specified	No	No	Unclear	Yes	0.0
Nielson *et al*, 1997	Not specified	Yes	Yes	Unclear	Yes	16.3
Ravid *et al*, 1998	Central	Yes	Yes	Unclear	No	19.6
Ruggenenti *et al*, 2004	Not specified	Yes	Yes	Yes	Yes	Unclear
Sano *et al*, 1994	Not specified	No	No	No	No	7.8
Stornello *et al*, 1989	Not specified	Yes	Yes	Unclear	Unclear	0.0
Viberti *et al*, 1994	Block randomisation	Yes	Yes	Unclear	Yes	7.6

Table 3 Results for dichotomous outcomes

Study ID (author, year)	Outcomes	Intervention group (number of patients with events/number of patients exposed)	Control group (number of patients with events/number of patients not exposed)	Relative risk (RR) [95% CI]	Risk difference (RD) [95% CI]
Agardh *et al*, 1996	Abdominal complaints	19/156	19/158	1.01 (95%CI: 0.56, 1.84)	0.00 (95%CI: –0.07, 0.07)
	Dizziness	14/156	12/158	1.18 (95%CI: 0.56, 2.47)	0.01 (95%CI: –0.05, 0.07)
Ahmad *et al*, 1997	Albuminuria	4/52	12/51	0.33 (95%CI: 0.11, 0.95)	–0.16 (95%CI: –0.30, –0.02)
Chan *et al*, 2000	Renal events	6/50	5/52	1.25 (95%CI: 0.41, 3.83)	0.00 (95%CI: –0.11, 3.83)
	Reversion to normoalbuminuria	12/50	8/52	1.56 (95%CI: 0.70, 3.49)	0.09 (95%CI: –0.07, 0.24)
	Development of microalbuminuria	10/50	16/52	0.65 (95%CI: 0.33, 1.29)	–0.11 (95%CI: –0.28, 0.06)
Chase *et al*, 1993	Decrease in Hb > 10%	4/7	3/9	1.71 (95%CI: 0.56, 5.28)	0.24 (95%CI: –0.24, 0.72)
	Worsened retinal grade	1/7	4/9	0.32 (95%CI: –0.72, 0.11)	–0.30 (95%CI: –0.72, 0.11)
	Improved retinal grade	2/7	0/9	6.25 (95%CI: 0.35, 112.52)	0.29 (95%CI: –0.06, 0.63)
EUCLID 1997	AER greater or equal to 20 μg/mL	13/213	18/227	0.77 (95%CI: 0.39, 1.53)	–0.02 (95%CI: –0.07, 0.03)
	Hypoglycaemia	12/265	8/265	1.50 (95%CI: 0.62, 3.61)	0.02 (95%CI: –0.02, 0.05)
Jerums *et al*, 2001	**Perindopril group:**				
	Regression to normoalbuminuria	7/13	0/10	11.79 (95%CI: 0.75, 184.66)	0.54 (95%CI: 0.25, 0.83)
	Microalbuminura	5/13	7/10	0.55 (95%CI: 0.25, 1.22)	–0.32 (95%CI: –0.70, 0.07)
	Progression to macroalbuminuria	1/13	3/10	0.26 (95%CI: 0.03, 2.11)	–0.22 (95%CI: –0.54, 0.10)
	Nifedipine group:				
	Regression to normoalbuminuria	0/10	0/10	Not estimable	0.00 (95%CI: –0.17, 0.17)
	Microalbuminura	6/10	7/10	0.86 (95%CI: 0.45, 1.64)	–0.10 (95%CI: –0.52, 0.32)
	Progression to macroalbuminuria	4/10	3/10	1.33 (95%CI: 0.40, 4.49)	0.10 (95%CI: –0.32, 0.52)
Laffel *et al*, 1995	Progression to clinical proteinuria	4/67	13/70	0.32 (95%CI: 0.11, 0.94)	–0.13 (95%CI: –0.23, –0.02)
	Progression to hypertension	2/70	8/73	0.26 (95%CI: 0.06, 1.19)	–0.08 (95%CI: –0.16, 0.00)
	Neutropaenia	1/70	0/73	3.13 (95%CI: 0.13, 75.49)	0.01 (95%CI: –0.02, 0.05)

Table 3 *Continued*

Study ID (author, year)	Outcomes	Intervention group (number of patients with events/number of patients exposed)	Control group (number of patients with events/number of patients not exposed)	Relative risk (RR) [95% CI]	Risk difference (RD) [95% CI]
Lebovitz *et al*, 1994	Progression to clinical albuminuria	2/30	8/38	0.32 (95%CI: 0.07, 1.38)	–0.14 (95%CI: –0.30, 0.01)
Lewis *et al*, 1993	Death	8/207	14/202	0.56 (95%CI: 0.24, 1.30)	–0.03 (95%CI: –0.07, 0.01)
	Doubling of serum creatinine	25/207	43/202	0.57 (95%CI: 0.36, 0.89)	–0.09 (95%CI: –0.16, –0.02)
	Neutropaenia	1/207	1/202	0.98 (95%CI: 0.06, 15.50)	0.00 (95%CI: –0.01, 0.01)
	Hyperkalaemia	3/207	0/202	6.83 (95%CI: 0.36, 131.43)	0.01 (95%CI: 0.00, 0.03)
Mosconi *et al*, 1996	Normoalbuminuria	4/7	4/6	0.86 (95%CI: 0.36, 2.02)	–0.10 (95%CI: –0.62, 0.43)
Nielsen *et al*, 1997	Headache	4/17	4/19	1.12 (95%CI: 0.33, 3.79)	0.02 (95%CI: –0.25, 0.30)
	Dizziness	4/17	4/19	1.12 (95%CI: 0.33, 3.79)	0.02 (95%CI: –0.25, 0.30)
	Depression	2/17	5/19	0.45 (95%CI: 0.10, 2.01)	–0.15 (95%CI: –0.40, 0.10)
	Impotency	10/17	19/19	0.59 (95%CI: 0.40, 0.88)	–0.41 (95%CI: –0.65, –0.17)
Ravid *et al*, 1998	Retinopathy at 6 yrs	12/77	20/79	0.62 (95%CI: 0.32, 1.17)	–0.10 (95%CI: –0.22, 0.03)
	Microalbuminuria	5/77	15/79	0.34 (95%CI: 0.13, 0.90)	–0.12 (95%CI: –0.23, –0.02)
Ruggenenti *et al*, 2004	**Trandolapril + verapamil group:**				
	Persistent microalbuminuria	17/300	30/300	0.57 (95%CI: 0.32, 1.01)	–0.04 (95%CI: –0.09, 0.00)
	CV death	0/300	3/300	0.14 (95%CI: 0.01, 2.75)	–0.01 (95%CI: –0.02, 0.00)
	Trandolapril alone:				
	Persistent microalbuminuria	18/301	30/300	0.60 (95%CI: 0.34, 1.05)	–0.04 (95%CI: –0.08, 0.00)
	CV death	1/301	3/300	0.33 (95%CI: 0.03, 3.18)	–0.01 (95%CI: –0.02, 0.01)
	Verapamil alone:				
	Persistent microalbuminuria	36/303	30/300	1.19 (95%CI: 0.75, 1.88)	0.02 (95%CI: –0.03, 0.07)
	CV death	1/303	3/300	0.33 (95%CI: 0.03, 3.15)	–0.01 (95%CI: –0.02, 0.01)
Viberti *et al*, 1994	Clinical proteinuria	4/46	12/46	0.33 (95%CI: 0.12, 0.96)	–0.17 (95%CI: –0.32, –0.02)

Table 4 Results for continuous outcomes

Study ID (author, year)	Outcomes	Intervention group (mean [SD])	Control group (mean [SD])	Difference in means [95% CI]
Agardh *et al*, 1996	SBP (mmHg)	147 (18)	150 (18)	–3.00 (95%CI: –6.98, 0.98)
	DBP (mmHg)	88 (10)	88 (9)	0.00 (95%CI: –2.11, 2.11)
	SBP AUC at 6 mo	3330 (380)	3323 (240)	–29990 (95%CI: –30133.76, 29846.24)
	SBP AUC at 12 mo	3330 (351)	3321 (244)	–29991.00 (95%CI: –30127.58, –29854.42)
	DBP AUC at 6 mo	1991 (214)	1978 (151)	13.00 (95%CI: –70.67, 96.67)
	DBP AUC at 12 mo	2032 (210)	1978 (159)	54.00 (95%CI: –300.08, 138.08)
	Cholesterol (mmol/L)	5.93 (1.07)	5.91 (1.16)	0.02 (95%CI: –0.23, 0.27)
	Serum creatinine (μmol/L)	96.5 (19.7)	97.1 (18.3)	–0.60 (95%CI: –4.81, 3.61)
	Creatinine clearance	104.72 (54.68)	105.40 (60.13)	–0.68 (95%CI: –13.33, 11.97)
	Glycosylated Hb (% of total Hb)	7.74 (1.70)	7.75 (1.56)	–0.01 (95%CI: –0.37, 0.35)
	Potassium (mmol/L)	4.29 (0.35)	4.19 (0.32)	0.10 (95%CI: 0.03, 0.17)
	Serum triglycerides	3.03 (2.44)	2.53 (1.90)	0.50 (95%CI: 0.02, 0.98)
Ahmad *et al*, 1997	Fasting plasma glucose (mmol/L)	4.7 (0.6)	4.8 (0.6)	–0.10 (95%CI: –0.33, 0.13)
	HbA_{1c} (%)	8.0 (0.5)	8.1 (0.4)	–0.10 (95%CI: –0.27, 0.07)
	SBP (mmHg)	134 (5.7)	134 (5.7)	0.00 (95%CI: –2.20, 2.20)
	DBP (mmHg)	80 (4.6)	83 (51)	–3.00 (95%CI: –4.88, –1.12)
	Albumin excretion rate (AER) (μg/min)	20 (59)	85 (90)	–65.00 (95%CI: –94.45, –35.55)
	Glomerular filtration rate (GFR) ($mL/min/1.73m^2$)	119 (12)	119 (15.5)	0.00 (95%CI: –5.36, 5.36)
	Renal plasma flow (RPF) ($mL/min/1.73m^2$)	585 (16.5)	557 (23.6)	27.00 (95%CI: 19.12, 34.88)
Chase *et al*, 1993	AER (μg/mL)	104.8 (72.2)	117.7 (83.6)	–12.90 (95%CI: –89.34, 63.54)
	Creatinine clearance	84.5 (5.01)	90.4 (34.3)	–5.90 (95%CI: –28.61, 16.81)
Ferder *et al*, 1992	24hr proteinuria (g/d)	0.56 (0.78)	2.66 (0.89)	–2.10 (95%CI: –2.72, –1.48)
	Creatinine clearance (mL/min)	66.6 (13.8)	51.4 (7.9)	15.20 (95%CI: 7.41, 22.99)
	Mean arterial BP (mmHg)	82 (8.3)	86 (7.0)	–4.00 (95%CI: –9.51, 1.51)
	Serum potassium	5.0 (0.4)	3.8 (1.3)	1.20 (95%CI: 0.44, 1.96)
Hallab *et al*, 1993	Mean arterial pressure (MAP) (mmHg)	89 (8)	93 (10)	–4.00 (95%CI: –11.14, 3.14)
	Urinary sodium excretion (mmol/24 hr)	142 (56)	197 (73)	–55.00 (95%CI: –106.31, –3.69)
	Plasma uric acid (μmol/L)	258 (106)	319 (92)	–61.00 (95%CI: –142.45, 20.45)
Laffel *et al*, 1995	Creatinine clearance ($mL/min/1.73m^2$)	83 (33.47)	72 (34.18)	11.00 (95%CI: –0.09, 22.09)
Lebovitz *et al*, 1994	Serum creatinine (mg/dL)	1.39 (0.33)	1.57 (0.61)	–0.18 (95%CI: –0.40, 0.04)
	MAP (mmHg)	958 (4.85)	100 (5.82)	–4.20 (95%CI: –6.62, –1.78)
	Protein excretion at 2 yrs (g/24hr)	2.53 (2.57)	4.36 (4.43)	–1.83 (95%CI: –4.09, 0.43)

Table 4 *Continued*

Study ID (author, year)	Outcomes	Intervention group (mean [SD])	Control group (mean [SD])	Difference in means [95% CI]
Lewis *et al*, 1993	MAP (mmHg)	96 (8)	100 (8)	–4.00 (95%CI: –5.55, –2.45)
Mathiesen *et al*, 1991	Body weight (kg)	66.7 (9)	69.8 (12)	–3.10 (95%CI: –9.33, 3.13)
	Serum potassium	3.8 (0.5)	3.9 (0.3)	–0.10 (95%CI: –0.35, 0.15)
	Serum total cholesterol (mmol/L)	5.03 (1.1)	5.01 (0.9)	0.02 (95%CI: –2.92, 2.96)
	Serum triglyceride (mmol/L)	0.84 (0.5)	1.25 (0.8)	–0.41 (95%CI: –0.80, –0.02)
Mosconi *et al*, 1996	Blood glucose	99.2 (8.3)	99.7 (11.2)	–0.50 (95%CI: –11.37, 10.37)
	SBP (mmHg)	105.3 (11.7)	146.6 (12.4)	3.70 (95%CI: –9.47, 16.87)
	DBP (mmHg)	84.9 (3.6)	93.7 (7.8)	–8.80 (95%CI: –15.59, –2.01)
	GFR (mL/min/1.73m^2)	81.2 (7.8)	79.9 (17.7)	1.30 (95%CI: –14.00, 16.60)
Nielsen *et al*, 1997	Ambulatory SBP 24 hr (mmHg)	145 (16.50)	148 (8.72)	–3.00 (95%CI: –11.77, 5.77)
	Ambulatroy DBP 24 hr (mmHg)	76 (8.25)	82 (8.72)	–6.00 (95%CI: –11.55, –0.45)
	Change in GFR (mL/min/mo)	–0.67 (0.41)	–0.60 (0.48)	–0.07 (95%CI: –0.36, 0.22)
	Haemoglobin (mmol/L)	7.9 (1.24)	8.7 (0.87)	–0.80 (95%CI: –1.51, –0.09)
	HbA_{1c} (%)	8.2 (1.65)	9.3 (2.62)	–1.10 (95%CI: –2.52, 0.32)
	Serum albumin (μmol/L)	523 (45.35)	475 (61.02)	48.00 (95%CI: 13.11, 82.89)
	Serum potassium (μmol/L)	4.3 (0.41)	4.2 (0.44)	0.10 (95%CI: –0.18, 0.38)
	Total cholesterol (mmol/L)	5.7 (1.24)	6.3 (1.74)	–0.60 (95%CI: –1.58, 0.38)
	Urinary sodium excretion	170 (78.34)	176 (74.10)	–6.00 (95%CI: –55.97, 43.97)
Ravid *et al*, 1998	Albumin excretion (mg/24h) at 6 yrs	15.8 (8.0)	26.5 (10)	–10.70 (95%CI: –13.54, –7.86)
	Creatinine clearance (mL/s) at 6 yrs	1.63 (0.12)	1.57 (0.17)	0.06 (95%CI: 0.01, 0.11)
	Mean blood pressure (mmHg) at 6 yrs	100 (4.7)	102 (4.2)	–2.00 (95%CI: –3.40, –0.60)
	Total cholesterol (mmol/L) at 6 yrs	5.34 (0.78)	5.47 (0.72)	–0.13 (95%CI: –0.37, 0.11)
	HbA_{1c} (%) at 6 yrs	8.7 (1.6)	8.5 (1.4)	0.20 (95%CI: –0.27, 0.67)
	BMI (kg/m^2) at 6 yrs	24.1 (3.3)	24.9 (2.6)	–0.80 (95%CI: –1.74, 0.14)
Ruggenenti *et al*, 2004	**Trandolapril + verapamil group:**			
	Trough SBP (mmHg)	139 (10)	142 (12)	–3.00 (95%CI: –4.77, –1.23)
	Trough DBP (mmHg)	80 (6)	83 (6)	–3.00 (95%CI: –3.96, –2.04)
	Trough MAP (mmHg)	100 (6)	103 (7)	–3.00 (95%CI: –4.04, –1.96)
	Trandolapril alone:			
	Trough SBP (mmHg)	139 (12)	142 (12)	–3.00 (95%CI: –4.92, –1.08)
	Trough DBP (mmHg)	81 (6)	83 (6)	–2.00 (95%CI: –2.96, –1.04)

	Trough MAP (mmHg)	101 (7)	103 (7)	–2.00 (95%CI: –3.12, –0.88)
	Verapamil alone:			
	Trough SBP (mmHg)	141 (10)	142 (12)	–1.00 (95%CI: –2.76, 0.76)
	Trough DBP (mmHg)	82 (6)	83 (6)	–1.00 (95%CI: –1.96, –0.04)
	Trough MAP (mmHg)	102 (6)	103 (7)	–1.00 (95%CI: –2.04, 0.04)
Sano *et al*, 1994	**Normotensive group:**			
	Weight (kg)	57.8 (9.35)	57.1 (11.43)	0.70 (95%CI: –7.66, 9.06)
	BMI (kg/m^2)	24.2 (2.77)	22.5 (3.11)	1.70 (95%CI: –0.66, 4.06)
	HbA_{1c}(%)	8.1 (1.39)	7.6 (2.68)	0.50 (95%CI: –1.21, 2.21)
	Creatinine clearance (mL/min)	94.1 (46.42)	88.5 (31.87)	5.60 (95%CI: –26.26, 37.46)
	Serum total cholesterol (mM)	5.46 (1.42)	4.93 (1.00)	0.53 (95%CI: –0.45, 1.51)
	Serum triglycerides (mM)	1.85 (1.00)	1.59 (0.83)	0.26 (95%CI: –0.48, 1.00)
	Urinary NAG (U/L)	4.1 (3.12)	5.0 (2.77)	–0.90 (95%CI: –3.26, 1.46)
	Well-controlled hypertension group:			
	Weight (kg)	58.0 (6.63)	57.6 (9.01)	0.40 (95%CI: –5.87, 6.67)
	BMI (kg/m^2)	23.8 (2.32)	23.2 (1.80)	0.60 (95%CI: –1.08, 2.28)
	HbA_{1c} (%)	8.00 (1.99)	8.0 (2.16)	0.00 (95%CI: –1.66, 1.66)
	Creatinine clearance (mL/min)	94.2 (26.86)	87.2 (30.29)	7.00 (95%CI: –15.87, 29.87)
	Serum total cholesterol (mM)	5.59 (1.09)	4.89 (1.15)	0.70 (95%CI: –0.20, 1.60)
	Serum triglycerides (mM)	1.77 (0.73)	1.19 (0.54)	0.58 (95%CI: 0.06, 1.10)
	Urinary NAG (U/L)	4.2 (1.99)	3.6 (1.44)	0.60 (95%CI: –0.81, 2.01)
Stornello *et al*, 1989	Urinary albumin excretion rate	180 (73.54)	352 (362.04)	–172.00 (95%CI: –428.00, 84.00)

Angiotensin II antagonists

Date written: September 2004
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GUIDELINES

Angiotensin II receptor antagonists offer specific renoprotection in diabetic nephropathy, beyond their antihypertensive benefit. (Level I evidence for Type 2 diabetics with microalbuminuria or overt nephropathy)

BACKGROUND

The beneficial effects of angiotensin-converting enzyme inhibitors (ACEIs) in preventing progression of diabetic nephropathy have been broadly assumed to transfer to angiotensin II receptor antagonists. Recent excellent studies have confirmed benefit in Type 2 diabetes, and are reviewed here.

SEARCH STRATEGY

Databases searched: The Cochrane Renal Group Specialised Register was searched for randomised controlled trials relating to the prevention of progression of kidney disease in people with diabetes mellitus Type 1 and Type 2. Specific interventions included antihypertensive therapies, ACE inhibitors, AII receptor antagonists, calcium channel blockers, dietary protein restriction and glucose control, and interventions to control hypercholesterolemia and hyperlipidemia.
Date of search: 16 December 2003.

WHAT IS THE EVIDENCE?

Recent studies have confirmed that AII receptor antagonists protect against progression of diabetic nephropathy. The number of studies remain small compared with those assessing ACE inhibitors, and have been largely confined to Type 2 diabetics. However, these studies are well designed and adequately powered.

Type I diabetes

One randomised controlled trial (RCT) [crossover design] of 16 Type 1 diabetics over 10 months[1] documented similar effects of losartan 100 mg and enalapril 20 mg on 24-h mean arterial pressure (MAP) and albuminuria, without change in GFR.

Type 2 diabetes

Microalbuminuric and proteinuric patients

Three major RCTs have recently been published, all showing an advantage of AII receptor antagonists.

The Irbesartan in patients with Type 2 Diabetes and MicroAlbuminuria (IRMA) Study – Parving *et al*[2]:

This multicentre RCT randomised 590 hypertensive Type 2 diabetics with microalbuminuria to irbesartan 150 or 300 mg/day, or placebo. Target BP was < 135/85 mmHg, achieved with agents other than ACEIs, angiotensin receptor blockers (ARBs) or calcium channel blockers (CCBs).

	Irbesartan 150	Irbesartan 300	Placebo
BP during study	143/ 83 mmHg	141/ 83 mmHg	144/ 83 mmHg
% patients reaching primary endpoint	9.7%	5.2%	14.9%
Hazard ratio (as %CI)	0.61 (.34–1.08)	0.3 (.14–.61)	
Regression to normal AER	12/100 Pts/ year	17/100 Pts/ year	10.5/100 Pts/year

Follow-up was for 2 years, with the primary endpoint of transition to overt proteinuria being decreased by 70% with irbesartan therapy. Serious adverse events were less frequent among the patients treated with irbesartan (P = 0.02).

The Irbesartan Collaborative Study of Lewis *et al.*[3] randomised 1715 hypertensive Type 2 diabetics with overt nephropathy in 210 centres, to irbesartan 300 mg/day, amlodipine 10 mg/day, or placebo. Antihypertensive agents other than ACEIs, ARBs, and CCBs were used as needed. Target blood pressure was 135/85 mmHg or less in all groups. Mean follow-up was 2.6 years, with the primary endpoint being the composite of time to a doubling of the baseline serum creatinine level, the onset of end-stage kidney disease (ESKD), or death from any cause.

The secondary endpoint was a composite of time to death from cardiovascular event(s).

Treatment with irbesartan resulted in the following outcomes:

- 20% risk reduction for the primary endpoint (P = 0.02) compared with placebo and 23% risk reduction compared with amlodipine (P = 0.006),

• 33% risk reduction for doubling the serum creatinine level ($P = 0.003$) compared with placebo and 37% risk reduction compared with amlodipine ($P = 0.001$),
• 23% risk reduction for development of ESKD ($P = 0.07$) compared with placebo and amlodipine, and
• 24% slower rise in serum creatinine level compared with placebo ($P = 0.008$) and 21% slower rise compared with amlodipine ($P = 0.02$).

These differences were not explained by differences in blood pressure that were achieved, and there were no significant differences in the rates of death from any cause or in the cardiovascular composite endpoint. Proteinuria predicted poor renal outcome, and irbesartan decreased proteinuria more than amlodipine or placebo.[4]

The RENAAL (Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan) Study – Brenner *et al*[5]:

This multinational (250 centres in 28 countries), double-blind, randomized, placebo-controlled study evaluated the effects of losartan in 1513 patients with type 2 diabetes mellitus and overt nephropathy (proteinuria > 500 mg/day and serum creatinine levels of 1.3–3.0 mg/dL) for a mean of 3.4 years. Randomization was to losartan 50–100 mg/day (71% received 100 mg) vs. placebo. Conventional antihypertensive therapy was used in both groups. The primary endpoint was the time to doubling of serum creatinine, ESKD, or death. Secondary endpoints were prespecified and included a composite of cardiovascular morbidity and mortality, changes in level of proteinuria, and the rate of progression of renal disease. Patients treated with losartan had better outcome, with the primary endpoint reached in 43.5% of losartan-treated patients vs. 47.1% of placebo patients. Treatment with losartan resulted in:
• 16% risk reduction for the primary endpoint ($P = 0.02$),
• 25% risk reduction for doubling the serum creatinine level ($P = 0.006$),
• 28% risk reduction for development of ESKD ($P = 0.002$),
• 20% risk reduction for ESKD death ($P = 0.01$),
• 32% risk reduction for rate of first hospitalization for heart failure ($P = 0.005$), and
• 35% decline in level of proteinuria ($P < 0.001$).

There was no significant difference between the groups for the composite endpoint of cardiovascular morbidity and mortality. It was estimated that losartan was associated with an average delay of 2 years in the need for dialysis or renal transplantation.

Are angiotensin II antagonists equivalent in renoprotective efficacy to ACEI?

Barnett *et al*[6] randomised 250 hypertensive Type 2 diabetics with AER 11–999 μg/min to either telmisartan 80 mg or enalapril 20 mg, and performed serial iohexol GFR measurements over 5 years. Double-dummy placebos were used. Rate of GFR decrease was equivalent in both groups (−15 and −18 mL/min/1.73 m^2 in enalapril and telmisartan groups, respectively), and there were no significant differences in AER, BP, ESKD or cardiovascular events, although the study was underpowered for the latter. This study had a 1/3 dropout rate, and these patients were not followed beyond 28 days.

Lacourciere *et al*[7] compared losartan (50–100 mg, mean 86.3 ± 22.5 mg) and enalapril (5–20 mg, mean 16.0 ± 6.2 mg) on kidney function in hypertensive Type 2 diabetics with early nephropathy.

SUMMARY OF THE EVIDENCE

There is a convincing body of Level I evidence that AII receptor antagonists offer renoprotection in diabetic nephropathy, beyond their antihypertensive benefit. Studies have mainly been done in Type 2 diabetic patients with either microalbuminuria or overt nephropathy.

WHAT DO THE OTHER GUIDELINES SAY?

American Diabetes Association (2001)[8]: ARBs reduce the rate of progression from micro to macroalbuminuria as well as ESRD in patients with type 2 diabetes. (A)

ARBs may induce a smaller rise in potassium than ACE inhibitors in people with nephropathy. In the treatment of both micro- and macroalbuminuria, either ACE inhibitors or ARBs should be used. (A)

There are no adequate head-to-head comparisons of ACE inhibitors and ARBs. If one class is not tolerated, the other should be substituted. (E)

If ACE inhibitors, ARBs, or diuretics are used, monitor serum potassium levels for the development of hyperkalemia. (B)

American Diabetes Association (2004)[9]: In hypertensive Type 2 diabetic patients with microalbuminuria, ACE inhibitors and ARBs have been shown to delay the progression to macroalbuminuria. (A)

In patients with Type 2 diabetes, hypertension, macroalbuminuria and renal insufficiency, ARBs have been shown to delay the progression of nephropathy. (A)

If ACE inhibitors or ARBs are used, monitor serum potassium levels for the development of hyperkalemia. (B)

Canadian Diabetes Association (2003)[10]: In people with Type 2 diabetes, albuminuria, and Ccr > 60 mL/min, an ACE inhibitor (Grade A, Level 1 A) or an ARB (Grade A, Level 1 A) should be given, to reduce urinary albumin and prevent progression of nephropathy (Grade A, Level 1 A).

In people with Type 2 diabetes, albuminuria, and Ccr < 60 mL/min, an ARB (Grade A, Level 1 A) should be given, to reduce urinary albumin and prevent progression of nephropathy (Grade A, Level 1 A).

Patients placed on an ACE inhibitor or an ARB should have their se Sr and K levels checked within 2 weeks of initiation of therapy and periodically thereafter (Grade D, consensus).

Kidney Disease Outcomes Quality Initiative (2004)[11]: Patients with diabetic kidney disease, with or without hypertension, should be treated with an ACE inhibitor or an ARB. Evidence for benefit of ARBs in slowing renal pro-

gression is strongest for Type 2 diabetics with macroalbuminuria. There is moderately strong evidence that diuretics may potentiate the beneficial effects of ACE inhibitors and ARBs in diabetic kidney disease.

IMPLEMENTATION AND AUDIT

No recommendation.

SUGGESTIONS FOR FUTURE RESEARCH

1 There is room for further head-to-head comparisons of ACE inhibitors and ARBs.
2 Maximum ACEI or ARB therapy have been inadequately compared with combination therapy in long-term studies with hard endpoints.

REFERENCES

1. Andersen S, Tarnow L, Rossing P *et al*. Renoprotective effects of angiotensin II receptor blockade in type 1 diabetic patients with diabetic nephropathy. *Kidney Int*. 2000; **57**: 601–6.
2. Parving HH, Lehnert H, Brochner-Mortensen J *et al*. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. *N Engl. J. Med*. 2001; **345**: 870–8.
3. Lewis EJ, Hunsickeler LG, Clarke WR *et al*. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl. J. Med*. 2001; **345**: 851–60.
4. Atkins RC, Briganti EM, Weigmann TB *et al*. Effect of baseline proteinuria and change in proteinuria with treatment on the risk of renal endpoints in the Irbesartan Diabetic Nephropathy Trial (IDNT) [abstract]. *J. Am. Soc. Nephrol*. 2002; **13**: A33.
5. Brenner BM, Cooper ME, de Zeeuw D *et al*. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl. J. Med*. 2001; **345**: 861–9.
6. Barnett AH, Bain SC, Bouter P *et al*. Diabetics exposed to telmisartan and enalapril study group. Angiotensin-receptor blockade versus converting-enzyme inhibition in type 2 diabetes and nephropathy. *N Engl. J Med*. 2004; **351**: 1952–61. Erratum in: *N Engl. J. Med*. 2005; **352**: 1731. **PMID**. **15516696**.
7. Lacourciere Y, Belanger A, Godin C *et al*. Long term comparison of losartan and enalapril on kidney function in hypertensive Type 2 diabetics with early nephropathy. *Kidney Int*. 2000; **58**: 762–9.
8. Molitch ME, De Fronzo RA, Franz MJ *et al*. Diabetic nephropathy. *Diabetes Care* 2001; **24** (Suppl 1): S69–S72.
9. American Diabetes Association. Standards in medical care in diabetes. *Diabetes Care* 2004; **27** (Suppl. 1): S15–S35.
10. Canadian Diabetes Association Clinical Practice Guidelines Expert Committee. Canadian Diabetes Association 2003. Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada. *Can J. Diabetes* 2003; **27** (Suppl. 2): S1–152.
11. National Kidney Foundation. K/DOQI Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification and Stratification 2004. [Cited 30 September 2004.] Available from http://www.kidney.org/professionals/kdoqi/guidelines/.

APPENDICES

Table 1 Characteristics of included studies

Study ID (author, year)	N	Study Design	Setting	Participants	Intervention (experimental group)	Intervention (control group)	Follow up (years)	Comments
Andersen *et al*, 2000	16	Randomised crossover clinical trial	Single diabetes centre	16 Type 1 diabetes patients	Losartan 50 mg, losartan 100 mg, enalapril 10 mg, enalapril 20 mg	Placebo	2 mo	
Barnett *et al*, 2004	250	Randomised controlled clinical trial	39 centres in Northern Europe	250 patients with Type 2 diabetes and early nephropathy	Telmisartan	Enalapril	5	
Brenner *et al*, 2001	1513	Randomised controlled clinical trial	250 centres from 28 countries	1513 patients with Type 2 diabetes and nephropathy	Losartan 50–100 mg once daily	Placebo	3.4	
Lacourciere *et al*, 2000	92	Randomised controlled clinical trial	8 clinical centres in Canada	92 hypertensive Type 2 diabetics with early nephropathy	Losartan	Enalapril	1	
Parving *et al*, 2001	590	Randomised controlled clinical trial	96 centres, worldwide	590 hypertensive patients with Type 2 diabetes and microalbuminuria	Irbesartan 150 mg	Placebo	1	Third arm intervention – 300 mg irbesartan

Table 2 Quality of randomised trials

Study ID (author, year)	Method of allocation concealment	Blinding			Intention-to-treat analysis	Loss to follow up (%)
		(participants)	(investigators)	(outcome assessors)		
Andersen *et al*, 2000	Not specified	Yes	Yes	Unclear	Unclear	0.0
Barnett *et al*, 2004	Central	Yes	Yes	Yes	No	0.8
Brenner *et al*, 2001	Central	Yes	Yes	Yes	Yes	0.2
Lacourciere *et al*, 2000	Within each centre	Yes	Yes	Unclear	Yes	Unclear
Parving *et al*, 2001	Not specified	Yes	Yes	Yes	Yes	0.5

Table 3 Results for dichotomous outcomes

Study ID (author, year)	Outcomes	Intervention group (number of patients with events/number of patients exposed)	Control group (number of patients with events/number of patients not exposed)	Relative risk (RR) [95% CI]	Risk difference (RD) [95% CI]
Barnett *et al*, 2004	Mortality	6/120	6/130	1.08 (95%CI: 0.36, 3.27)	0.00 (95%CI: –0.05, 0.06)
	CV death	3/120	2/130	1.63 (95%CI: 0.28, 9.56)	0.01 (95%CI: –0.03, 0.04)
	Adverse events	115/120	130/130	0.96 (95%CI: 0.92, 0.99)	–0.04 (95%CI: –0.08, 0.00)
Brenner *et al*, 2001	Doubling of serum creatinine	327/751	359/762	0.92 (95%CI: 0.83, 1.03)	–0.04 (95%CI: –0.09, 0.01)
	End-stage renal disease	147/751	194/762	0.77 (95%CI: 0.64, 0.93)	–0.06 (95%CI: –0.10, –0.02)
	Mortality	158/751	155/762	1.03 (95%CI: 0.85, 1.26)	0.01 (95%CI: –0.03, 0.05)
	Hospitalisation with heart failure	89/751	127/762	0.71 (95%CI: 0.55, 0.91)	–0.05 (95%CI: –0.08, –0.01)
	Myocardial infarction	50/751	68/762	0.75 (95%CI: 0.53, 1.06)	–0.02 (95%CI: –0.05, 0.00)
Lacourciere *et al*, 2000	Sitting DBP ≤ 85 mmHg	24/49	25/49	0.96 (95%CI: 0.65, 1.43)	–0.02 (95%CI: –0.22, 0.18)
Parving *et al*, 2001	Diabetic nephropathy (150 mg irbesartan daily)	19/195	30/201	0.65 (95%CI: 0.38, 1.12)	–0.05 (95%CI: –0.12, 0.01)
	Diabetic nephropathy (300 mg irbesartan daily)	10/194	30/201	0.35 (95%CI: 0.17, 0.69)	–0.10 (95%CI: –0.16, –0.04)

Table 4 Results for continuous outcomes

Study ID (author, year)	Outcomes	Intervention group (mean [SD])	Control group (mean [SD])	Difference in means [95% CI]
Andersen *et al*, 2000	**Losartan 50 mg**			
	Mean arterial BP (24 hr mmHg)	95 (8)	104 (8)	–9.00 (95%CI: –14.54, –3.46)
	SBP (24 hr mmHg)	137 (16)	147 (12)	–10.00 (95%CI: –19.80, –0.20)
	DBP (24 hr mmHg)	75 (4)	82 (8)	–73.00 (95%CI: –11.38, –2.62)
	GFR (mL/min/1.73m^2)	91 (24)	90 (24)	1.00 (95%CI: –15.63, 17.63)
	Losartan 100 mg			
	Mean arterial BP (24 hr mmHg)	96 (8)	104 (8)	–8.00 (95%CI: –13.54, –2.46)
	SBP (24 hr mmHg)	135 (12)	147 (12)	–12.00 (95%CI: –20.32, –3.68)
	DBP (24 hr mmHg)	75 (4)	82 (8)	–6.00 (95%CI: –11.54, –0.46)
	GFR (mL/min/1.73m^2)	91 (24)	90 (24)	–1.00 (95%CI: –17.63, 15.63)
	Enalapril 10 mg			
	Mean arterial BP (24 hr mmHg)	98 (12)	104 (8)	–6.00 (95%CI: –13.07, 1.07)
	SBP (24 hr mmHg)	141 (16)	147 (12)	–6.00 (95%CI: –15.80, 3.80)
	DBP (24 hr mmHg)	77 (8)	82 (8)	–5.00 (95%CI: –10.54, 0.54)
	GFR (mL/min/1.73m^2)	89 (24)	90 (24)	–1.00 (95%CI: –17.63, 15.63)
	Enalapril 20 mg			
	Mean arterial BP (24 hr mmHg)	93 (12)	104 (8)	–11.00 (95%CI: –18.07, –3.93)
	SBP (24 hr mmHg)	135 (16)	147 (12)	–12.00 (95%CI: –21.80, –2.20)
	DBP (24 hr mmHg)	73 (8)	82 (8)	–9.00 (95%CI: –14.54, –3.46)
	GFR (mL/min/1.73m^2)	89 (24)	90 (24)	–1.00 (95%CI: –17.63, 15.63)
Lacourciere *et al*, 2000	SBP (mmHg)	148.3 (17.1)	145.5 (18.2)	2.80 (95%CI: –4.19, 9.79)
	DBP (mmHg)	86.8 (9.6)	94.4 (8.4)	2.40 (95%CI: –1.17, 5.97)

SBP, systolic blood pressure; DBP, diastolic blood pressure; GFR, glomerular filtration rate.

ACE inhibitor and angiotensin II antagonist combination treatment

Date written: September 2004
Final submission: September 2005
Author: Kathy Nicholls

GUIDELINES

No recommendations possible based on Level I or II evidence

SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on Level III and IV sources)

- **There is currently insufficient evidence that angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor antagonists are of additive specific benefit in diabetic nephropathy, beyond additional antihypertensive benefit.**
- **Although dual blockade is not yet established as a first-line treatment for all patients with diabetic nephropathy, it may be helpful in reaching treatment goals for blood pressure (BP) and albuminuria in individual patients.**
- **Both ACEIs and angiotensin receptor blockers (ARBs) should be suspended in situations where water and sodium depletion is present, e.g. in gastroenteritis.**
- **Studies demonstrate that dual blockade causes hypotension in 5% of patients, hyperkalaemia in 3%, and an increase in creatinine in 8%.**[1]

BACKGROUND

Blockade of the renin angiotensin system (RAS) is a major therapeutic tool in the prevention of diabetic nephropathy evolution. Relative benefit of the use of ACEIs, angiotensin receptor antagonists (ARAs) and their combination remains unclear. This section reviews data on dual RAS blockade in diabetic nephropathy.

SEARCH STRATEGY

Databases searched: The Cochrane Renal Group Specialised Register was searched for randomised controlled trials relating to the prevention of progression of kidney disease in people with diabetes mellitus Type 1 and Type 2. Specific interventions included antihypertensive therapies, ACE inhibitors, AII receptor antagonists, calcium channel blockers, dietary protein restriction and glucose control, and interventions to control hypercholesterolemia and hyperlipidemia.
Date of search: 16 December 2003.

WHAT IS THE EVIDENCE?

There is as yet insufficient data documenting additional specific benefit from adding AII antagonist to ACEI treatment for protection against progression of diabetic nephropathy.

The effect of dual blockade of the RAS in patients with diabetes has been investigated only in short-term studies using surrogate endpoints for progression of diabetic nephropathy, i.e. antiproteinuric effects.

Studies have often used submaximal doses of the single agents, and the combination regimens have been more potently antihypertensive than the single drugs.

Type 2 diabetes

The CALM study,[2] a prospective, randomised, double-blind study of 199 microalbuminuric hypertensive Type 2 diabetic patients, documented better BP control (BP reduced a further 10/6 mmHg) with the combination of lisinopril 20 mg and candesartan 16 mg, compared to the same doses of either single agent. No significant changes in microalbuminuria or glomerular filtration rate (GFR) were detectable over 24 weeks.

Rossing *et al*[3] reported a randomised, double-blind, crossover study of combination therapy in 18 Type 2 diabetics with overt nephropathy and blood pressure >135/85 mmHg despite antihypertensive therapy including recommended doses of ACE inhibitors. Candesartan 8 mg administered once daily or placebo were each added for 2 months, in random order.

Addition of candesartan reduced albuminuria by 25% (95%CI: 2–58, P = 0.04), 24–h systolic blood pressure (SBP) by 10 mmHg (95%CI: 2–18, P = 0.02) and GFR by 5 mL/min/1.73 m^2 (95%CI: 0.1–9, P = 0.045). The GFR reduction was reversible on stopping candesartan. Significant variability in individual response to treatment was noted.

Type 1 diabetes

Jacobsen *et al*[1,4] reported several small randomised, controlled, double-blind, crossover studies in Type 1 diabetic patients with nephropathy and GFR > 30 mL/min.

Table 1 Characteristics of main studies

Study ID (author, year)	N	Randomization	Continuing therapy	Albuminuria	ABP	GFR
Jacobsen *et al*, 2003[5]	18	8-week periods of placebo/80 mg valsartan/20 mg benazepril/ combination	Loop diuretics	Albuminuria was reduced by all 3 active treatments by 65% with either single agent, and by 80% with combination.	144/79 on placebo, 129/73 on either single agent, and 122/66 on dual blockade.	Combination therapy induced a reversible decrease in GFR of 12%.
Jacobsen *et al*, 2002[4]	21	Placebo/irbesartan 300 mg	Previous antihypertensives including ACEI	37% reduction (20–49, $P < 0.001$)	SBP NS DBP reduced 5 mmHg (1–9, $P = 0.01$)	No change (K increase required intervention in 2 patients, mean 4.3–4.6)
Jacobsen *et al*, 2003[1]	24	Placebo/irbesartan 300 mg	Enalapril 40 mg	25% reduction (15–34, $P < 0.001$)	reduced 8/4 mmHg (4–12/2–7, $P < 0.005$)	No change (K unchanged)

ABP, arterial blood pressure.

WHAT DO THE OTHER GUIDELINES SAY?

Kidney Disease Outcomes Quality Initiative: No recommendation.
UK Renal Association: No recommendation.
Canadian Society of Nephrology: No recommendation.
European Best Practice Guidelines: No recommendation.
International Guidelines: No recommendation.

IMPLEMENTATION AND AUDIT

No recommendation.

SUGGESTIONS FOR FUTURE RESEARCH

No recommendation.

REFERENCES

1. Jacobsen P, Andersen S, Rossing K *et al*. Dual blockade of the renin-angiotensin system versus maximal recommended dose of ACE inhibition in diabetic nephropathy. *Kidney Int*. 2003; **63**: 1874–80.
2. Mogensen CE, Neldam S, Tikkanen I *et al*. Randomised controlled trial of dual blockade of renin-angiotensin system in patients with hypertension, microalbuminuria, and non-insulin dependent diabetes: the candesartan and lisinopril microalbuminuria (CALM) study. *BMJ*. 2000; **321**: 1440–4.
3. Rossing K, Christensen PK, Jensen BR *et al*. Dual blockade of the renin-angiotensin system in diabetic nephropathy: a randomized double-blind crossover study. *Diabetes Care* 2002; **25**: 95–100.
4. Jacobsen P, Andersen S, Rossing K *et al*. Dual blockade of the renin-angiotensin system in type 1 patients with diabetic nephropathy. *Nephrol. Dial Transplant* 2002; **17**: 1019–24.
5. Jacobsen P, Andersen S, Jensen BR *et al*. Additive effect of ACE inhibition and angiotensin II receptor blockade in type 1 diabetic patients with diabetic nephropathy. *J. Am. Soc. Nephrol*. 2003; **14**: 992–99.

Protein restriction to prevent the progression of diabetic nephropathy

Date written: September 2004
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Author: Kathy Nicholls

GUIDELINES

a. A small volume of evidence suggests that all patients with renal involvement from diabetes should restrict protein intake to 0.75 g/kg/day (WHO recommended minimum safe daily intake). The expected benefit is modest in comparison with the benefits of good blood pressure (BP) control and angiotensin-converting enzyme inhibitor (ACEI) therapy.

b. There is Level I evidence for Type 1 diabetes with microalbuminuria or overt nephropathy.

c. Evidence is lacking in Type 2 diabetes with established diabetic nephropathy.

BACKGROUND

Clinicians commonly recommend dietary protein restriction in patients with chronic kidney disease (CKD) of any cause. The general evidence has been reviewed by Johnson[1]. This guideline is restricted to evidence of the effect of protein restriction on the progression of diabetic nephropathy. Studies have generally been marred by small numbers, limited follow-up, compliance problems, failure to adequately assess nutritional impact of protein restriction, publication bias, and overlap between "low" and "high" protein intake groups.

SEARCH STRATEGY

Databases searched: The Cochrane Renal Group Specialised Register was searched for randomised controlled trials (RCTs) relating to the prevention of progression of kidney disease in people with diabetes mellitus Type 1 and Type 2. Specific interventions included antihypertensive therapies, ACE inhibitors, AII receptor antagonists, calcium channel blockers, dietary protein restriction and glucose control, and interventions to control hypercholesterolemia and hyperlipidemia.
Date of search: 16 December 2003.

WHAT IS THE EVIDENCE?

Type 1 diabetes

Raal *et al.*[2] studied the effects of 0.8 g/kg/day protein restriction over 6 months on Type 1 diabetics with overt proteinuria. Proteinuria decreased and GFR stabilized on this reduction of protein intake to 50% of their previously unrestricted diet (> 1.6 g/kg/day).

Zeller *et al*[3] studied 35 Type 1 diabetics with overt nephropathy: over 37 months, the rate of renal functional decline (iodothalamate clearance) on 0.6 g/kg/day protein intake was 0.0055 mL/ s/month vs. 0.0168 mL/ s/month in the control group.

Pedrini *et al.*[4] reported a meta-analysis of 5 RCTs ($n = 108$) of low protein diet in both diabetic nephropathy and non-diabetic kidney disease patients. Included in the MDRD study were 40% of patients (see below), but only 3% of these had Type 1 diabetes. The analysis concluded that protein restriction significantly reduced the risk of kidney failure or death (RR 0.67, 95% CI: 0.50–0.89), but it is unclear whether symptoms were simply limited by lower protein intake, delaying the need for dialysis.

While the Modification of Diet in Renal Disease (MDRD)[5] was the largest trial examining dietary protein restriction in the progression of renal disease ($n = 840$), it has limited relevance because it included few diabetic patients. It failed to demonstrate clear benefit, although further analysis by Klahr *et al*[6] suggested some benefit.

Waugh and Robertson[7] for the Cochrane Diabetes Group, meta-analysed 5 trials (4 RCTs) of low protein diet in Type 1 diabetes (Table 1) and concluded that protein restriction is beneficial.

Kasiske *et al*[8] pooled 13 RCTs of protein restriction (mean 0.7 g/kg/day vs. 1.0 g/kg/day) in both diabetic and non-diabetic kidney disease (only 4 of the 13 entered only diabetics). Total $n = 1919$. In the diabetic subgroup, protein restriction had greater effect on GFR than in the non-diabetic patients, with dietary protein restriction in diabetics reducing the rate of GFR decline by 5.4 mL/min/ year. However, the confidence intervals on this figure were wide at 0.3–10.5 mL/min/year. No analysis of nutritional impact was attempted.

Type 2 diabetes

There is a little data for low protein diet showing progression in Type 2 diabetics with overt nephropathy.

Permerlalu *et al*[9] showed in a randomised crossover trial that moderate protein intake at 0.8 g/kg/day compared to high protein at 2 g/kg/day improved GFR and decreased proteinuria.

Parving *et al.*[10] failed to show a benefit of protein restriction in Type 2 diabetics with overt proteinuria.

What is the evidence in children?

There is no evidence available in diabetic nephropathy.

SUMMARY OF THE EVIDENCE

Three meta-analyses (one Cochrane analysis) support the recommendation of modest protein intake in diabetic nephropathy, to the level of the WHO recommended minimum daily intake of 0.75 g/kg/day. The benefit is quantitatively small in comparison with the effects of blood pressure control and renin-angiotensin system blockade.

WHAT DO THE OTHER GUIDELINES SAY?

Kidney Disease Outcomes Quality Initiative: American Diabetes Association: With the onset of overt nephropathy, initiate protein restriction to 0.8 g/kg/day (19% of daily calories), the current adult RDA for protein. Further restriction may be useful in slowing the decline of GFR in these patients. (B)
UK Renal Association: No recommendation.
Canadian Society of Nephrology: No recommendation.
European Best Practice Guidelines: No recommendation.
International Guidelines:

World Health Organization: WHO recommendations for minimum daily protein intake are 1.1 g/kg/day in infants, decreasing to 0.75 g/kg/day in adolescents.

Australian Paediatric Endocrinology Group (2005): Daily energy intake 15%–20% protein, 50%–55% carbohydrate, 25%–40% fat (< 10% as saturated fat).

IMPLEMENTATION AND AUDIT

No recommendation.

SUGGESTIONS FOR FUTURE RESEARCH

No recommendation.

REFERENCES

1. Johnson DW. Evidence-based guide to slowing the progression of early renal insufficiency. *Intern. Med. J.* 2004; **34**: 50–7.
2. Raal FJ, Kalk WJ, Lawson M *et al.* Effect of moderate dietary protein restriction on the progression of overt diabetic nephropathy: a 6-month prospective study. *Am. J. Clin. Nutr.* 1994; **60**: 579–85.
3. Zeller K, Whittaker E, Sullivan L *et al.* Effect of restricting dietary protein on the progression of renal failure in patients with insulin-dependent diabetes mellitus. *N Engl. J. Med.* 1991; **324**: 78–84.
4. Pedrini MT, Levey AS, Lau J *et al.* The effect of dietary protein restriction on the progression of diabetic and non-diabetic renal diseases: a meta analysis. *Ann. Intern. Med.* 1996; **124**: 627–32.
5. Levey AS, Beck GJ, Caggiula AW. Trends towards a beneficial effect of low protein diet during additional follow-up in the MDRD Study [abstract]. *J. Am. Soc. Nephrol.* 1994; **5**: 336A.
6. Klahr S, Levey AS, Beck GJ *et al.* The effects of dietary protein restriction and blood pressure control on the progression of chronic renal disease. *N Engl. J. Med.* 1994; **330**: 877–84.
7. Waugh NR, Robertson AM. Protein restriction for diabetic renal disease. *The Cochrane Database of Systematic Reviews* 1997; **Issue 4**.
8. Kasiske BL, Lakatua JD, Ma JZ. *et al.* A meta-analysis of the effects of dietary protein restriction on the rate of decline in renal function. *Am. J. Kidney Dis* 1998; **31**: 954–61.
9. Pemerlalu J, Berdy M, Garrel ER *et al.* Effect of protein intake and glycaemic control on renal function in type 2 diabetes mellitus. *Diabetology* 1993; **36**: 829–39.
10. Parving HH. Renoprotection in diabetes: genetic and non-genetic risk factors and treatment. *Diabetologia* 1998; **41**: 745–59.
11. Barsotti G, Navalesi R, Giampietro O *et al.* Effects of a vegetarian, supplemented diet on renal function, proteinuria and glucose metabolism in patients with 'overt' diabetic nephropathy and renal insufficiency. *Contrib. Nephrol.* 1988; **65**: 87–94.
12. Dullaart RP, Beusekamp BJ, Meijer S *et al.* Long-term effects of protein-restricted diet on albuminuria and renal function in IDDM patients without clinical nephropathy and hypertension. *Diabetes Care* 1993; **16**: 483–92.
13. Ciavarella A, Di Miz G, Stefoni S *et al.* Reduced albuminuria after dietary protein restriction in insulin-dependent diabetic patients with clinical nephropathy. *Diabetes Care* 1987; **10**: 407–13.

APPENDICES

Table 1 Studies in Cochrane meta-analysis – Protein restriction in Type 1 diabetes

Study	Patients	Mean duration (months)	Design	Dietary protein/day	Dietary – other	Proteinuria/ Albuminuria	Usual diet (pre-study)	Endpoint Ccr decrease UPD	Endpoint Ccr decrease LPD
Barsotti *et al*, 1988[11]	8 Type 1, overt nephropathy, renal impairment	11	Before (16 m) and after	0.3 g/kg	Vegetarian, low phosphate, high carbohydrate, AA and KA supplements	–	> 1.2 g/kg/day protein unrestricted carbohydrate	1.48 mL/min/mo	0.13 mL/min/mo
Dullaart *et al*, 1993[12]	31 Type 1, microalbuminuria	2 years	RCT	0.7 g/kg	High carbohydrate	AER (mcg/min) UPD 31–29 LPD 36–30	1.1 g/kg/day	122–112 mL/min	131–113 mL/min
Raal *et al*, 1994[2]	26 Type 1, overt diabetic nephropathy (1/2 taking ACEI)	6	RCT	0.8 g/kg	–	Proteinuria (g/day) UPD 1.9–2.2 LPD 2.2–1.1	> 1.6 g/kg/day	66–58 mL/min	50–53 mL/min
Ciavarella *et al*, 1987[13]	16 Type 1, overt nephropathy Cr < 0.2 Uprotein > 0.5 g/day	4.5	RCT	0.7 g/kg	–	AER (mcg/min) UPD 452–850 LPD 434–205	1.5 g/kg/day	0.9 mL/min/mo	Increased by 3.3 mL/min/m
Zeller *et al*, 1991[3]	47 Type 1, Uprotein > 0.5 g/day	35	RCT	0.6 g/kg	–	UPD increase LPD decrease	> 1 g/kg/day	0.014 mL/min/mo	0.005 mL/min/m

m, month; UPD, usual protein diet; LPD, low protein diet; RCT, randomised controlled trial.

Table 2 Characteristics of included studies

Study ID (author, year)	N	Study Design	Setting	Participants	Intervention (experimental group)	Intervention (control group)	Follow up (months)	Comments
Ciavarella *et al*, 1987	16	Randomised controlled clinical trial	Outpatient clinic	16 patients with Type 1 diabetes and nephropathy	Low protein diet	Normal protein diet	6 mo	
Dullaart *et al*, 1993	31	Randomised controlled clinical trial	Referral-based diabetic clinic	31 patients with overnight albuminuria, without hypertension	Low protein diet/ usual protein diet	Unrestricted	2 yrs	
Raal *et al*, 1994	32	Randomised controlled clinical trial	Renal diabetic clinic	26 IDDM patients with proteinuria	Low protein diet	Unrestricted protein diet	6 mo	
Zeller *et al*, 1991	47	Randomised controlled clinical trial	University clinic	35 patients with IDDM Type 1 diabetes and nephropathy	Low protein/ phosphorus diet	Usual diet	35 mo	

Table 3 Quality of randomised trials

Study ID (author, year)	Method of allocation concealment	Blinding			Intention-to-treat analysis	Loss to follow up (%)
		(participants)	(investigators)	(outcome assessors)		
Ciavarella *et al*, 1987	Not specified	No	No	No	Unclear	0.0
Dullaart *et al*, 1993	Not specified	No	No	No	Yes	0.0
Raal *et al*, 1994	Not specified	No	No	No	Unclear	15.4
Zeller *et al*, 1991	Not specified	No	No	No	No	0.0

Table 4 Results for continuous outcomes

Study ID (author, year)	Outcomes	Intervention group (mean [SD])	Control group (mean [SD])	Difference in means [95% CI]
Ciavarella *et al*, 1987	Albumin excretion rate (μg/min)	205 (212)	850 (288)	–645.00 (95%CI: –833.80, –456.20)
	Blood glucose (mg/dL)	172 (46)	185 (41)	–13.00 (95%CI: –56.34, 30.34)
	Glycosylated Hb (%)	8.7 (1.7)	8.6 (1.4)	0.10 (95%CI: –1.46, 1.66)
	Insulin dose (U/day)	41 (7.5)	41 (9)	0.00 (95%CI: –8.09, 8.09)
	Serum creatinine (mg/dL)	1.26 (0.34)	0.97 (0.32)	0.29 (95%CI: –0.04, 0.62)
	Creatinine clearance (mL/min/1.73m^2)	112 (21)	92 (23)	20.00 (95%CI: –1.63, 41.63)
Dullaart *et al*, 1992	Serum urea (mM)	4.9 (0.6)	5.7 (0.8)	–0.80 (95%CI: –1.30, –0.30)
	Serum albumin (g/L)	43.3 (1.9)	43.8 (2.5)	–0.50 (95%CI: –2.08, 1.08)
	Urinary urea (mmol/24 hr)	274 (85)	386 (91)	–107.00 (95%CI: –170.01, –43.99)
	Urinary phosphate (mmol/24 hr)	27.1 (8.0)	31.4 (6.7)	–4.30 (95%CI: –9.62, 1.02)
	Urinary sodium (mmol/ 24 hr)	151 (50)	158 (39)	–7.00 (95%CI: –1.49, 1.35)
	Urinary calcium (mmol/24 hr)	4.50 (1.91)	4.57 (2.07)	–0.07 (95%CI: –1.49, 1.35)
	GFR at 2 yrs (mL/min/1.73m^2)	113 (24)	112 (21)	1.00 (95%CI: –15.25, 17.25)
Raal *et al*, 1994	GFR (mL/min/1.73m^2)	53 (23)	58 (26)	–5.00 (95%CI: –25.51, 15.51)
Zeller *et al*, 1991	Glycosylated Hb (%)	7.8 (0.89)	8.0 (1.55)	–0.20 (95%CI: –1.08, 0.68)
	Mean arterial BP (mmHg)	102.3 (5.37)	105.5 (3.49)	–3.20 (95%CI: –6.14, –0.26)

Specific effects of calcium channel blockers in diabetic nephropathy

Date written: September 2004
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Author: Kathy Nicholls

GUIDELINES

Non-dihydropyridine calcium channel blockers (CCBs) offer a small protective effect on proteinuria in diabetic nephropathy, beyond their antihypertensive action (Level II evidence – Type 2 diabetes, small volume). There is no evidence that CCBs influence decline of glomerular filtration rate (GFR) in diabetic nephropathy, beyond their antihypertensive effect. One RCT in hypertensive normoalbuminuric Type 2 diabetic patients shows no benefit of verapamil over placebo in progression to microalbuminuria.

SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on Level III and IV sources)

- **There is insufficient evidence to recommend routine use of dihydropyridine calcium channel blockers (CCBs) in diabetic nephropathy, unless required for antihypertensive action.**
- **There is a small additional benefit on proteinuria from addition of non-dihydropyridine CCBs to angiotensin-converting enzyme inhibitors (ACEIs). (Level III evidence – Type 2 diabetes, small volume)**
- **CCBs are recommended as second-line treatment in diabetic nephropathy, and are frequently required for optimal blood pressure (BP) control. There is a small benefit of non-dihydropyridines over dihydropyridines for protection against progression of proteinuria.**

BACKGROUND

Calcium channel blocking drugs differ in their effects on glomerular haemodynamics and urinary albumin excretion (UAE), both in normal and in disease states. Non-dihydropyridine CCBs reduce albumin excretion. This section questions whether or not CCBs have any specific renoprotective effect, beyond BP lowering, in diabetic renal disease.

SEARCH STRATEGY

Databases searched: The Cochrane Renal Group Specialised Register was searched for randomised controlled trials relating to the prevention of progression of kidney disease in people with diabetes mellitus Type 1 and Type 2. Specific interventions included antihypertensive therapies, ACE inhibitors, AII receptor antagonists, calcium channel blockers, dietary protein restriction and glucose control, and interventions to control hypercholesterolemia and hyperlipidemia.
Date of search: 16 December 2003.

WHAT IS THE EVIDENCE?

Studies are limited in number, and patient numbers are small. The Benedict trial is the only RCT which provides a head-to-head study of CCBs vs ACEI with adequate control of BP.[1] It is adequately controlled and we lack long-term studies with functional endpoints.

Ruggenenti *et al*[1] studied hypertensive normoalbuminuric Type 2 diabetic patients and showed no benefit of verapamil over placebo in progression to microalbuminuria, while trandolapril reduced risk of progression to microalbuminuria by 51% compared with verapamil.

Non-dihydropyridine CCBs offer a small protective effect on proteinuria in diabetic nephropathy, beyond their antihypertensive action. (Level II evidence – Type 2 diabetes, small volume).

There is no evidence that CCBs influence decline of GFR in diabetic nephropathy, beyond their antihypertensive effect.

Non-dihydropyridine calcium channel blockers in diabetic nephropathy

Type 2 diabetes

Bakris *et al*:[2] In this study, 52 Type 2 diabetics with hypertension were randomised to lisinopril, verapamil/diltiazem, or beta blockers and followed for a mean of 5.3 years. Endpoint was change in slope of creatinine clearance. Mean arterial pressure was equivalent in all three groups. Functional decline in the atenolol group was greater than the other two groups, and albuminuria decreased with verapamil/diltiazem to an extent similar to lisinopril.

Bakris *et al*[3] studied 34 African Americans with renal impairment due to Type 2 diabetes and overt nephropathy randomised to verapamil or atenolol, with additional diuretic in both groups to achieve BP < 140/90 mmHg. After a mean follow-up of 54 months, creatinine clearance was better maintained in the verapamil group, and proteinuria was less.

Velussi *et al*[4] followed 44 hypertensive Type 2 diabetics with normo- or microalbuminuria randomised to either amlodipine or cilozapril for 3 years, and found similar efficacy in the two groups in delaying GFR decline and reducing AER at BP < 140/85 mmHg.

Mosconi *et al*[5] performed a 3-phase, parallel group study in 16 hypertensive microalbuminuric patients with Type 2 diabetes and biopsy-proven nephropathy and slight GFR depression. Both nitrendipine and enalapril treatment groups controlled BP, lowered albuminuria, and preserved GFR over 27 months.

The Benedict trial[1] studied 1204 hypertensive (defined as BP > 130/80 mmHg or on antihypertensive therapy) Type 2 diabetics without albuminuria, to assess whether ACEIs and non-dihydropyridine CCBs, alone or in combination, prevent microalbuminuria in subjects with hypertension, Type 2 diabetes mellitus, and normal urinary albumin excretion. Patients were randomised to trandolapril 2 mg (T), trandolapril 2 mg plus verapamil 180 SR (T + V), verapamil alone 240 SR (V) or placebo (P) for 3 years. The primary endpoint of development of persistent microalbuminuria was reached in 12% of V, and 10% of placebo patients (NS), and in 6% of each of the T alone and T + V groups (P = 0.01, T + V vs. P).

Target BP was 120/80 mmHg, achieved if required via prescribed stepwise addition of drugs without RAS blockade action or non-dihydropyridine CCBs. Actual BP was slightly but significantly lower in the T + V group, potentially confounding the outcome. SAEs and numbers on statin therapy were comparable in all groups.

Dihydropyridine calcium channel blockers

There is a significant difference in antiproteinuric effect between dihydropyridines and non-dihydropyridines, despite both being effective antihypertensive agents. This probably relates to differential effect on glomerular permeability.[6] This group randomised 21 hypertensive patients with Type 2 diabetes and nephropathy to either diltiazem CD or nifedipine and followed them 3-monthly for 21 months. Despite similar levels of blood pressure control, proteinuria was reduced only in the diltiazem group, with improvement in glomerular size selectivity. No significant differences in GFR were found.

Addition of non-dihydropyridine calcium channel blockers to ACEI

Evidence that the protective effect of ACEI and of non-dihydropyridine CCBs in Type 2 diabetic nephropathy are additive is limited to the studies of Bakris *et al*[7] who reported an open-label, parallel group study of 37 Type 2 diabetics with overt nephropathy, randomised to trandolapril (T), verapamil (V) or combination (T + V). Doses of drug were titrated over 8 weeks to achieve a goal blood pressure of < 140/90 mmHg in all 3 groups. Baseline proteinuria was 1342 ± 284 mg/dL. Proteinuria reduction in the T + V group (62 ± 10%) was greater than either T alone (33 ± 8%) or V alone (27 ± 8%), despite lower doses of both T and V in the T + V group. The mean daily dose of the individual components of T + V (T 2.9 ± 0.8 mg, V 219 ± 21.1 mg) was significantly lower than the dose of either T alone (5.5 ± 1.1 mg/day (P < 0.01) or V alone (314.8 ± 46.3 mg, given in two divided doses, P < 0.01).

GFR did not change over 1 year in any group.

SUMMARY OF THE EVIDENCE

There is no evidence that calcium channel blockade retards renal function deterioration in diabetic nephropathy. Studies have been small and largely confined to Type 2 diabetes. One RCT has indicated superiority of trandolapril over verapamil in preventing progression to microalbuminuria in hypertensive normoalbuminuric Type 2 diabetic patients. This is good evidence that non-dihydropyridine CCBs reduce proteinuria. However, the clinical benefit of CCBs seem on current data, to be largely confined to their antihypertensive action.

WHAT DO THE OTHER GUIDELINES SAY?

Kidney Disease Outcomes Quality Initiative (2004): Nondihydropyridine CCBs consistently demonstrate reduction in proteinuria, alone and when added to ACE inhibitor. It is reasonable to use a combination of ACE inhibitor and/or ARB and non-dihydropyridine CCB in hypertensive patients.[8]

UK Renal Association: No recommendation.

Canadian Society of Nephrology: No recommendation.

European Best Practice Guidelines: No recommendation.

International Guidelines:

Canadian Diabetes Association (2003): The use of non-dihydropyridine CCBs may be considered to reduce urinary albumin excretion in proteinuric hypertensive patients (Grade B, Level 2).[9]

American Diabetes Association (2004): With regards to slowing the progression of nephropathy, the use of DCCBs as initial therapy is not more effective than placebo. Their use in nephropathy should be restricted to additional therapy to further lower blood pressure in patients already treated with ACE inhibitors or ARBs. (B)[10]

In the setting of albuminuria or nephropathy, in patients unable to tolerate ACE inhibitors and/or ARBs, consider the use of non-DCCBs, beta-blockers, or diuretics for the management of blood pressure. (E)

IMPLEMENTATION AND AUDIT

No recommendation.

SUGGESTIONS FOR FUTURE RESEARCH

No recommendation.

REFERENCES

1. Ruggenenti P, Fassi A, Ilieva AP *et al*. Bergamo Nephrologic Diabetes Complications Trial (BENEDICT) Investigators. Preventing microalbuminuria in type 2 diabetes. *N Engl. J. Med*. 2004; **351**: 1941–51.
2. Bakris GL, Copley JB, Vicknair N *et al*. Calcium channel blockers versus other antihypertensive therapies on progression of NIDDM-associated nephropathy. *Kidney Int*. 1996; **50**: 1641–50.
3. Bakris GL, Mangrum A, Copley JB *et al*. Effect of calcium channel or beta-blockade on the progression of diabetic nephropathy in African Americans. *Hypertension* 1997; **29**: 744–50.
4. Velussi M, Brocco E, Frigato F *et al*. Effects of cilazapril and amlodipine on kidney function in hypertensive NIDDM patients. *Diabetes* 1996; **45**: 216–22.
5. Mosconi L, Ruggenenti P, Perna A *et al*. Nitrendipine and enalapril improve albuminuria and glomerular filtrate rate in non-insulin dependent diabetes. *Kidney Int*. 1996; **49** (Suppl. 55): S91–S93.
6. Smith AC, Toto R., Bakris GL. Differential effects of calcium channel blockers on size selectivity of proteinuria in diabetic glomerulopathy. *Kidney Int*. 1998; **54**: 889–96.
7. Bakris GL, Weir MR, DeQuattro V *et al*. Effects of an ACE inhibitor/calcium antagonist combination on proteinuria in diabetic nephropathy. *Kidney Int*. 1998; **54**: 1283–9.
8. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification and stratification. National Kidney Foundation. *Am. J. Kidney Dis* 2002; **39** (2 Suppl. 1): S1–S266.
9. Canadian Diabetes Association. *2003 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada*. Available from http://www.diabetes.ca/cpg2003/default.aspx
10. American Diabetes Association. Standards of medical care in diabetes. *Diabetes Care* 2004; **27** (Suppl. 1): S15–S35.

APPENDICES

Table 1 Characteristics of included studies

Study ID (author, year)	N	Study design	Setting	Participants	Intervention (experimental group)	Intervention (control group)	Follow up (months)	Comments
Bakris *et al*, 1997	34	Randomised controlled clinical trial	Nephrology clinic	34 African-Americans with diabetic nephropathy	Verapamil	Atenolol	54	
Mosconi *et al*, 1996	13	Randomised controlled clinical trial	Hospital	13 micro-albuminuric NIDDM patients with mild hypertension and diabetic glomerulopathy	Nitrendipine	Enalapril	27	

Table 2 Quality of randomised trials

Study ID (author, year)	Method of allocation concealment	Blinding			Intention-to-treat analysis	Loss to follow up (%)
		(participants)	(investigators)	(outcome assessors)		
Bakris *et al*, 1997	Not specified	No	No	Unclear	Yes	14.7
Mosconi *et al*, 1996	Not specified	Yes	Yes	Unclear	No	18.8

Table 3 Results for dichotomous outcomes

Study ID (author, year)	Outcomes	Intervention group (number of patients with events/ number of patients exposed)	Control group (number of patients with events/ number of patients not exposed)	Relative risk (RR) [95% CI]	Risk difference (RD) [95% CI]
Bakris *et al*, 1997	Doubling of serum creatinine	5/18	3/16	1.48 (95%CI: 0.42, 5.24)	0.09 (95%CI: –0.19, 0.37)
Mosconi *et al*, 1996	From microalbuminuric to normo-albuminuric	4/7	4/6	0.86 (95%CI: 0.36, 2.02)	–0.10 (95%CI: –0.62, 0.43)

Table 4 Results for continuous outcomes

Study ID (author, year)	Outcomes	Intervention group (mean [SD])	Control group (mean [SD])	Difference in means [95% CI]
Bakris *et al*, 1997	Mean change in protein excretion (g/dL)	–1.3 (0.7)	–0.278 (0.382)	–1.02 (95%CI: –1.39, –0.65)
	Rate of decline in creatinine clearance (mg/dL)	–1.7 (0.9)	–3.7 (1.4)	2.00 (95%CI: 1.20, 2.80)
Mosconi *et al*, 1996	Blood glucose (mg/dL)	99.2 (8.3)	99.7 (11.2)	–0.50 (95%CI: –11.37, 10.37)
	SBP (mmHg)	105.3 (11.7)	146.6 (12.4)	3.70 (95%CI: –9.47, 16.87)
	DBP (mmHg)	84.9 (3.6)	93.7 (7.8)	–8.80 (95%CI: –15.59, –2.01)
	GFR (mL/min/1.73m^2)	81.2 (7.8)	79.9 (17.7)	1.30 (95%CI: –14.00, 16.60)

Glucose control and progression of diabetic nephropathy

Date written: September 2004
Final submission: September 2005
Author: Kathy Nicholls

GUIDELINES

a. In both Type 1 and Type 2 diabetics, glycosolated haemoglobin (HbA_{1c}) should be maintained at or < 7% for primary prevention of diabetic nephropathy, and for prevention of progression from microalbuminuria to overt nephropathy. (Level I evidence for Type 1 diabetes – moderate volume; Level I evidence for Type 2 diabetes – small volume)

b. Optimal glycaemic control – preprandial blood glucose 4.4–6.7 mmol/L and HbA_{1c} < 7% carries increased risk of hypoglycaemia. (We do not have evidence that tight control in Type 2 diabetics with overt nephropathy will alter outcome)

SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on Level III and IV sources)

- **The Australian Diabetes Association is attempting to standardize HbA_{1c} assays nationally. Some older assays are falsely elevated by carbamylated Hb in chronic kidney disease (CKD).**
- **The risk of hypoglycaemia can be minimized by frequent blood glucose monitoring with appropriate intervention (AACE).**
- **There is evidence that renal damage rarely occurs in patients with either Type 1 or Type 2 diabetes if HbA_{1c} is < 7.5% and postprandial blood glucose is < 10.1 mmol/L. Data from the Joslin Clinic (Type 1) suggests that a low incidence rate of diabetic nephropathy occurs when HbA_{1c} < 8.0%. Lower levels of HbA_{1c} may be required for macrovascular protection.**
- **A major limitation of the available data is that they do not identify the optimum level of control for particular patients, as there are individual differences in the risks of hypoglycaemia, weight gain, and other adverse effects.**
- **It is unclear how different components of multifactorial interventions (e.g. educational interventions, glycaemic targets, lifestyle changes, and pharmacological agents) contribute to the reduction of complications.**
- **There are no clinical trial data available for the effects of glycaemic control in patients with advanced complications, the elderly (> 65 years of age), or children < 13 years.**
- **In the United Kingdom Prospective Diabetes Study (UKPDS) and the Diabetes Control and Complications Trial (DCCT), intensive control trebled the risks of hypoglycaemia and increased weight gain.**
- **Epidemiological analyses suggest that there is no lower limit of A_{1c} at which further lowering does not reduce risk of complications. However, the absolute risks and benefits of lower targets are unknown.**
- **The risks and benefits of an A_{1c} goal of < 6% are currently being tested in an ongoing study (ACCORD, Action to Control Cardiovascular Risk in Diabetes) in Type 2 diabetes.**
- **Elevated postchallenge (2-h OGTT) glucose values have been associated with increased cardiovascular risk independent of fasting plasma glucose (FPG) in some epidemiological studies. Postprandial plasma glucose (PPG) levels > 7.8 mmol/L are unusual in non-diabetics, although large evening meals can be followed by plasma glucose values up to 10 mmol/L.**
- **The longer patients can maintain a target HbA_{1c} level of 7.0%, which is achievable with current methods, the greater their protection from nephropathy.**

BACKGROUND

Although disputed for many years, the causal relationship between poor glycaemic control and development and progression of complications is now proven, as outlined in this section.

The risk of a rapid decline of glomerular function abruptly increases when glycated haemoglobin exceeds 7.5% and postprandial blood glucose is > 11 mmol/L.[1]

SEARCH STRATEGY

Databases searched: The Cochrane Renal Group Specialised Register was searched for randomised controlled trials relating to the prevention of progression of kidney disease in people with diabetes mellitus Type 1 and Type 2. Specific interventions included antihypertensive therapies, ACE inhibitors, AII receptor antagonists, calcium channel blockers, dietary protein restriction and glucose control, and interventions to control hypercholesterolemia and hyperlipidemia.
Date of search: 16 December 2003.

WHAT IS THE EVIDENCE?

Type 1 diabetes

The Diabetes Control and Complications Trial Research group[2] conducted a 10-year, prospective, randomised con-

trolled trial (RCT) of intensive glucose control (target HbA_{1c} < 7%) in 1441 normotensive Type 1 diabetics with albumin excretion rate (AER) < 139 μg/min (<200 mg/24 h). Adolescents > 13 years were included. The primary (n = 726) and secondary (n = 715) cohorts were each randomised to either intensive treatment (3–4 injections of insulin or continuous subcutaneous insulin infusion and 4 self-monitored blood glucose tests daily) or conventional treatment (1–2 injections of insulin and either home urine glucose testing several times per day, or later in the study, self blood glucose testing once per day). The DCCT was stopped prematurely in 1993, after a mean duration of follow-up of 6.5 years. Although the mean HbA_{1c} levels of the 2 DCCT treatment groups reached their maximum separation by 6 months post-randomization, it took 3–4 years of different treatment regimens with separation of HbA_{1c} levels by 2.0%, before the cumulative incidence curves of nephropathy began to diverge distinctly.

Intensive treatment prevented the development and progression of nephropathy: the onset of proteinuria was reduced by 54% and microalbuminuria by 39%, most prominently in the primary prevention cohort. The absolute risk of nephropathy was proportional to the mean HbA_{1c} level over the follow-up period. For each 10% decrease in HbA_{1c}, there was a 25% decrease in the risk of microalbuminuria, and no glycaemic threshold for nephropathy was detected above the non-diabetic range of HbA_{1c} by any form of modelling of the data.

The DCCT found no influence of intensive treatment on GFR (^{125}I-iothalamate clearance) or creatinine clearance, which remained within the normal range for most subjects during the DCCT.

Further follow-up after 4 years confirmed persistent protection despite increasing hyperglycaemia.[3]

The DCCT patient cohort has converted to the Epidemiology of Diabetes Interventions and Complications (EDIC) observational study,[4] which reports sustained benefits of intensive treatment well beyond the period of its most intensive implementation. Risk reduction for intensive treatment has been maintained through 7 years although HbA_{1c} levels have converged. At 1 year, the difference in mean HbA_{1c} of the 2 former randomised groups was only 0.4% (P < 0.001) – 8.3% in the former conventional treatment group vs. 7.9% in the former intensive treatment group. The difference continued to narrow, losing statistical significance by 5 years (8.1% vs. 8.2%, P = 0.09). However, the further rate of progression of complications from their levels at the end of the DCCT remains less in the former intensive treatment group on intention-to-treat analysis.

At the fifth- and sixth-year examinations of 1298 EDIC participants, the prevalence of microalbuminuria in those without it at DCCT closeout remains less in the former intensive treatment group than in the conventional treatment group (4.5% vs. 12.3%, RRR 67%; P < 0.001). In subjects with either normoalbuminuria or microalbuminuria at DCCT closeout, the risk reduction in subsequent development of clinical albuminuria in the former intensive treatment group was 84% (P < 0.001). Furthermore, an aggregate endpoint of serum creatinine (0.18 mmol/L) chronic dialysis therapy, or renal transplantation, was reached by only 6 of the original intensive treatment group vs. 17 of the original conventional group. While the prevalence of hypertension at the end of the DCCT was equivalent in the conventional and intensive groups (12% vs. 11%) the EDIC at 6 years documented significantly greater hypertension in the conventional group (33% vs. 25%, P < 0.001).

The Minnesota Transplant group[5] looked at intensive vs. standard glucose control in 48 diabetic renal transplant recipients. Good glucose control resulted in histologically confirmed protection from subsequent nephropathy.

Type 2 diabetes

In Type 2 diabetics, only recently has good data emerged for glycaemic control protecting from microvascular complications.

In the Kumamoto Study,[6] significantly less nephropathy developed in Type 2 diabetes patients intensively treated with insulin. This prospective 6-year study identified a primary prevention cohort (no albuminuria) and a secondary intervention cohort (overt microalbuminuria). Glycaemic control in the two groups was HbA_{1c} 7.1% vs. 9.4%; percentage of patients developing nephropathy was 8 vs. 28 in the prevention cohort, while in the microalbuminuric group, 12% vs. 28% progressed to nephropathy. However, this is one small study and the patients were thin Type 2 diabetics – we should probably not extrapolate freely from it.

The UKPDS[7,8] studied 4075 newly-diagnosed Type 2 diabetic patients from 23 UK centres over 20 years. Intensive glycaemic control produced better microvascular outcome with less kidney failure, and two-thirds reduction in risk of doubling of serum creatinine. There was less development of both microalbuminuria and proteinuria in the intensive treatment group (RRR 33% for microalbuminuria development). A 37% decrease in the incidence rates of micro-macroalbuminuria was observed for any decrease of HbA_{1c} by 1%.[9]

Blood glucose levels as well as HbA_{1c} may be important. (Level III evidence)

Nosadini and Tonolo[1] followed 74 hypertensive patients with Type 2 diabetes and elevated AERs, while achieving BP < 140/90 mmHg with ACEIs, CCBs and diuretics. Every 6 months for 4 years, GFR, HbA_{1c} and daily fasting and postprandial glucose levels were measured. GFR decreased in 75% of patients, all of whom had HbA_{1c} > 7.5%. Postprandial blood glucose was closely correlated with rapid GFR decline (R^2 = 0.55, P < 0.00001). No significant change was observed when postprandial glucose was < 10.1 mmol/L.

In Type 2 diabetes, there is no evidence that strict metabolic control retards progression once overt nephropathy is present.[10]

SUMMARY OF THE EVIDENCE

Long-term studies, especially in Type 1, but also in Type 2 diabetic patients, indicate that good glycaemic control

results in clinically significant preservation of renal function. However, benefit is greatest when control is instigated earlier in the course of nephropathy. In Type 2 diabetics with overt nephropathy, there is no evidence that tight control will alter the renal function outcome.

WHAT DO THE OTHER GUIDELINES SAY?

Kidney Disease Outcomes Quality Initiative (2004): No recommendation.
UK Renal Association: No recommendation.
Canadian Society of Nephrology: No recommendation.
European Best Practice Guidelines: No recommendation.
International Guidelines:

American Diabetes Association: $HbA_{1c} < 7\%$ (DCCT reference method). Review therapy if consistently > 8. Recommended plasma glucose ranges are 5–7.2 mmol/L preprandial, 6.1–8.3 mmol/L bedtime.

American Diabetes Association (Revision 2004): Aim for normoglycaemia, $HbA_{1c} < 7\%$ (B), and consider < 6% in individual patients (B), but less stringent goals may be appropriate for patients with severe hypoglycaemia, limited life expectancies, or comorbid conditions, and for very young children or older adults (E).[11]

American Association of Clinical Endocrinology: $HbA_{1c} < 7\%$.

Canadian Diabetes Association: 'Best possible glucose control' recommended in all diabetics for prevention, onset and delay in progression of early nephropathy. (Grade A, level 1A) Therapy in most patients with Type 1 or 2 diabetes should be targeted to achieve $HbA_{1c} \leq 7.0\%$ in order to reduce the risk of microvascular (Grade A, Level 1A0 and macrovascular complications (Grade C, level 3).[12]

To achieve $A_{1c} \leq 7.0\%$, aim for FPG or preprandial PG targets of 4–7 mmol/L, and 2- h post prandial PG targets of 5–10 (Grade B, Level 2).

If it can safely be achieved, lowering PG targets toward the normal range should be considered (Grade C, Level 3): $A_{1c} \leq 6.0$ (grade D, consensus), FPG/preprandial PG 4–6 (grade D, consensus) 2- h postprandial PG 5–8 (grade D, consensus).

Australian Paediatric Endocrinology Group (2005): HbA_{1c} target < 7.5% for older children & adolescents, younger children 'may set a little higher'. Blood glucose > 4.0 mmol/L.[13]

IMPLEMENTATION AND AUDIT

No recommendation.

SUGGESTIONS FOR FUTURE RESEARCH

No recommendation.

REFERENCES

1. Nosadini R., Tonolo G. Relationship between blood glucose control, pathogenesis and progression of diabetic nephropathy. *J. Am. Soc. Nephrol.* 2004; **15** (Suppl. 1): S1–S5.
2. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl. J. Med.* 1993; **329**: 977–86.
3. The Diabetes Control and Complications Trial Research Group. Retinopathy and nephropathy in patients with type 1 diabetes four years after a trial of intensive therapy. *N. Engl. J. Med.* 2000; **342**: 381–9.
4. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. Effect of intensive therapy on the microvascular complications of type 1 diabetes mellitus. *JAMA* 2002; **287**: 2563–9.
5. Barbosa J, Steffes MW, Sutherland DE *et al.* Effect of glycemic control on early diabetic renal lesions. A 5-year randomized controlled clinical trial of insulin-dependent diabetic kidney transplant recipients. *JAMA* 1994; **272**: 600–6.
6. Ohkubo Y, Kishikawa H, Araki E *et al.* Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomised prospective 6-year study. *Diabetes Res. Clin. Pract* 1995; **28**: 103–17.
7. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* 1998; **352**: 854–65.
8. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998; **352**: 837–53.
9. Stratton IM, Adler AI, Neil HA *et al.* Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ.* 2000; **321**: 405–12.
10. Parving HH. Renoprotection in diabetes: genetic and non-genetic risk factors and treatment. *Diabetologia* 1998; **41**: 745–59.
11. American Diabetes Association. Standards of medical care in diabetes. *Diabetes Care* 2004; **27** (Suppl. 1): S15–S35.
12. Canadian Diabetes Association. *2003 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada.* Available from http://www.diabetes.ca/cpg2003/default.aspx
13. Australasian Paediatric Endocrine Group. Clinical practice guidelines: Type 1 diabetes in children and adolescents. 2005. Available from: http://www.chw.edu.au/prof/services/endocrinology/apeg/.

APPENDICES

Table 1 Characteristics of included studies

Study ID (author, year)	N	Study design	Setting	Participants	Intervention (experimental group)	Intervention (control group)	Follow up (years)	Comments
Barbosa *et al*, 1994	99	Randomised controlled clinical trial	University hospital, US	48 Type 1 diabetics with terminal diabetic renal failure undergoing renal transplantation	Subcutaneous insulin given several times a day or continuously	Subcutaneous insulin once or twice per day	5	
DCCT, 1993	1441	Randomised controlled clinical trial	29 centres	1441 insulin-dependent diabetes mellitus patients	Intensive therapy ≥ 3 insulin injections daily plus frequent blood glucose monitoring	Conventional therapy, 1–2 insulin injections daily	6.5	

Table 2 Quality of randomised trials

Study ID (author, year)	Method of allocation concealment	Blinding			Intention-to-treat analysis	Loss to follow up (%)
		(participants)	(investigators)	(outcome assessors)		
Barbosa *et al*, 1994	Not specified	No	No	Unclear	No	52
DCCT, 1993	Not specified	Yes	Yes	Yes	No	1

Table 3 Results for dichotomous outcomes

Study ID (author, year)	Outcomes	Intervention group (number of patients with events/number of patients exposed)	Control group (number of patients with events/number of patients not exposed)	Relative risk (RR) [95% CI]	Risk difference (RD) [95% CI]
Barbosa *et al*, 1994	Mortality	7/52	8/47	0.79 (95%CI: 0.31, 2.01)	–0.04 (95%CI: –0.18, 0.11)
	Graft loss/chronic rejection	2/52	2/47	0.90 (95%CI: 0.13, 6.16)	0.00 (95%CI: –0.08, 0.07)
DCCT, 1993	Proliferative or severe non-proliferative retinopathy in primary prevention cohort	2/348	4/378	0.54 (95%CI: 0.10, 2.95)	0.00 (95%CI: –0.02, 0.01)
	Clinically important macular oedema	1/348	4/378	0.27 (95%CI: 0.03, 2.42)	–0.01 (95%CI: –0.02, 0.00)

Table 4 Results for continuous outcomes

Study ID (author, year)	Outcomes	Intervention group (mean [SD])	Control group (mean [SD])	Difference in means [95% CI]
Barbosa *et al*, 1994	SBP (mmHg) at 5 years	131 (7)	129 (9)	2.00 (95%CI: –2.59, 6.59)
	DBP (mmHg) at 5 years	77 (6)	75 (8)	2.00 (95%CI: –2.03, 6.03)
	Glomerular morphometric measure at 5 years (GBM width [nm])	430 (73)	475 (181)	–45.00 (95%CI: –124.31, 34.31)
	Glomerular structural change (GBM width [nm])	91 (73)	148 (166)	–57.00 (95%CI: –130.63, 16.63)

Smoking and the progression of diabetic nephropathy

Date written: September 2004
Final submission: September 2005
Author: Kathy Nicholls

GUIDELINES

No recommendations are possible based on Level I or II evidence

SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on Level III and IV sources)

- **Smoking accelerates the development and progression of diabetic nephropathy. (Level III evidence – large retrospective cohort studies; clinically relevant outcomes; consistent strong effects)**
- **Cessation of smoking retards progression of diabetic nephropathy. (Level III evidence – small volume, several small cohort studies; clinically relevant outcomes; consistent strong effects)**
- **Current smoking confers a greater risk than former smoking.**
- **All patients with Type 1 or Type 2 diabetes should be strongly advised against commencement/continuation of smoking, to reduce the risk of developing and accelerating diabetic nephropathy as well as for vascular health.**

BACKGROUND

Smoking has been associated with increased risks of developing diabetic kidney disease, and of accelerating its progression. The objective of this guideline is to evaluate the available clinical evidence of the impact of smoking on diabetic kidney disease.

SEARCH STRATEGY

Databases searched: The Cochrane Renal Group Specialised Register was searched for randomised controlled trials relating to the prevention of progression of kidney disease in people with diabetes mellitus Type 1 and Type 2. Specific interventions included antihypertensive therapies, ACE inhibitors, AII receptor antagonists, calcium channel blockers, dietary protein restriction and glucose control, and interventions to control hypercholesterolemia and hyperlipidemia.
Date of search: 16 December 2003.

WHAT IS THE EVIDENCE?

There are no randomised controlled trials (RCTs). Evidence is limited to retrospective analysis, and may therefore be subject to recall and selection bias. It is not absolutely established that smoking is a true independent risk factor independent of possible associated confounders such as non-compliance, accelerated vascular disease, and hypertension.

Type 1 diabetes

In Type 1 diabetes, smoking increases the risks of:

- Developing microalbuminuria

Chase *et al.*[1] – 359 young Type 1 diabetics were studied. The authors found abnormal albumin excretion ratio (AER) risk to be increased 2.8 times in smokers.

Rossing *et al.*[2] – median 9-year follow up of a cohort of 537 Type 1 normotensive, normoalbuminuric diabetics at the Steno centre. The study identified RR of smoking in progression to microalbuminuria or macroalbuminuria as 1.61 (95%CI: 1.11–2.33).

- Progression from microalbuminuria to overt proteinuria[2]
- Decreasing the time over which these developments occur, and end-stage kidney disease (ESKD) develops.[3,4]

Sawicki *et al.*[5] calculated that the adjusted odds ratios for a 20% increase in proteinuria/year, and/or a > 20%/year reduction in GFR increased by 2.7 for every 10 pack years smoked.

One prospective observational cohort study at the Steno Diabetes Centre[6] reported conflicting results. A total of 301 albuminuric Type 1 diabetics followed for at least 3 years, the study was unable to demonstrate statistically significant differences in GFR decline between non-smokers, former smokers or current smokers. These negative results may reflect a type 2 statistical error, or may be influenced by the stringent definition of 'smoking' as > 1 cigarette/day for part or all of the study.

Cessation of smoking has been associated with reduction in AER[1] and in progression of kidney failure.[5]

Type 2 diabetes

In Type 2 diabetes, smoking increases the risks of developing microalbuminuria.[7] Gambaro *et al*[8] followed 273 Type 2 diabetics for 3 years, identifying smoking as an important and graded risk factor for development and progression of microalbuminuria.

Chuahirun and Wesson[9] prospectively sought predictors of kidney function decline in 33 Type 2 diabetic patients, successfully targeting a mean blood pressure goal of 92 mmHg (about 125/75 mmHg) with antihypertensives,

including ACE inhibitors. Initial plasma creatinine was < 1.4 mg/dL and follow-up was 64.0 ± 1.1 months. Regression analysis showed that smoking was the only examined parameter that significantly predicted renal function decline. In the 13 smokers, serum creatinine increased from 1.05 ± 0.08 mg/dL to 1.78 ± 0.20 mg/dL although mean arterial pressure was the same. The 20 non-smokers had a lesser creatinine rise at 1.08 ± 0.03 mg/dL to 1.32 ± 0.04 mg/dL.

The effect of smoking appears to counteract the protective effects of improved blood pressure control and angiotensin-converting enzyme inibition in diabetic nephropathy.[10] In this study of 84 hypertensive Type 2 diabetics, smoking and albuminuria were interrelated risk factors for renal function deterioration over 64 months' mean follow-up.

The same group[11] reported a 6-month study in 157 Type 2 diabetic smokers and non-smokers along a spectrum of normo-, micro- and macroalbuminuria, and an additional 80 Type 2 diabetic quitters. Urinary transforming growth factor (TGF)-beta-1 excretion was measured as a surrogate for progression, and was higher in smokers than non-smokers in each albuminuria group, and returned to non-smokers' levels in quitting smokers.

Baggio *et al*[12] evaluated GFR, metabolic profile, and quantitative renal biopsy findings in 96 patients with Type 2 diabetes and increased AER, 48 of whom smoked.

Compared with non-smokers, smokers had higher HbA_{1c} ($P = 0.002$), AER ($P = 0.026$), GFR ($P = 0.004$), and glomerular basement membrane (GBM) width ($P = 0.002$). GFR was higher in current smokers than in former smokers ($P = 0.001$), and GBM width was related to heavy smoking ($F = 5.4$; $P = 0.006$).

What is the evidence in children?

Couper *et al*[13] documented increased risk of microalbuminuria in adolescent diabetics who smoke.

SUMMARY OF THE EVIDENCE

There are no randomised clinical trials, but the consensus from multiple large cohort studies is that smoking accelerates both the development and progression of nephropathy in both Type 1 and Type 2 diabetes, and that the size of this effect is clinically important. Cessation of smoking is associated with improvement in the rate of progression in smaller cohort studies.

WHAT DO THE OTHER GUIDELINES SAY?

Kidney Disease Outcomes Quality Initiative (2004): "... the large sample sizes and adequate methodological quality and applicability of the studies supporting the association of smoking with faster rate of GFR decline provide reasonable evidence that there may be a deleterious effect of smoking on rate of progression."[14]
UK Renal Association: No recommendation.
Canadian Society of Nephrology: No recommendation.
European Best Practice Guidelines: No recommendation.
International Guidelines:
American Association of Clinical Endocrinologists (2002): These guidelines advise 'cessation of smoking'.
American Diabetes Association (2004): Advise all patients not to smoke. (A), include smoking cessation counselling and other forms of treatment as routine components of diabetes care. (B).[15]

IMPLEMENTATION AND AUDIT

No recommendation.

SUGGESTIONS FOR FUTURE RESEARCH

No recommendation.

REFERENCES

1. Chase HP, Garg SK, Marshall G *et al*. Cigarette smoking increases the risk of albuminuria among subjects with Type 1 diabetes. *JAMA* 1991; **265**: 614–7.
2. Rossing P, Hougaard P, Parving HH. Risk factors for development of incipient and overt diabetic nephropathy in type 1 diabetic patients: a 10-year prospective observational study. *Diabetes Care* 2002; **25**: 859–64.
3. Stegmayr BG. A study of patients with diabetes mellitus (Type 1) and end-stage renal failure: tobacco use may increase risk of nephropathy and death. *J. Intern. Med.* 1990; **228**: 121–4.
4. Stegmayr B, Lithner F. Tobacco and end stage diabetic nephropathy. *Br. Med. J.* 1987; **295**: 581–2.
5. Sawicki PT, Didjurgeit U, Muhlhauser I *et al*. Smoking is associated with progression of diabetic nephropathy. *Diabetes Care* 1994; **17**: 126–31.
6. Hovind P, Rossing P, Tarnow L *et al*. Smoking and progression of diabetic nephropathy in type 1 diabetes. *Diabetes Care*. 2003; **26**: 911–6.
7. Biesenbach G, Grafinger P, Janko O *et al*. Influence of cigarette smoking on the progression of clinical diabetic nephropathy in type 2 diabetic patients. *Clin. Nephrol.* 1997; **48**: 146–50.
8. Gambaro G, Bax G, Fusaro M *et al*. Cigarette smoking is a risk factor for nephropathy and its progression in type 2 diabetes mellitus. *Diabetes Nutr Metab*. 2001; **14**: 337–42.
9. Chuahirun T, Wesson DE. Cigarette smoking predicts faster progression of type 2 established diabetic nephropathy despite ACE inhibition. *Am. J. Kidney Dis*. 2002; **39**: 376–82.
10. Chuahirun T, Khanna A, Kimball K *et al*. Cigarette smoking and increased urine albumin excretion are interrelated predictors of nephropathy progression in type 2 diabetes. *Am. J. Kidney Dis*. 2003; **41**: 13–21.
11. Chuahirun T, Simoni J, Hudson C *et al*. Cigarette smoking exacerbates and its cessation ameliorates renal injury in type 2 diabetes. *Am. J. Med. Sci*. 2004; **327**: 57–67.
12. Baggio B, Budakovic A, Dalla Vestra M *et al*. Effects of cigarette smoking on glomerular structure and function in type 2 diabetic patients. *J. Am. Soc. Nephrol*. 2002; **13**: 2730–6.
13. Couper J, Staples AJ, Cocciolone R *et al*. Relationship of smoking and albuminuria in children with insulin-dependent diabetes. *Diabet Med*. 1994: 11: 666–9.
14. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease. Evaluation, classification, and stratification. *Am. J. Kidney Dis*. 2002; **39** (2 Suppl. 1): SI–S266.
15. American Diabetes Association. Standards of medical care in diabetes. *Diabetes Care* 2004; **27** (Suppl. 1): S15–S35.

Control of hypercholesterolaemia and progression of diabetic nephropathy

Date written: September 2004
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GUIDELINES

All hypercholesterolaemic diabetics should be treated with HMG-CoA reductase inhibitor to retard progression of nephropathy. (Level III evidence for Type 1 diabetes; Level II evidence for Type 2 diabetes – small volume of data) There is no evidence on which to base recommendations for target total cholesterol, LDL, HDL or triglyceride levels. All diabetic patients should receive statin therapy for cardiovascular protection. (Level I evidence)

SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on Level III and IV sources)

- **In the absence of evidence to guide target lipid levels for renal endpoints, it is reasonable to follow the recommendations of the National Heart Foundation and the Australian Diabetes Association Guidelines – recommend fasting total cholesterol level < 5.0 mmol/L, LDL < 3.0 mmol/L.**

BACKGROUND

Hyperlipidaemia is a risk factor for progression of multiple experimental models of renal disease, and human studies indicate that it may also accelerate non-diabetic renal disease, as well as being a well-recognized vascular risk factor. This section reviews the evidence that therapy to lower lipids protects against the progression of diabetic nephropathy. Evidence that lowering lipid levels with HMG-CoA reductase inhibitors has cardiovascular benefit is strong, and for practical purposes will drive therapy in diabetic patients. This evidence will not be reviewed here.

SEARCH STRATEGY

Databases searched: The Cochrane Renal Group Specialised Register was searched for randomised controlled trials (RCTs) relating to the prevention of progression of kidney disease in people with diabetes mellitus Type 1 and Type 2. Specific interventions included antihypertensive therapies, ACE inhibitors, AII receptor antagonists, calcium channel blockers, dietary protein restriction and glucose control, and interventions to control hypercholesterolemia and hyperlipidemia.
Date of search: 16 December 2003.

WHAT IS THE EVIDENCE?

There are no large long-term RCTs designed to determine whether or not control of hypercholesterolaemia, and/or treatment with HMG-CoA reductase inhibitors retard progression of diabetic nephropathy. One meta-analysis[1] studied rate of renal function decline in 13 prospective controlled studies, done over 3–24 months and published between 1991 and 1999. Of a total of 404 patients, 253 were diabetic. There was a lower rate of glomerular filtration rate (GFR) decline in patients on lipid-lowering agents (95%CI: 0.026–0.285 mL/min/month, P = 0.008), especially in the longer follow-up groups. There was also a trend to lower proteinuria or albuminuria (P = 0.077).

Type 1 diabetes

Mulec[2] followed 31 diabetics with established nephropathy, and observed a greater GFR decline rate in hypercholesterolaemic patients (Chol >7 mmol/L GFR decline 8.4 mL/min/year; Chol <7 mmol/L GFR decline 2.3 mL/min/year).

The Joslin Group also demonstrated hypercholesterolaemia to predict rapid loss of renal function in Type 1 diabetics with overt nephropathy.[3]

Type 2 diabetes

Nielsen *et al*[4] performed a very small RCT (double-blind, randomized and placebo-controlled) of the effect of simvastatin (10–20 mg/day) on renal function and insulin sensitivity in 18 Type 2 diabetics with microalbuminuria and moderate total cholesterol ≥ 5.5 mmol/L. Simvastatin ($n = 8$) for 36 weeks significantly reduced total cholesterol, LDL-cholesterol and apolipoprotein B, but neither GFR nor urinary albumin excretion rate changed significantly during the study in either group.

Gall *et al*[5] followed a cohort of 176 patients with Type 2 diabetes mellitus and normoalbuminuria for median follow-up of 5.8 years to determine the risk factors associated with the development of incipient and overt diabetic nephropathy.

They documented that increased cholesterol level was an independent risk factor for progression to nephropathy (RR 1.4, 95%CI: 1.1–1.7, $P < 0.01$).

Lam *et al*[6] (RCT, placebo-controlled study) showed benefit of HMG-CoA reductase inhibition over 2 years in 34 Type 2 diabetics with hypercholesterolaemia and overt nephropathy with stabilized GFR, whereas the placebo group had decreased GFR. There was no significant change in proteinuria.

The GREACE study[7,8] was not a RCT, but prospectively evaluated the effect of 3 years of 'structured' treatment with atorvastatin (to LDL < 2.6 mmol/L, mean dose 23.7 mg/day) vs. non-standardized 'usual care' on morbidity and mortality of 1600 patients with coronary heart disease (CHD), with analysis of the subgroup with diabetes ($n = 313$). A total of 17% of the usual care patients were on long-term hypolipidemic drug treatment. During the study, 46 of 152 (30%) diabetic CHD patients on usual care vs. 20 of 161 (12.5%) patients on structured care experienced a major vascular event or died; RRR 58%, P < 0.0001. The RRRs for the primary endpoints were: all-cause mortality 52%, P = 0.049; coronary mortality 62%, P = 0.042; coronary morbidity 59%, P < 0.002; and stroke 68%, P = 0.046. Event rate curves started deviating from the sixth treatment month and the RRR was almost 60% by the 12th month, remaining stable for the next 2 years.

Renal functional decline was reported separately.[8] All patients had initially normal plasma creatinine, with 642 patients K/DOQI Stage 1, 864 Stage 2, and 94 Stage 3. Creatinine clearance (Ccr) was estimated (for up to 48 months) by the Cockroft-Gault formula, at baseline, 6 weeks, then 6-monthly. Patients from both groups not treated with statins showed a 5.2% decrease in Ccr (P < 0.0001). Usual care patients on various statins (simvastatin, pravastatin, atorvastatin or fluvastatin, in total 97 patients) had a 4.9% increase in Ccr (P = 0.003). Structured care patients on atorvastatin had a 12% increase in Ccr (P < 0.0001). This effect was more prominent in the lower two quartiles of baseline Ccr (patients with a GFR < 77 mL/min had a mean increase in Ccr of 15.4%) and with higher atorvastatin doses (40–80 mg/day; $n = 112$, showed 13.8% increase in Ccr, while in those on 10–20 mg/day; $n = 688$, Ccr increase was 10.9%, P = 0.001). Statin treatment prevented the decline in renal function seen in untreated dyslipidaemic patients with CHD. In treatment-based analysis, 687 patients in the usual care group showed a mean reduction in Ccr of 5.3% (P < 0.0001). Seventeen patients in the structured care group who discontinued atorvastatin for various reasons, had a decrease in Ccr of 4.9% (P = 0.02).

Whether or not HMG-CoA reductase inhibition confers benefit for renal endpoints in diabetes is highly unlikely to ever be adequately studied in humans, because the weight of evidence for cardiovascular benefit is strong, even in normolipaemic patients without evidence of cardiovascular disease. Studies in microalbuminuric diabetic patients are limited by small patient numbers, short duration of follow-up, and lack renal functional endpoints.

The diabetic patient subgroup ($n = 5963$) of the MRC/BHF Heart Protection Study,[9] in which patients were randomly allocated to receive 40 mg simvastatin daily or matching placebo, had a 22% (95%Cl: 13–30) reduction in first event rate (major coronary event, stroke or revascularization) on simvastatin (601 [20·2%] simvastatin vs. 748 [25·1%] placebo, P < 0·0001). There were also highly significant reductions of 33% (95%Cl: 17–46, P = 0·0003) among the 2912 diabetic participants who did not have any diagnosed occlusive arterial disease at entry, and of 27% (95%Cl: 13–40, P = 0·0007) among the 2426 diabetic participants whose pretreatment LDL cholesterol concentration was below 3.0 mmol/L (116 mg/dL). Risk reduction was similar in Type 1 and Type 2 diabetics. In participants who had a first major vascular event following randomization, allocation to simvastatin reduced the rate of subsequent events. The average difference in LDL cholesterol was 1·0 mmol/L during the 5-year treatment period. In diabetic patients without occlusive arterial disease, 5 years of treatment would be expected to prevent about 45 people per 1000 from having at least one major vascular event, and among these 45, to prevent 70 first or subsequent events.

Another primary prevention randomised, placebo-controlled trial in Type 2 diabetic patients[10] showed a 37% risk reduction in cardiovascular events in patients treated with atorvastatin 10 mg/day.

SUMMARY OF THE EVIDENCE

There are no adequate RCTs with functional endpoints and long-term follow up. One metaanalysis of 13 small, prospective, controlled studies in which diabetics were enrolled suggested benefit of HMG-CoA reductase inhibition, as did cohort studies. The GREACE prospective cohort study in 1600 patients included diabetic subjects and indicated risk reduction for progression of renal dysfunction in hyperlipidaemic patients with coronary disease when they were treated with high-dose statins. For practical purposes, the argument to treat dyslipidaemia for renal outcome is overwhelmed by the very large body of Level I evidence for vascular risk reduction.

WHAT DO THE OTHER GUIDELINES SAY?

Kidney Disease Outcomes Quality Initiative (2004): No recommendation.

UK Renal Association: No recommendation.

Canadian Society of Nephrology: No recommendation.

European Best Practice Guidelines: No recommendation.

American Diabetic Association (2001): For adult diabetics, aim LDL < 2.6, HDL > 1.15 male, 1.40 female. Initiate drug therapy at LDL > 3.35. Aim TG < 2.3. Children – LDL < 2.8.[11]

American Diabetic Association (2004): Use statin in all diabetics > 40 with total cholesterol 5.5, to achieve an LDL reduction of approximately 30% regardless of baseline LDL (A).[12]

The first priority of pharmacological therapy is to lower LDL cholesterol to 2.60 mmol/L. For LDL lowering, statins are the drugs of choice and should be added to lifestyle modification focusing on the reduction of saturated fat and cholesterol intake, weight loss, increased physical activity, and smoking cessation (A).

Lowering LDL cholesterol with a statin is associated with a reduction in cardiovascular events (A).

In children and adolescents with diabetes, LDL cholesterol should be lowered to 2.60 mmol/L (E).

ACE (2000): Goal LDL < 2.6.

National Heart Foundation Australia: Total cholesterol < 5.0, LDL < 3.0.

Scottish Intercollegiate Guideline Network (2001): Use drug therapy as primary cardiovascular prevention in Type 2 diabetics without nephropathy when 10-year risk of major cardiovascular event > 30%.

American College of Physicians: Control lipid levels in type 2 diabetes to macrovascular risks: use as secondary prevention in all patients with known coronary artery disease and as primary prevention in patients with any other cardiovascular risk factor. Recommendations apply equally to men and to women. Once lipid-lowering therapy is initiated, patients should take at least a moderate dose of a statin: e.g. atorvastatin 20 mg, lovastatin 40 mg, pravastatin 40 mg or simvastatin 40 mg. Trials have generally not helped in defining target levels for either total cholesterol or LDL cholesterol. Benefits have been obtained regardless of baseline lipids, and when treatment targets were set in earlier trials they were sometimes higher than those commonly accepted today.[13]

Canadian Diabetes Association: Treat patients at high risk of vascular event: LDL-C < 2.5 mmol/L and TC: HDL-C < 4.0; and for patients at moderate risk of vascular event LDL-C < 3.5 mmol/L and TC: HDL-C <5.0 (Grade D, consensus). Although current evidence does not support specific targets for apoB or TG, the optimal TG level is < 1.5, and optimal apoB < 0.9 g/L for high-risk, and < 1.05 g/L for moderate-risk patients (Grade D, consensus).

IMPLEMENTATION AND AUDIT

No recommendation.

SUGGESTIONS FOR FUTURE RESEARCH

No recommendation.

APPENDICES

Table 1 Characteristics of included studies

Study ID (author, year)	N	Study design	Setting	Participants	Intervention (experimental group)	Intervention (control group)	Follow up (months)	Comments
Lam *et al*, 1995	36	Randomised controlled clinical trial	University hospital	34 Chinese NIDDM patients	Lovastatin	Placebo	2 years	

REFERENCES

1. Fried LF, Orchard TJ, Kasiske BL. Effect of lipid reduction on the progression of renal disease: a meta-analysis. *Kidney Int*. 2001; **59**: 260–9.
2. Mulec H, Johnson SA, Bjorck S. Relationship between serum cholesterol and diabetic nephropathy. *Lancet* 1990; **335**: 1537–8.
3. Krolewski AS, Warram JH, Christlieb AR. Hypercholesterolemia: a determinant of renal function loss and deaths in IDDM patients with nephropathy. *Kidney Int. Suppl*. 1994; **45**: S125–S31.
4. Nielsen S, Schmitz A, Rehling M *et al*. Systolic blood pressure relates to the rate of decline of glomerular filtration rate in type II diabetes. *Diabetes Care* 1993; **16**: 1427–32.
5. Gall MA, Hougaard P, Borch-Johnsen K *et al*. Risk factors for development of incipient and overt diabetic nephropathy in patients with non-insulin dependent diabetes mellitus: prospective, observational study. *BMJ*. 1997; **314**: 783–8.
6. Lam KSL, Cheng IKP, Janus ED *et al*. Cholesterol-lowering therapy may retard the progression of diabetic nephropathy. *Diabetologia* 1995; **38**: 604–9.
7. Athyros VG, Papageorgiou AA, Symeonidis AN *et al*; GREACE Study Collaborative Group. Early benefit from structured care with atorvastatin in patients with coronary heart disease and diabetes mellitus. *Angiology* 2003; **54**: 679–90.
8. Athyros VG, Mikhailidis DP, Papageorgiou AA *et al*. The effect of statins versus untreated dyslipidaemia on renal function in patients with coronary heart disease. A subgroup analysis of the Greek atorvastatin and coronary heart disease evaluation (GREACE) study. *J. Clin. Pathol*. 2004; **57**: 728–34.
9. Lindholm LH. Major benefits from cholesterol lowering in patients with diabetes. *Lancet* 2003; **361**: 2000–1.
10. Colhoun HM, Betteridge DJ, Durrington PN *et al*. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet* 2004; **364**: 685–96.
11. Molitch ME, De Fronzo RA, Franz MJ *et al*. Diabetic nephropathy. *Diabetes Care* 2003; **26** (Suppl. 1): S94–S98.
12. American Diabetes Association. Standards of medical care in diabetes. *Diabetes Care* 2004; **27** (Suppl. 1): S15–S35.
13. Snow V, Aronson MD, Hornbake ER *et al*. Lipid control in the management of type 2 diabetes mellitus: a clinical practice guideline from the American College of Physicians. *Ann. Intern. Med*. 2004; **140**: 644–9.

Table 2 Quality of randomised trials

Study ID (author, year)	Method of allocation concealment	Blinding			Intention-to-treat analysis	Loss to follow up (%)
		(participants)	(investigators)	(outcome assessors)		
Lam *et al*, 1995	Block randomisation	Yes	No	No	No	5.6

Table 3 Results for continuous outcomes

Study ID (author, year)	Outcomes	Intervention group (mean [SD])	Control group (mean [SD])	Difference in means [95% CI]
Lam *et al*, 1995	Mean arterial BP (mmHg) at 24 mo	105.9 (12.8)	103.4 (11.9)	2.50 (95%CI: –5.84, 10.84)
	BMI (kg/m^2) at 24 mo	26.3 (4.4)	25.0 (4.24)	1.30 (95%CI: –1.61, 4.21)
	HbA_{1c} (%) at 24 mo	6.6 (1.6)	6.8 (1.70)	–0.20 (95%CI: –1.31, 0.91)
	Total cholesterol (mmol/L) at 24 mo	4.9 (0.4)	6.4 (0.85)	–1.50 (95%CI: –1.94, –1.06)
	Triglyceride (mmol/L) at 24 mo	2.0 (1.6)	3.7 (2.55)	–1.70 (95%CI: –3.12, –0.28)
	HDL–cholesterol (mmol/L) at 24 mo	1.09 (0.24)	0.99 (0.30)	0.10 (95%CI: –0.08, 0.28)
	LDL–cholesterol (mmol/L) at 24 mo	3.0 (0.8)	3.8 (0.85)	–0.80 (95%CI: –1.35, –0.25)
	Apo A1 (h/L) at 24 mo	1.98 (0.32)	1.90 (0.30)	0.08 (95%CI: –0.13, 0.29)
	Apo B (g/L) at 12 mo	1.27 (0.2)	1.50 (0.30)	–0.23 (95%CI: –0.40, –0.06)

Multifactorial therapy and the progression of diabetic nephropathy

Date written: September 2004
Final submission: September 2005
Author: Kathy Nicholls

GUIDELINES

Intensive combination therapy protects against progression of diabetic nephropathy. (Level II evidence for Type 2 diabetes – single RCT) and Level III evidence for Type 1 diabetes – single small cohort study, small volume)

SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on Level III and IV evidence)
• **Patient motivation, compliance and total cost of therapy may be limiting issues. Multifactorial therapy is likely to be embraced long-term only by highly motivated patients. For motivated patients, the limited available data suggest possible synergistic effects of multifactorial intervention, for both micro- and macrovascular endpoints.**

BACKGROUND

The evolution of evidence for multiple single interventions being beneficial in diabetic nephropathy has spawned multiple further questions. Should all patients have all interventions? Will all the variably effective individual interventions be synergistic if used concomitantly? This guideline evaluates the evidence for multiple-intervention strategies in the progression of diabetic nephropathy.

SEARCH STRATEGY

Databases searched: The Cochrane Renal Group Specialised Register was searched for randomised controlled trials relating to the prevention of progression of kidney disease in people with diabetes mellitus Type 1 and Type 2. Specific interventions included antihypertensive therapies, ACE inhibitors, AII receptor antagonists, calcium channel blockers, dietary protein restriction and glucose control, and interventions to control hypercholesterolemia and hyperlipidemia.
Date of search: 16 December 2003.

WHAT IS THE EVIDENCE?

Combined therapy targeting multiple risk factors in diabetic nephropathy has been tested in two studies.

Type 1 diabetes

In an open longitudinal study of 14 Type 1 diabetics, Manto *et al*[1] intensively treated all patients with multiple daily insulin injections, angiotensin-converting enzyme inhibitor (ACEI) antihypertensive treatment to BP 120/75 mmHg, and an 0.8 g/kg/day protein diet. They achieved a rise in glomerular filtration rate (GFR) and decrease in albuminuria over the 3-year study.

Type 2 diabetes

Gaede *et al*[2] randomised 160 microalbuminuric Type 2 diabetics to standard care (treated in accordance with national guidelines for Type 2 diabetes) or to stepwise 'intensive' treatment comprising low-fat diet and exercise, smoking cessation if needed, ACEI (or ARB) independent of BP, Vitamins C, E, and folate, low-dose aspirin, and stepwise pharmacological therapy to reduce glucose levels (aim $HbA_{1c} < 7.0\%$), BP (aim < 140/85 mmHg) and lipid levels (aim cholesterol < 5 mmol/L), with follow up of 3.8 years. In this unblinded trial, the intensive treatment group had lower risk of progression to proteinuria (11% vs. 25% RRR 56%, 95%CI: 9–79, P = 0.01).

The 7.8 years follow-up of this (Steno 2) study was reported by Pedersen and Gæde.[3] There was no difference in weight gain between groups during follow up and no major side-effects. The primary endpoint was a composite macrovascular outcome of death from cardiovascular causes, non-fatal myocardial infarction, coronary artery bypass grafting, percutaneous coronary intervention, non-fatal stroke, amputation for ischemia, or vascular surgery for peripheral arterial atherosclerosis. A total of 44% of patients in the conventional group had a cardiovascular event compared with 24% in the intensive group, hazard ratio 0.47. The secondary endpoints of progression to overt proteinuria (HR 0.39), retinopathy (HR 0.42), and autonomic neuropathy (HR 0.37) were also diminished in the intensively-treated group.

SUMMARY OF THE EVIDENCE

Evidence is sparse, but the effect seems clinically significant.

WHAT DO THE OTHER GUIDELINES SAY?

Kidney Disease Outcomes Quality Initiative: Multiple interventions are required to slow progression of kidney dis-

ease and reduce the risk of cardiovascular disease (CVD) events in diabetic kidney disease. Generally, the approach requires at least 3 antihypertensive agents, intensive insulin therapy in Type 1 diabetes, two drugs for glucose control in Type 2, at least 1 lipid-lowering agent, and emphasis on lifestyle modification including diet and exercise.

UK Renal Association: No recommendation.

Canadian Society of Nephrology: No recommendation.

European Best Practice Guidelines: No recommendation.

International Guidelines:

The American and Canadian Diabetes Associations: recommend aspirin (enteric coated, 81–325 mg/day) for primary cardiovascular prevention in all diabetics > 30 years, especially if another risk factor is present, and also for secondary prevention in all diabetics with evidence of large vessel disease.

The American Diabetes Association Position Statement (2004): recommends aspirin (75–162 mg/day) for:
1) primary cardiovascular prevention in all diabetics with increased cardiovascular risk, including age > 40 or presence of another risk factor (A for Type 2, C for Type 1).
2) secondary cardiovascular prevention in diabetics with a history of myocardial infarction, vascular bypass procedure, stroke or transient ischemic attack, peripheral vascular disease, claudication, and/or angina. (A)
Avoid < 21 years old due to risk of Reye's syndrome. People under the age of 30 have not been studied. Other antiplatelet agents, e.g. clopidogrel may be a reasonable alternative for patients with high risk. (E)

American Association of Clinical Endocrinology (2000): Low dose aspirin > 30 mg/day recommended in all diabetics for primary and secondary prevention.

Canadian Diabetes Association: People with Type 1 or 2 diabetes should be encouraged to adopt a healthy lifestyle to lower their risk of CVD. This entails healthy eating habits, achieving and maintaining a healthy weight, regular physical activity, and stopping smoking (Grade D, consensus).

Scottish Intercollegiate Guideline Network (2001): Use aspirin 75 mg/day as primary cardiovascular prevention in all diabetics with well-controlled hypertension when 10-year risk of major cardiovascular event > 20%.

IMPLEMENTATION AND AUDIT

K-DOQI (2004): The number of medications is one obstacle to adherence – need to consider the cost, side-effects and convenience.

SUGGESTIONS FOR FUTURE RESEARCH

No recommendation.

REFERENCES

1. Manto A, Cotroneo P, Marra G *et al*. Effect of intensive treatment on diabetic nephropathy in patients with type 1 diabetes. *Kidney Int*. 1995; **47**: 231–5.
2. Gaede P, Vedel P, Parving HH *et al*. Intensified multifactorial intervention in patients with type 2 diabetes mellitus and microalbuminuria: the Steno type 2 randomized study. *Lancet* 1999; **353**: 617–22.
3. Pedersen O, Gaede P. Intensified multifactorial intervention and cardiovascular outcome in type 2 diabetes: the Steno-2 study. *Metabolism* 2003; **52** (8 Suppl. 1): 19–23.

APPENDICES

Table 1 Characteristics of included studies

Study ID (author, year)	N	Study design	Setting	Participants	Intervention (experimental group)	Intervention (control group)	Follow up (years)	Comments
Gaede *et al*, 1999	160	Randomised controlled clinical trial	Renal clinic	160 patients with microalbuminuria	Intensive treatment	Standard treatment	3.8	

Table 2 Quality of randomised trials

Study ID (author, year)	Method of allocation concealment	Blinding			Intention-to-treat analysis	Loss to follow up (%)
		(participants)	(investigators)	(outcome assessors)		
Gaede *et al*, 1999	Not specified	No	No	Yes	No	6.9

Table 3 Results for dichotomous outcomes

Study ID (author, year)	Outcomes	Intervention group (number of patients with events/ number of patients exposed)	Control group (number of patients with events/ number of patients not exposed)	Relative risk (RR) [95% CI]	Risk difference (RD) [95% CI]
Gaede *et al*, 1999; Pedersen & Gaede, 2003	CV mortality	3/77	2/78	1.52 (95%CI: 0.26, 8.84)	0.01 (95%CI: –0.04, 0.07)
	Non-fatal myocardial infarction	4/77	4/78	1.01 (95%CI: 0.26, 3.91)	0.00 (95%CI: –0.07, 0.07)
	Non-fatal stroke	1/77	8/78	0.13 (95%CI: 0.02, 0.99)	–0.09 (95%CI: –0.16, –0.02)
	Cardiovascular event	18/73	33/76	0.57 (95%CI: 0.35, 0.91)	–0.19 (95%CI: –0.364, –0.04)

Table 4 Results for continuous outcomes

Study ID (author, year)	Outcomes	Intervention group (mean [SD])	Control group (mean [SD])	Difference in means [95% CI]
Gaede *et al*, 1999	SBP (mmHg)	–8 (18)	–4 (17)	–4.00 (95%CI: –9.63, 1.63)
	DBP (mmHg)	–7 (10)	–5 (10)	–2.00 (95%CI: –5.21, 1.21)
	Total cholesterol (mmol/L)	–0.6 (0.9)	–0.2 (1.3)	–0.40 (95%CI: –0.76, –0.04)
	LDL cholesterol (mmol/L)	–0.4 (0.8)	–0.1 (1.4)	–0.30 (95%CI: –0.66, 0.06)
	HDL cholesterol (mmo/L)	0.02 (0.2)	0.03 (0.2)	–0.01 (95%CI: –0.07, 0.05)
	Serum creatinine (mmol/L)	13 (21)	11 (17)	2.00 (95%CI: –4.15, 8.15)
	GFR (ml/min/1.73 m^2)	–11 (20)	–13 (15)	2.00 (95%CI: –3.69, 7.69)

Analgesic-associated kidney disease

Date written: July 2005
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Author: Merlin Thomas

GUIDELINES

a. Analgesic intake should be discontinued in patients with analgesic nephropathy. (Level II-III evidence)

b. Non-selective COX-1 and COX-2 inhibitors (with the specific exception of low dose aspirin) should be avoided, where possible, in patients with hypertension, as their use is associated with loss of BP control and reduction in efficacy of antihypertensive drug therapy. (Level I evidence)

c. Analgesic and anti-inflammatory therapy form an important component of the management of a variety of chronic degenerative diseases. (Level I evidence) The beneficial effects of these agents should be balanced against the risk of progressive renal damage and hypertension associated with their chronic and habitual use.

SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on Level III and IV evidence)

- **Continued analgesic intake is associated with an increased faster rate of decline of renal function and increased risk of end-stage kidney disease (ESKD) in patients with analgesic nephropathy. (Level II-III evidence; large prospective cohort studies; clinically relevant outcomes; consistent strong effects)**
- **Cessation of analgesic use has been associated with retardation of kidney failure progression. (Level II-III evidence; several retrospective cohort studies; clinically relevant outcomes; variable effects)**
- **The use of non-selective COX-1 and COX-2 inhibitors is associated with loss of BP control and reduction in efficacy of antihypertensive drug therapy. (Level I-II evidence; large meta-analyses and RCTs, clinically relevant outcomes; consistent strong effects)**

BACKGROUND

Combinations of antipyretic analgesics taken in large doses over long periods of time are associated with the development of a slowly progressive kidney disease characterized by papillary necrosis and interstitial scarring. Currently, at least 6% of patients reaching ESKD in Australia have analgesic nephropathy.[1] The objective of this guideline is to evaluate the available clinical evidence pertaining to the impact of interventions on renal functional decline in analgesic nephropathy (AN). This guideline does not address the known associations between AN and malignancy, peptic ulcer disease and cardiovascular disease that may be positively influenced by habitual analgesic use.

SEARCH STRATEGY

Databases searched: The search for MeSH terms and text words for analgesic nephropathy was carried out in Medline (1966 to September Week 2, 2004).
Date of search: 17 September 2004.

WHAT IS THE EVIDENCE?

Habitual analgesic use has been associated with renal impairment and progression to ESKD in a number of large prospective cohort studies:

- 200 patients with active analgesic abuse were followed for 7 years and the rate of decline in renal function compared to age-matched controls. Renal function decline was significantly greater in patients with ongoing analgesic abuse, including a 6.1 times relative risk of renal impairment compared to the control population.[2]
- In a large prospective, longitudinal, epidemiological study of 623 healthy women 30–49 years old who had evidence of a regular intake of phenacetin and a matched control group of 621 women, the relative risk for deaths due to urological or kidney disease was 16.1 (95%CI: 3.9–66.1).[3]

There are no randomised controlled trials (RCTs) in AN.

Australia and New Zealand Dialysis Registry data shows a progressive decline in AN as a cause of ESKD after the withdrawal of phenacetin from compound analgesics in Australia.[4]

In prospective, observational, cohort studies, continued use of analgesics has been associated with an accelerated rate of progression of renal insufficiency in AN.[5,6]

In retrospective, cohort studies, patients with analgesic nephropathy who discontinued using analgesics were less likely to develop ESKD, than those who continued their consumption of analgesics.[7,8] Cessation of analgesic intake may also slow the rate of loss of renal function, even when renal insufficiency is well advanced.[4]

Recent case-control studies have raised the possibility that habitual analgesic use could increase the likelihood or rate of progression of chronic kidney disease (CKD) *per se*. In the study by Sandler *et al.*,[9] the odds ratios for the development of CKD was highest for patients with interstitial nephritis and renal insufficiency of unknown cause who habitually used analgesics. However, there was a borderline increase in the odds ratios for patients with a diagnosis of nephrosclerosis, diabetic nephropathy, and glomerulonephritis. Similarly, Perneger *et al*[10] found the increased risk of CKD was similar in the four groups of patients with renal disease due to diabetic nephropathy, hypertension, other specific causes, and unknown causes. However, there is currently insufficient evidence for a causal association between habitual use of analgesic and an increased risk of ESKD.

Regular use of analgesic drugs containing phenacetin is associated with an increased risk of hypertension (a known risk factor for progressive nephropathy).

- In a large prospective, longitudinal epidemiological study of 623 healthy women 30–49 years old who had evidence of a regular intake of phenacetin and a matched control group of 621 women, the odds ratio for the incidence of hypertension was 1.6 (95%CI: 1.2–2.1).[3] Some of this reflects the increased risk of cardiovascular disease and kidney disease.

Similarly, regular use of non-selective COX-1 and COX-2 inhibitors is associated with an increased risk of hypertension and destabilization of blood pressure control in patients with hypertension.

- Two separate meta-analyses that examine the effects of non-selective COX-1 inhibitors including over-the-counter preparations such as naproxen, indomethacin, and ibuprofen implicate them as contributing to loss of BP control and reduction in efficacy of antihypertensive drug therapy.[11,12]
- COX-2 inhibitors have also been associated with destabilization of blood pressure control in RCTs.[13]

It should be noted that chronic low-dose aspirin has not been associated with detrimental effects on blood pressure control.[11,14,15]

SUMMARY OF THE EVIDENCE

Therapy with non-selective COX-1 and COX-2 inhibitors is associated with loss of BP control and reduction in efficacy of antihypertensive drug therapy in some patients. As blood pressure control is a key component part of the management of patients with CKD, it is recommended that these agents should be avoided, where possible, in patients with CKD. This recommendation does not apply to low dose aspirin, which has neutral effects on BP control, together with beneficial effects on cardiovascular outcomes.

Analgesic intake should be discontinued in patients with analgesic nephropathy, as early as possible, to have the greatest likelihood of slowing the progressive kidney scarring associated with habitual analgesic use.

Analgesic and anti-inflammatory therapy form an important component part of the management of a variety of chronic degenerative diseases. The beneficial effects of these agents should be balanced against the risk of progressive kidney damage and hypertension associated with their chronic and habitual use.

WHAT DO THE OTHER GUIDELINES SAY?

Kidney Disease Outcomes Quality Initiative: Attempts should be made to prevent and correct acute decline in GFR. Frequent causes of acute decline in GFR include non-steroidal anti-inflammatory agents, including cyclo-oxygenase type 2 inhibitors.[16]
UK Renal Association: No recommendation.
Canadian Society of Nephrology: No recommendation.
European Best Practice Guidelines: No recommendation.
International Guidelines:
Analgesic-Associated Kidney Disease. NIH Consensus Statement 1984:[8]

The main strategies of management must include:

1 Avoidance of antipyretic-analgesic agents, as well as non-steroidal anti-inflammatory drugs.
2 Prompt treatment of proven urinary tract infections.
3 Awareness that a necrotic papilla may slough and obstruct the urinary tract, sometimes requiring prompt intervention to prevent further loss of renal function.
4 Careful supervision of hypertension.
5 Recognition that tumours of the urinary tract may occur more frequently in patients with analgesic nephropathy. Unexplained episodes of haematuria, including a marked increase in microscopic haematuria, should therefore be evaluated carefully.
6 Consideration of the non-renal manifestations of the analgesic abuse syndrome.

Ad Hoc Committee of the International Study Group on Analgesics and Nephropathy:[17]
1 There is insufficient evidence to associate non-phenacetin combined analgesics with nephropathy.
2 New studies should be done to provide appropriate data to resolve the question.
US Food and Drug Administration (FDA): Analgesic combination containing paracetamol, aspirin, and caffeine is safe and effective for the use in uncomplicated migraine.

IMPLEMENTATION AND AUDIT

No recommendation.

SUGGESTIONS FOR FUTURE RESEARCH

The recent reintroduction of compound analgesics containing paracetamol and caffeine as OTC medications in New

Zealand and Asia (but not Australia) should be closely monitored by renal physicians.

REFERENCES

1. McDonald SP, Russ G. New Patients, pp. 8–14. ANZDATA Registry Report 2003. Australia and New Zealand Dialysis and Transplant Registry, Adelaide, South Australia.
2. Elseviers MM, De Broe ME. A long-term prospective controlled study of analgesic abuse in Belgium. *Kidney Int*. 1995; **48**: 1912–3.
3. Dubach UC, Rosner B, Sturmer T. An epidemiologic study of abuse of analgesic drugs. Effects of phenacetin and salicylate on mortality and cardiovascular morbidity (1968–87) *N Engl. J. Med*. 1991; **324**: 155–60.
4. McCredie M, Stewart JH, Mathew TH *et al*. The effect of withdrawal of phenacetin-containing analgesics on the incidence of kidney and urothelial cancer and renal failure. *Clin. Nephrol*. 1989; **31**: 35–9.
5. MacKinnon B, Boulton-Jones M, McLaughlin K. Analgesic-associated nephropathy in the West of Scotland: a 12-year observational study. *Nephrol. Dial. Transplant* 2003; **18**: 1800–5.
6. Hauser AC, Derfler K, Balcke P. Progression of renal insufficiency in analgesic nephropathy: impact of continuous drug abuse. *J. Clin. Epidemiol*. 1991; **44**: 53–6.
7. Gonwa TA, Hamilton RW, Buckalew VM Jr. Chronic renal failure and end-stage renal disease in northwest North Carolina. Importance of analgesic-associated nephropathy. *Arch. Intern. Med*. 1981; **141**: 462–5.
8. Kindler J, Giani G, Handt S *et al*. The effect of various factors on the progression of kidney insufficiency cause by analgesic nephropathy. *Klin Wochenschr* 1990; **68**: 1042–9.
9. Sandler DP, Smith JC, Weinberg CR *et al*. Analgesic use and chronic renal disease. *N Engl. J. Med*. 1989; **320**: 1238–43.
10. Perneger TV, Whelton PK, Klag MJ. Risk of kidney failure associated with the use of acetaminophen, aspirin, and nonsteroidal antiinflammatory drugs. *N Engl. J. Med*. 1994; **331**: 1675–9.
11. Johnson AG, Nguyen TV, Day RO. Do nonsteroidal anti-inflammatory drugs affect blood pressure? A meta-analysis. *Ann. Intern. Med*. 1994; 121: 289–300.
12. Pope JE, Anderson JJ, Felson DT. A meta-analysis of the effects of nonsteroidal anti-inflammatory drugs on blood pressure. *Arch Intern Med* 1993; **153**: 477–484.
13. Sowers JR, White WB, Pitt B *et al*. Celecoxib Rofecoxib Efficacy and Safety in Comorbidities Evaluation Trial (CRESCENT) Investigators. The effects of cyclooxygenase-2 inhibitors and nonsteroidal anti-inflammatory therapy on 24-hour blood pressure in patients with hypertension, osteoarthritis, and type 2 diabetes mellitus. *Arch Intern Med* 2005; **165**: 161–8.
14. Avanzini F, Palumbo G, Alli C *et al*. Effects of low-dose aspirin on clinic and ambulatory blood pressure in treated hypertensive patients. Collaborative Group of the Primary Prevention Project (PPP) – Hypertension Study. *Am. J. Hypertens*. 2000; **13**: 611–6.
15. Nawarskas JJ, Townsend RR, Cirigliano MD *et al*. Effect of aspirin on blood pressure in hypertensive patients taking enalapril or losartan. *Am. J. Hypertens* 1999; **12**: 784–9.
16. National Kidney Foundation. K/DOQI Clinical Practice Guidelines for Chronic Kidney Disease; Evaluation, Classification and Stratification. *Am. J. Kidney Dis* 2002; **39** (Suppl. 1): S1–S266.
17. Feinstein AR, Heinemann LA, Curhan GC *et al*. Relationship between nonphenacetin combined analegesics and nephropathy: a review. Ad Hoc Committee of the International Study Group on Analgesics and Nephropathy. *Kidney Int*. 2000; **58**: 2259–64.

Renal artery stenosis

Date written: July 2005
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Author: Merlin Thomas

GUIDELINES

a. Correction of renal artery stenosis (RAS), either by re-vascularization surgery or percutaneous methods, has been shown to be effective in treating hypertension associated with renal artery stenosis. (Level II evidence)

b. Balloon angioplasty has not been shown to be superior to medical management for preserving renal function in patients with renal artery stenosis. (Level I evidence)

c. Balloon angioplasty has not been shown to be superior to angioplasty with stenting for preserving renal function in patients with renal artery stenosis. (Level II evidence – multiple studies)

d. Balloon angioplasty has not been shown to be superior to surgical management in experienced centres for preserving renal function in patients with renal artery stenosis. (Level II evidence – one RCT)

SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on Level III and IV evidence)

- **In the absence of trials showing benefit from revascularization over conventional therapy and the significant risk of complications it seems reasonable to restrict procedures to patients who fail medical therapy with resistant or poorly-controlled hypertension; recurrent flash pulmonary oedema; dialysis-dependent kidney failure resulting from renal artery stenosis; chronic renal insufficiency and bilateral renal artery stenosis; or renal artery stenosis to a solitary functioning kidney.**
- **In the absence of significant differences in long-term outcome measures, given the rates of restenosis following simple balloon angioplasty and the complications and costs of surgical intervention, it would seem reasonable to consider angioplasty with stenting as the revascularization procedure of choice for medically recalcitrant renal artery stenosis. (Level IV evidence)**
- **The above clinical guidelines refer to patients with significant de novo renal artery stenosis (generally more than 50–80% reduction in luminal diameter). There have been no studies in patients identified with lesser degrees of stenosis. It seems reasonable to offer medical therapy in these individuals, given the natural history of progressive stenosis in atherosclerotic renal disease.**

BACKGROUND

RAS is an important cause of renal insufficiency, having an estimated prevalence of 10% to 15% among patients approaching end-stage kidney disease (ESKD).[1] Stenosis of the extra-parenchymal renal arteries caused by atherosclerotic lesions may lead to progressive renal ischaemia and the development of an 'ischaemic atrophic nephropathy', chronic renal insufficiency and loss of renal mass. Fifty per cent of patients with RAS have some degree of renal excretory function impairment, and nearly one third have only a single functioning kidney.[2] The objective of this guideline is to evaluate the available clinical evidence pertaining to the impact of interventions on renal functional decline in patients with RAS. This guideline does not address the potential utility of these interventions in reducing cardiovascular risk.

SEARCH STRATEGY

Databases searched: MeSH terms and text words for renal artery stenosis were searched for in Medline (1966 to September Week 2, 2004). The Cochrane Renal Group Trials Register was also searched for trials not indexed in Medline.
Date of searches: 17 September 2004.

WHAT IS THE EVIDENCE?

Correction of RAS, either by re-vascularization surgery or percutaneous methods, has been shown to be effective in treating hypertension. Some uncontrolled studies report either a cure or improvement of hypertension of between 59% to 78% of patients,[3] although blood pressure (BP) improvements may have been overestimated in some of these studies due to optimization of drug treatment in interventional arms.[4] While improvements may be achieved with re-vascularization, it is sometimes at the expense of serious complications, including mortality. The extent to which any intervention delays the progression to ESKD independent of BP control has not been clearly established. Moreover, accurate interpretation of renal function outcomes in many of these studies is difficult, given the short duration of many of these trials.

A. Balloon angioplasty

There have been three randomised controlled trials (RCTs) comparing balloon angioplasty with medical therapy in

hypertensive patients with significant RAS (greater than 50% reduction in luminal diameter) involving 210 patients.

- In the DRASTIC study,[5] 106 patients with hypertension, significant atherosclerotic RAS and a serum creatinine concentration less than 200 μmol/L were randomly assigned to undergo percutaneous transluminal renal angioplasty or to receive antihypertensive drug therapy, followed by balloon angioplasty (if needed) at 3 months. Overall BPs and renal function were similar in the two groups at 3 and 12 months, although angioplasty reduced the need for 1 additional daily antihypertensive agent. However, after subgroup analysis, it was found that in patients with bilateral stenoses, the creatinine clearance (Ccr) improved in the angioplasty group, but fell in patients assigned to the delayed intervention group.
- A Scottish group reported a prospective randomised trial of percutaneous angioplasty vs. medical therapy in patients with bilateral or unilateral atherosclerotic RAS and sustained hypertension.[6] In the bilateral group ($n = 28$), the drop in systolic pressure was significantly larger following angioplasty than following medical therapy, but diastolic pressure and creatinine after 24 months was not different with either intervention. In the unilateral group ($n = 27$), there was no difference in serum creatinine or BP control between angioplasty or medical therapy.
- In the EMMA study,[7] hypertensive patients were randomly assigned antihypertensive drug treatment ($n = 26$) or angioplasty ($n = 23$). They also found that BP at 6 months did not differ between control ($141 \pm 15/84 \pm 11$ mmHg) and angioplasty ($140 \pm 15/81 \pm 9$ mmHg) groups. Angioplasty reduced the requirement for antihypertensive therapy at the cost of some procedural morbidity.
- A meta-analysis of these studies determined that there was a consistent but statistically non-significant trend towards lower blood pressure in the balloon angioplasty group. In addition, there were no differences in renal function. However, patients treated with balloon angioplasty required fewer antihypertensive drugs in 2 of 3 trials. In addition, there were significantly fewer cardiovascular and renovascular complications in patients treated with angioplasty (OR 0.32, 95%CI: 0.15–0.70, test for heterogeneity $P > 0.1$).

Despite achieving changes in arterial patency, none of these studies has shown significant advantage in slowing of renal progression through renal angioplasty over and above conventional medical therapy. Interpretation is limited by the fact that each of these studies has focused on patients with hypertension rather than those with documented progressive renal impairment.

B. Renal artery stenting

Some studies have suggested that angioplasty followed by intravascular stenting is a better technique than angioplasty alone to achieve vessel patency, particularly in ostial atherosclerotic renal-artery stenosis.[8] It has also been suggested that hypertension is better controlled, re-stenosis is minimized and athero-embolic injury limited with stenting compared with conventional balloon angioplasty.[9] There have been 5 uncontrolled prospective studies on the effect of renal stenting on progression of kidney disease.

- Watson *et al*[10] prospectively studied the effect of renal artery stenting on renal function and size in 33 patients with chronic renal insufficiency and bilateral renal artery stenosis or unilateral stenosis in the presence of a solitary or single functional kidney. Before stent deployment, all patients had evidence of progressive renal insufficiency. After stent deployment, renal function improved in 18 and slowed in 7 patients. Ultrasonography revealed preservation of kidney size.
- Harden *et al*[11] studied 33 patients with atherosclerotic RAS undergoing renal stenting. Renal function improved or stabilized in 69% of patients.
- Rundback *et al*[12] evaluated the effect of renal artery stenting in 45 patients with renal impairment (creatinine ≥ 1.5 mg/dL) and atheromatous renal artery stenosis untreatable by, or recurrent after, balloon angioplasty. Stent implantation was unilateral in 32 cases and bilateral in 11 cases. With use of life-table analysis, clinical benefit was seen in 78% of patients at 6 months ($n = 36$) and 72% at 1 year ($n = 24$). In patients with clinical benefit, average creatinine concentration was reduced from 2.21 mg/dL ± 0.91 before treatment to 2.05 mg/dL ± 1.05 after treatment. Lower initial serum creatinine concentration was associated with a better chance of clinical benefit.
- Shannon *et al*[13] described the use of renal artery stents in the solitary functioning kidney of 21 patients with impaired renal function as a result of atherosclerotic RAS. At follow-up (range, 6–25 months), renal function had returned to normal in five patients (24%), improved in four patients (19%), stabilized in six patients (29%), and deteriorated in six patients (29%). Dialysis was discontinued in all four dialysis patients.
- Bucek *et al*[14] prospectively followed 40 patients who had undergone successful stenting of a main renal artery. All patients still suffered from arterial hypertension but compared with the preinterventional situation, arterial hypertension was improved in 37.5%. Serum creatinine was increased in 25% of patients, mean creatinine level was 1.3 ± 0.4 mg/dL.
- Dorros *et al*[15] followed 544 patients who underwent 714 successful RAS stent revascularizations. The mean serum creatinine was unchanged at 4 years (1.6 ± 1.0 mg/dL vs. 1.6 ± 0.9 mg/dL) when compared with baseline values.
- At this time, there are no controlled studies comparing renal arterial stenting with medical therapy alone.

Leertouwer *et al*[16] performed a meta-analysis of renal arterial stent placement in comparison with renal angioplasty in patients with renal arterial stenosis, including studies published up to August 1998. The cure rate for hypertension was higher after stent placement than after renal angioplasty but probability of improvement in renal function following intervention was lower after stenting compared to conventional angioplasty (20% vs. 10% and 30% vs. 38%, respectively; $P < 0.001$). This may be because the stent studies included more patients with impaired renal function instead of hypertension, which may affect the clinical outcome in terms of renal function. In addition, many

of these studies used an isolated serum creatinine concentration as a measure of renal impairment, which is an imprecise measure of renal progression.

Since this meta-analysis, there have been two additional studies.[16]

Van de Ven *et al*[17] undertook a randomised prospective study to compare angioplasty ($n = 43$) to angioplasty with stenting ($n = 42$) in patients with ostial atherosclerotic renal-artery stenosis. At 6 months, the primary patency rate was 29% (12 patients) for angioplasty alone, and 75% (30 patients) for angioplasty with stenting. However, the proportion of patients with cured or improved hypertension was not different between the two groups.

Current large clinical trials including ASTRAL and CORAL will also specifically address the issue of whether renal arterial revascularization with balloon angioplasty and/or endovascular stenting can safely prevent progressive renal failure among a wide range of patients with RAS.

C. Surgical intervention for RAS

Some researchers have suggested that surgical interventions may produce better outcomes than angioplasty or stenting. Certainly, some patients have improved renal function following surgery in centres of expertise. However, results of surgery may be highly variable between centres. Moreover, significant comorbid vascular disease with atherosclerotic RAS means that major surgery can only be considered in selected individuals.

In one study, arterial reconstruction was shown to be superior to surgical nephrectomy in preserving renal function in patients with unilateral RAS and severe hypertension.[18]

There are no randomised studies comparing the renal outcomes of surgical re-vascularization to conservative (medical) therapy.

There is one randomised study comparing surgical correction of RAS to angioplasty.

In this study, Weibull *et al*[19] compared surgery and percutaneous angioplasty in 58 patients with unilateral atherosclerotic RAS with severe hypertension, who did not have diabetes. Hypertension was said to be cured or improved after additional treatment in 90% of the patients after angioplasty and 86% after operation. Renal function was improved or unchanged in 83% of the patients after angioplasty and 72% after surgery. Although 17% of the patients initially treated with angioplasty required subsequent surgery, BP, renal function and renal artery patency rate did not differ between angioplasty and surgery arms 24 months after treatment. Critics of this study have argued that surgical patency may produce better outcomes in the long term (5–10 years) although this remains to be reproduced in other studies and probably depends on surgical expertise.

D. Type of medical therapy

Medical therapies in the above-mentioned trials have focused on the use of agents to control BP without specifying agents of a particular class. The drugs that are most effective in medical management of renovascular hypertension–angiotensin-converting enzyme inhibitors and angiotensin receptor-1 blockers – have tended to be avoided because of potential risk of acute renal failure in patients with bilateral renal artery stenosis or unilateral stenosis in a single functioning kidney.

Only one trial exists of angiotensin-converting enzyme inhibition vs. alternative medical therapy.[20]

SUMMARY OF THE EVIDENCE

Correction of RAS, either by re-vascularization surgery or percutaneous methods, including stenting, has been shown to be effective in treating hypertension associated with RAS. While hypertension is a key component of progressive nephropathy in these patients, none of these interventions appear to be significantly superior to medical management of hypertension and other risk factors, for preserving renal function in patients with RAS. Consequently, it seems reasonable to consider procedures to correct RAS in patients who fail medical therapy with resistant or poorly-controlled hypertension; recurrent flash pulmonary oedema; dialysis-dependent renal failure resulting from RAS; chronic renal insufficiency and bilateral RAS; or RAS to a solitary functioning kidney.

WHAT DO THE OTHER GUIDELINES SAY?

Kidney Disease Outcomes Quality Initiative: No recommendation.
UK Renal Association: No recommendation.
Canadian Society of Nephrology: No recommendation.
European Best Practice Guidelines: No recommendation.
International Guidelines: No recommendation.

IMPLEMENTATION AND AUDIT

No recommendation.

SUGGESTIONS FOR FUTURE RESEARCH

No recommendation.

REFERENCES

1. Rimmer JM, Gennari FJ. Atherosclerotic renovascular disease and progressive renal failure. *Ann. Intern. Med.* 1993; **118**: 712–9.
2. Mailloux LU, Napolitano B, Bellucci AG *et al*. Renal vascular disease causing end-stage renal disease, incidence, clinical correlates, and outcomes: a 20-year clinical experience. *Am. J. Kidney Dis* 1994; **24**: 622–9.
3. Scoble JE, Maher ER, Hamilton G *et al*. Atherosclerotic renovascular disease causing renal impairment – A case for treatment. *Clin. Nephrol.* 1989; **31**: 119–22.
4. Ritz E. Intervention in renal artery stenosis: quite appropriate in selected cases. *Dtsch Med. Wochenschr* 2001; **126**: 1348.

5. Ritz E, Mann JF. Renal angioplasty for lowering blood pressure. *N Engl. J. Med.* 2000; **342**: 1007–14.
6. van Jaarsveld BC, Krijnen P, Pieterman H *et al.* The effect of balloon angioplasty on hypertension in atherosclerotic renal-artery stenosis. Dutch Renal Artery Stenosis Intervention Cooperative Study Group. *N Engl. J. Med.* 2000; **342**: 1007–14.
7. Webster J, Marshall F, Abdalla M *et al.* Randomised comparison of percutaneous angioplasty vs continued medical therapy for hypertensive patients with atheromatous renal artery stenosis. Scottish and Newcastle Renal Artery Stenosis Collaborative Group. *J. Hum Hypertens* 1998; **12**: 329–35.
8. Plouin PF, Chatellier G, Darne B *et al.* Blood pressure outcome of angioplasty in atherosclerotic renal artery stenosis: a randomized trial. Essai Multicentrique Medicaments vs Angioplastie (EMMA) Study Group. *Hypertension* 1998; **31**: 823–9.
9. Burket MW, Cooper CJ, Kennedy DJ *et al.* Renal artery angioplasty and stent placement: predictors of a favorable outcome. *Am. Heart J.* 2000; **139**: 64–71.
10. Watson PS, Hadjipetrou P, Cox SV *et al.* Effect of renal artery stenting on renal function and size in patients with atherosclerotic renovascular disease. *Circulation* 2000; **102**: 1671–7.
11. Harden PN, MacLeod MJ, Rodger RS *et al.* Effect of renal artery stenting on progression of renovascular renal failure. *Lancet* 1997; **349**: 1133–6.
12. Rundback JH, Gray RJ, Rozenblit G *et al.* Renal artery stent placement for the management of ischemic nephropathy. *J. Vasc Interv Radiol.* 1998; **9**: 413–20.
13. Shannon HM, Gillespie IN, Moss JG. Salvage of the solitary kidney by insertion of a renal artery stent. *AJR Am. J. Roentgenol.* 1998; **171**: 217–22.
14. Bucek RA, Puchner S, Reiter M *et al.* Long-term follow-up after renal artery stenting. *Wien Klin Wochenschr* 2003; **115**: 788–92.
15. Dorros G, Jaff M, Mathiak L *et al.* Renal function and survival after renal artery stent revascularization may be influenced by embolic debris. *J. Invasive Cardiol.* 2004; **16**: 189–95.
16. Leertouwer TC, Gussenhoven EJ, Bosch JL *et al.* Stent placement for renal arterial stenosis: where do we stand? A meta-analysis. *Radiology* 2000; **216**: 78–85.
17. van de Ven PJ, Kaatee R, Beutler JJ *et al.* Arterial stenting and balloon angioplasty in ostial atherosclerotic renovascular disease: a randomised trial. *Lancet* 1999; **353**: 282–6.
18. Mackay A, Brown JJ, Lever AF *et al.* Reconstructive surgery versus nephrectomy in renal artery stenosis: comparison of effects on total and divided renal function and on blood pressure. *Br. Med. J.* 1980; **281**: 1313–5.
19. Weibull H, Bergqvist D, Bergentz SE *et al.* Percutaneous transluminal renal angioplasty versus surgical reconstruction of atherosclerotic renal artery stenosis: a prospective randomized study. *J. Vasc Surg.* 1993; **18**: 841–50; discussion 850–2.
20. Spence JD. Treatment options for renovascular hypertension. *Expert Opin. Pharmacother* 2002; **3**: 411–6.

APPENDICES

Table 1 Characteristics of included studies

Study ID (author, year)	N	Study design	Setting	Participants	Intervention (experimental group)	Intervention (control group)	Follow up (months)	Comments
Jaarsveld *et al*, 2000	106	Randomised controlled clinical trial	Multicentre, US	106 patients with hypertension who had atherosclerotic renal-artery stenosis	Percutaneous transluminal renal angioplasty	Anti-hypertensive drug therapy	12	
van de Ven *et al*, 1999	85	Randomised controlled clinical trial	Utrecht University hospital, Netherlands	85 patients with ostial atherosclerotic renal artery stenosis	Percutaneous transluminal angioplasty (PTA)	Angioplasty with stent placement (PTAS)	6	
Weibull *et al*, 1993	58	Randomised controlled clinical trial	Hospital, Sweden	58 patients without diabetes with severe hypertension and significant stenosis	Percutanesous transluminal renal angioplasty (PTRA)	Operation	24	

Table 2 Quality of randomised trials

Study ID (author, year)	Method of allocation concealment	Blinding			Intention-to-treat analysis	Loss to follow up (%)
		(participants)	(investigators)	(outcome assessors)		
Jaarsveld *et al*, 2000	Central	No	Yes	Not specified	Yes	1.9
van de Ven *et al*, 1999	Independent nurse	No	No	Yes	Yes	4.7
Weibull *et al*, 1993	Sealed envelopes	No	No	No	Yes	6.9

Table 3 Results for continuous outcomes

Study ID (author, year)	Outcomes	Intervention group (mean [SD])	Control group (mean [SD])	Difference in means [95% CI]
Jaarsveld *et al*, 2000	Mean SBP at 12 months (mmHg)	160 (26)	163 (25)	–3.00 (95%CI: –12.72, 6.72)
	Mean DBP at 12 months (mmHg)	93 (13)	96 (10)	–3.00 (95%CI: –7.39, 1.39)

Table 4 Results for dichotomous outcomes

Study ID (author, year)	Outcomes	Intervention group (number of patients with events/ number of patients exposed)	Control group (number of patients with events/ number of patients not exposed)	Relative risk (RR) [95% CI]	Risk difference (RD) [95% CI]
Jaarsveld *et al*, 2000	Improved BP control at 12 mo	38/56	18/48	1.81 (95%CI: 1.20, 2.72)	0.30 (95%CI: 0.12, 0.49)
	Worsened BP control at 12 mo	5/56	16/48	0.27 (95%CI: 0.11, 0.68)	–0.24 (95%CI: –0.40, –0.09)
	Cured hypertension	4/56	0/48	7.74 (95%CI: 0.43, 140.15)	0.07 (95%CI: 0.00, 0.15)
	Occlusion of affected artery	0/56	8/48	0.05 (95%CI: 0.00, 0.85)	–0.17 (95%CI: –0.28, –0.06)
	Increase of ≥ 50% serum Cr	2/56	6/48	0.29 (95%CI: 0.06, 1.35)	–0.09 (95%CI: –0.19, 0.02)
van de Van *et al*, 1999	Success rate (< 50% residual stenosis)	24/42	37/43	0.66 (95%CI: 0.50, 0.89)	–0.29 (95%CI: –0.47, –0.11)
	Patency at 6 mo	12/42	30/43	0.41 (95%CI: 0.24, 0.69)	–0.41 (95%CI: –0.61, –0.22)
	Death	1/42	0/43	3.07 (95%CI: 0.13, 73.30)	0.02 (95%CI: –0.04, 0.09)
	Technical failure	3/42	3/42	1.00 (95%CI: 0.21, 4.67)	0.00 (95%CI: –0.11, 0.11)
	Acute restenosis	15/42	2/42	7.50 (95%CI: 1.83, 30.78)	0.31 (95%CI: 0.15, 0.47)
	Bleeding	8/42	8/42	1.00 (95%CI: 0.41, 2.42)	0.00 (95%CI: –0.17, 0.17)
	Femoral artery aneurysm	2/42	3/42	0.67 (95%CI: 0.12, 3.79)	–0.02 (95%CI: –0.12, 0.08)
	Renal artery injury	2/42	3/42	0.67 (95%CI: 0.12, 3.79)	–0.02 (95%CI: –0.12, 0.08)
	Cholesterol embolism	4/42	4/42	1.00 (95%CI: 0.27, 3.74)	0.00 (95%CI: –0.13, 0.13)
	Improved renal function	4/41	5/40	0.78 (95%CI: 0.23, 2.70)	–0.03 (95%CI: –0.16, 0.11)
	Deteriorated renal function	8/41	9/40	0.87 (95%CI: 0.37, 2.02)	–0.03 (95%CI: –0.21, 0.15)
	Cured hypertension	2/41	6/40	0.33 (95%CI: 0.07, 1.52)	–0.10 (95%CI: –0.23, 0.03)
	Improved hypertension	18/41	17/40	1.03 (95%CI: 0.63, 1.70)	0.01 (95%CI: –0.20, 0.23)
	Failing hypertension	21/41	17/40	1.21 (95%CI: 0.75, 1.92)	–0.01 (95%CI: –0.23, 0.20)
Weibull *et al*, 1993	Technical success	24/29	28/29	0.86 (95%CI: 0.72, 1.03)	–0.14 (95%CI: –0.29, 0.01)
	Technical failure	5/29	1/29	5.00 (95%CI: 0.62, 40.20)	0.14 (95%CI: –0.01, 0.29)
	Patency rate at 24 mo	21/29	27/29	0.78 (95%CI: 0.61, 0.99)	–0.21 (95%CI: –0.39, –0.02)
	Hypertension cured or improved	26/29	25/29	1.04 (95%CI: 0.86, 1.26)	0.03 (95%CI: –0.13, 0.20)
	Renal function improved or unchanged	24/29	21/29	1.14 (95%CI: 0.86, 1.51)	0.10 (95%CI: –0.11, 0.32)
	Death	1/29	0/29	3.00 (95%CI: 0.13, 70.74)	0.03 (95%CI: –0.06, 0.12)
	Major complications	5/29	9/29	0.56 (95%CI: 0.21, 1.46)	–0.14 (95%CI: –0.36, 0.08)

Specific management of IgA nephropathy: role of steroid therapy

Date written: July 2005
Final submission: September 2005
Author: Merlin Thomas

GUIDELINES

Steroid therapy may protect against progressive renal damage in patients with IgA nephropathy with persistent proteinuria at risk of progressive renal failure. (Level I evidence – consistent effects)

SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on level III and IV evidence)

Who to treat?

Patients with persistent and heavy proteinuria, renal impairment and/or hypertension at presentation are more likely to develop progressive renal impairment and seem to warrant intervention. It should be noted that large randomised controlled trials (RCTs) have included only those patients at risk for developing progressive renal disease and who are likely to respond to therapy (proteinuria, mild histopathological changes, etc.).

At this time, there is no evidence to suggest patients with IgA nephropathy and established renal impairment (< 60 mL/min) benefit from steroid therapy (Level III evidence). In addition, steroids do not prevent recurrent disease in transplant patients, and do not prevent progression in these patients.

Many patients with IgA nephropathy do not progress to renal impairment and do not require treatment. Patients with recurrent macroscopic haematuria in association with infection episodes tend to have a more benign course and can be managed expectantly in the absence of poor prognostic features. (Level III evidence)

A threshold for treatment?

The threshold for initiating steroid treatment is controversial. Some believe that greater than 1 g/d is a reasonable threshold for concern, while others would accept greater than 2 g/d. There is universal consensus that proteinuria greater than 3 g/d is associated with a very high likelihood of a subsequent progressive decline in renal function. (Level III evidence, consistent findings)

Histological features such as glomerular sclerosis, tubulointerstitial atrophy or fibrosis and scarring also presage a poor outcome. (Level III evidence)

Patients with trivial (< 1.0 g/d) or no proteinuria, normal renal function, normal or easily-controlled hypertension who have only minor histological changes on biopsy are at low risk of progression. There is currently no data supporting the treatment of these patients. (Level III evidence)

However, even the evaluation of standard prognostic markers sometimes fails to correctly predict outcome, probably because of the heterogeneity of the disease and the discontinuous activity of some injuring mechanisms during its course. Even in the absence of specific therapeutic intervention, patients with IgA nephropathy should therefore continue to be monitored. Patients who subsequently develop markers of progressive renal disease should then be considered for intervention. (Level IV evidence)

What dose of steroid? What duration?

Optimal dosing and duration of therapy remain to be established. The RCTs that have shown benefit from steroid therapy have treated with an initial dose of approximately 1 mg/kg/day with a gradual tapering over the duration of treatment.

A reduction in proteinuria after 6 months of treatment, or at the very least no increase in proteinuria during follow-up appear to presage a more favourable outcome. (Level III evidence)

Alternate day therapy may limit toxicity. (Level III evidence)

All the studies that have shown benefit from steroid therapy have treated for more than 4 months. (Level III evidence)

There are no studies comparing longer courses to continuous therapy *ad infinitum*.

BACKGROUND

IgA nephropathy is the most common glomerular disease in Australia and New Zealand.[1] Although the natural history of IgA nephropathy is variable, many patients develop progressive loss of renal function over many years. End-stage kidney disease (ESKD) is said to develop in 20% of cases after 10 years and in 30% after 20 years, whereas another

30% show some decline in renal function.[2] In addition to non-specific renal interventions (control of hypertension, ACE inhibition, etc.), there is evidence that interventions to specifically treat IgA nephropathy may also slow the progression to ESKD. The objective of this guideline is to evaluate the available clinical evidence pertaining to the impact of steroid therapy on renal functional decline in chronic IgA nephropathy. While proliferative or crescentic IgA nephropathy also causes renal impairment and ESKD, these guidelines only refer to chronic progressive IgA nephropathy.

SEARCH STRATEGY

Databases searched: MeSH terms and text words for IgA nephropathy were combined with MeSH terms and text words for steroid therapy. The search was carried out in Medline (1966 to September Week 2, 2004). The Cochrane Renal Group Trials Register was also searched for trials not indexed in Medline.
Date of searches: 17 September 2004.

WHAT IS THE EVIDENCE?

Corticosteroids, given on a daily or alternate day basis, have been shown to produce remission of proteinuria and slow the progression to ESKD in adults with IgA nephropathy in some studies.[3]

There have been a number of RCTs in which steroids have been tested against no treatment:

- Lai *et al*[4] studied 34 patients with IgA nephropathy with mild glomerular histopathological changes and nephrotic syndrome. Seventeen patients were randomised to receive daily oral steroids for 4 months and compared with 17 controls who received supportive care alone. Corticosteroid treatment resulted in a remission of nephrotic syndrome in 80% of patients, but side-effects were experienced in over 40% of patients. Some of these patients may also have had minimal change in disease on a background of IgA. No significant difference in creatinine clearance was demonstrated between the two groups during the mean study period of 38 months.
- In a longer and larger study by Pozzi *et al*,[5] 86 patients with biopsy-proven IgA nephropathy, urine protein excretion of 1.0–3.5 g daily, and plasma creatinine concentrations of 133 mmol/L or less were randomly assigned either supportive care or steroid treatment. Treatment consisted of intravenous methylprednisolone 1 g per day for 3 consecutive days at the beginning of months 1, 3, and 5, plus oral prednisone 0.5 mg/kg on alternate days for 6 months. Nine of 43 patients in the steroid group and 14 of 43 in the control group had a 50% increase in plasma creatinine by year 5 of follow-up ($P < 0.048$).

In a subsequent follow-up of this study, 10-year renal survival was significantly better in steroid-treated patients than in the control group (97% vs. 53%; $P = 0.0003$). Steroids also significantly reduced proteinuria and protected against renal function deterioration.

- Julian and Barker[6] prospectively reviewed 18 adults with moderate disease treated with steroids for 2 years. A non-statistically significant trend towards improved renal function was seen in the treated group at 2 years, but no beneficial effects on proteinuria were observed.
- Kobayashi *et al*[7] reported an uncontrolled retrospective study of 29 patients with proteinuria over 2 g/day who were given daily prednisone for 12–36 months. Steroids stabilized kidney function in the subgroup with preserved initial creatinine clearance (> 70 mL/min). They later published a prospective controlled study in which a subgroup of the original study was compared with an untreated group. After long-term follow-up of 10 years or more, patients in this study with initially well-preserved renal function (creatinine clearance > 70 mL/min) tended to have stable renal function or progressed more slowly when treated with glucocorticoids, whereas untreated patients continued to progress. However, patients with initial impaired renal function (creatinine clearance < 70 mL/min) did poorly with or without glucocorticoid therapy.
- Welch *et al*[8] followed 20 children and adolescents with IgA nephropathy. Each received 12 weeks of prednisolone therapy and 12 weeks of placebo dosing. At the end of the short study period, there was no evidence that corticosteroid therapy was effective in reducing proteinuria or preserving renal function.
- Katafuchi *et al*.[9] conducted a prospective RCT of low-dose prednisolone therapy in 90 patients with IgA nephropathy. Although baseline proteinuria was significantly greater in the steroid group than in controls, steroids resulted in a greater reduction in albumin creatinine ratio compared to untreated controls (steroid group, -0.84 ± 1.78; controls, 0.26 ± 1.65; $P = 0.0034$). However, kidney survival was similar in both groups possibly because this study was too short to see differences in this outcome and insufficient doses of prednisolone were given.

There have been two meta-analyses:

- Schena *et al*[10] analysed eight small RCTs prior to 1990 involving 196 patients with IgA nephropathy and moderate to heavy proteinuria. Only those patients with heavy proteinuria (>3 g/d), whether or not associated with the nephrotic syndrome appeared to benefit from therapy. In contrast, no beneficial effect was observed in IgA nephropathy patients with moderate proteinuria (1–2 g/d).
- In the most recent meta-analysis,[11] there was a lower risk of reaching ESKD in the steroid-treated group compared with the no treatment or placebo group (six trials, 341 patients: RR 0.44, 95%CI: 0.25–0.80). Although this analysis was dominated by the Kobayashi[7] study, there was no significant heterogeneity between these trials.

Steroids vs. antiplatelet therapy

- Shoji *et al*[12] studied 21 adults with diffuse IgA nephropathy with proteinuria less than 1.5 g/d of protein, and serum creatinine level less than 1.5 mg/dL. Patients were randomly assigned to the corticosteroid or antiplatelet group. After 1 year of treatment, proteinuria was signifi-

cantly decreased in the corticosteroid group, associated with improved histological findings on repeat biopsy.

Chronic IgA nephropathy in children

In contrast to adult nephropathy, there have only been a few small RCTs with chronic IgA nephropathy in children, each reporting variable success with steroids. Many of these studies have included patients with crescentic nephropathy, which is not specifically considered here and is certainly steroid-responsive in some cases. In addition, children with IgA nephropathy and pathological changes of minimal change disease (with diffuse foot process fusion and nephrotic range proteinuria) readily respond to steroid therapy, in the manner of patients with minimal change alone.

- Waldo *et al.*[13] reported their experience in non-randomised concurrent cohort comparison, of alternate-morning dose of prednisone for 2–4 years compared to historical control (untreated). The treated patients had a significant improvement in urinalysis ($P < 0.00001$) and preservation of normal glomerular filtration rate (GFR) ($P = 0.03$).
- Welch *et al*[8] followed 20 children and adolescents with IgA nephropathy. Each received 12 weeks of prednisolone therapy and 12 weeks of placebo dosing. At the end of the short study period, there was no evidence that corticosteroid therapy was effective in reducing proteinuria or preserving renal function.

SUMMARY OF THE EVIDENCE

The use of glucocorticoids for high-risk patients with IgA nephropathy is associated with a slower rate of progression to ESKD, lower risk of doubling of serum creatinine and a significant reduction in urinary protein excretion. GFR is also better preserved with steroids compared with placebo/other treatment.

WHAT DO THE OTHER GUIDELINES SAY?

Kidney Disease Outcomes Quality Initiative: No recommendation.
UK Renal Association: No recommendation.
Canadian Society of Nephrology: Patients with proteinuria over 3 g/day, mild glomerular changes only, and preserved renal function (creatinine clearance over 70 mL/min) should be treated with steroids.
European Best Practice Guidelines: No recommendation.
International Guidelines: No recommendation.

IMPLEMENTATION AND AUDIT

No recommendation.

SUGGESTIONS FOR FUTURE RESEARCH

No recommendation.

REFERENCES

1. ANZDATA Registry Report 1999. Australia and New Zealand Dialysis and Transplant Registry. Adelaide, South Australia.
2. Rekola S, Bergstrand A, Bucht H. Deterioration of GFR in IgA nephropathy as measured by 51Cr-EDTA clearance. *Kidney Int*. 1991; **40**: 1050–4.
3. Locatelli F, Del vecchio L, Pozzi C. The patient with IgA glomerulonephritis – what is the role of steroid treatment? *Nephrol. Dial Transplant*. 1999; **14**: 1057–60.
4. Lai KN, Lai FM, Ho CP *et al*. Corticosteroid therapy in IgA nephropathy with nephrotic syndrome: a long-term controlled trial. *Clin. Nephrol*. 1986; **26**: 174–80.
5. Pozzi C, Bolasco PG, Fogazzi GB *et al*. Corticosteroids in IgA nephropathy: a randomised controlled trial. *Lancet* 1999; **353**: 883–7.
6. Julian BA, Barker C. Alternate-day prednisone therapy in IgA nephropathy. Preliminary analysis of a prospective, randomized, controlled trial. *Contrib Nephrol*. 1993; **104**: 198–206.
7. Kobayashi Y, Hiki Y, Fujii K *et al*. Moderately proteinuric IgA nephropathy: prognostic prediction of individual clinical courses and steroid therapy in progressive cases. *Nephron*. 1989; **53**: 250–6.
8. Welch TR, Fryer C, Shely E *et al*. Double blind, controlled trial of short-term prednisone therapy in immunoglobulin A glomerulonephritis. *J. Pediatr*. 1992; **121**: 474–7.
9. Katafuchi R., Ikeda K, Mizumasa T *et al*. Controlled, prospective trial of steroid treatment in IgA nephropathy. a limitation of low-dose prednisolone therapy. *Am. J. Kidney Dis*. 2003; **41**: 972–83.
10. Schena FP, Montenegro M, Scivittaro V. Meta-analysis of randomised controlled trials in patients with primary IgA nephropathy (Berger's disease). *Nephrol. Dial Transplant* 1990; **5** (Suppl. 1): 47–52.
11. Samuels JA, Strippoli GF, Craig JC *et al*. Immunosuppressive agents for treating IgA nephropathy. *The Cochrane Database of Systematic Reviews* 2003; Issue 4.
12. Shoji T, Nakanishi I, Suzuki A *et al*. Early treatment with corticosteroids ameliorates proteinuria, proliferative lesions, and mesangial phenotypic modulation in adult diffuse proliferative IgA nephropathy. *Am. J. Kidney Dis*. 2000; **35**: 194–201.
13. Waldo FB, Wyatt RJ, Kelly DR *et al*. Treatment of IgA nephropathy in children: efficacy of alternate-day oral prednisone. *Pediatr Nephrol*. 1993; **7**: 529–32.

APPENDICES

Table 1 Characteristics of included studies

Study ID (author, year)	N	Study design	Setting	Participants	Intervention (experimental group)	Intervention (control group)	Follow up (months)	Comments
Julian *et al*, 1993	35	Randomised controlled clinical trial	Multicentre, Switzerland	35 patients 15–62 yrs with CrCl > 25 ml/min/1.73 m^2	Alternate day prednisone 60 mg × 3 mo, subsequent tapering	No treatment	6–24	
Kobayashi *et al*, 1996	46	Randomised controlled clinical trial	University hospital, Japan	46 patients 23–43 yrs, proteinuria 1–2 g/d. CrCl > 70 mL/min/ 1.73 m^2	Prednisolone 40 mg/d then tapering over 7 mo total treatment	No treatment	120	
Lai *et al*, 1986	34	Randomised controlled clinical trial	University hospital, Hong Kong	34 Chinese patients 14–42 yrs	Prednisolone 40–60 mg/d × 2 mo, then $^1/_2$ dose for 2 mo	No treatment	38	
Pozzi *et al*, 1999	86	Randomised controlled clinical trial	7 renal units, Italy	86 patients 15–69 yrs, SCr < 1.5mg/dL, urinary protein excretion 1–3.5 g/d	Methylprednisolone 1 g × 3 d and prednisone 0.5 mg/kg/d × 6 mo	No treatment	60	
Welch *et al*, 1992	20	Crossover, randomised controlled clinical trial	University hospital, Ohio	20 patients, mean age 13 yrs, SCr > 1.6 mg/dL	Prednisolone 2 mg/kg/d for 2 wks, then qod for 10 wks	Placebo	3	

Table 2 Quality of randomised trials

Study ID (author, year)	Method of allocation concealment	Blinding			Intention-to-treat analysis	Loss to follow up (%)
		(participants)	(investigators)	(outcome assessors)		
Julian *et al*, 1993	Not specified	No	No	No	No	5.7
Kobayashi *et al*, 1996	Inadequate	No	No	No	No	49.0
Lai *et al*, 1986	Not specified	No	No	No	No	0.0
Pozzi *et al*, 1999	Not specified	No	No	No	Yes	3.5
Welch *et al*, 1992	Not specified	Yes	Yes	No	Unclear	15.0

Table 3 Results for continuous outcomes

Study ID (author, year)	Outcomes	Intervention group (mean [SD])	Control group (mean [SD])	Difference in means [95% CI]
Julian *et al*, 1993	Urinary protein excretion (g/24) at end of treatment	1.30 (1.24)	1.80 (2.97)	–0.50 (95%CI: –1.99, 0.99)
	Serum creatinine (μmol/L) at end of treatment	95.00 (11.00)	157.00 (41.00)	–62.00 (95%CI: –82.14, –41.86)
Kobayashi *et al*, 1996	Urinary protein excretion (g/24) at end of treatment	0.80 (0.50)	1.50 (1.30)	–0.70 (95%CI: –1.25, –0.15)
	GFR (any measure) at end of treatment	54.00 (35.00)	20.00 (29.00)	34.00 (95%CI: 15.04, 52.96)
Lai *et al*, 1986	Urinary protein excretion (g/24) at end of treatment	2.30 (2.20)	3.30 (2.10)	–1.00 (95%CI: –2.45, 0.45)
	Serum creatinine (μmol/L) at end of treatment	126.90 (77.70)	130.70 (55.00)	–3.80 (95%CI: –49.05, 41.45)
	GFR (any measure) at end of treatment	74.10 (24.10)	64.60 (20.90)	9.50 (95%CI: –5.66, 24.66)
Pozzi *et al*, 1999	Urinary protein excretion (g/24) at end of treatment	0.70 (0.53)	1.80 (2.30)	–1.10 (95%CI: –2.14, –0.06)
	Serum creatinine (μmol/L) at end of treatment	105.60 (45.76)	154.00 (55.44)	–48.40 (95%CI: –80.24, –16.56)
	GFR (any measure) at end of treatment	95.60 (28.20)	71.60 (21.70)	24.00 (95%CI: 8.15, 9.85)

Table 4 Results for dichotomous outcomes

Study ID (author, year)	Outcomes	Intervention group (number of patients with events/ number of patients exposed)	Control group (number of patients with events/ number of patients not exposed)	Relative risk (RR) [95% CI]	Risk difference (RD) [95% CI]
Julian *et al*, 1993	ESRD	1/18	2/17	0.47 (95%CI: 0.05, 4.74)	–0.06 (95%CI: –0.25, 0.12)
	Doubling of serum creatinine	1/18	2/17	0.47 (95%CI: 0.05, 4.74)	–0.06 (95%CI: –0.25, 0.12)
Kobayashi *et al*, 1996	ESRD	7/28	31/49	0.40 (95%CI: 0.20, 0.78)	–0.24 (95%CI: –0.51, 0.02)
	Doubling of serum creatinine	7/28	31/49	0.40 (95%CI: 0.20, 0.78)	–0.24 (95%CI: –0.51, 0.02)
Lai *et al*, 1986	ESRD	0/17	0/17	Not estimable	0.00 (95%CI: –0.11, 0.11)
	Doubling of serum creatinine	0/17	0/17	Not estimable	0.00 (95%CI: –0.11, 0.11)
	Remission of proteinuria	7/17	0/17	15.00 (95%CI: 0.92, 243.52)	0.41 (95%CI: 0.17, 0.65)
Pozzi *et al*, 1999	ESRD	0/43	3/43	0.14 (95%CI: 0.01, 2.68)	–0.07 (95%CI: –0.16, 0.02)
	Doubling of serum creatinine	10/43	23/43	0.43 (95%CI: 0.24, 0.80)	–0.30 (95%CI: –0.50, –0.11)

Specific management of IgA nephropathy: role of fish oil

Date written: July 2005
Final submission: September 2005
Author: Merlin Thomas

GUIDELINES

Early and prolonged treatment with fish oil may retard the rate of decline in renal function in adults with progressive IgA nephropathy. (Level I evidence – conflicting)

SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on level III and IV evidence)

- **There is currently insufficient data to confirm the efficacy of fish oil supplementation in adults with IgA nephropathy**.
- **However, in patients at risk for progressive renal impairment, some patients will wish to consider fish oil supplements in addition to other relevant supportive strategies. Although the risk of side-effects is low, possible marginal benefits should be weighted against the costs of compliance.**
- **Optimal dosing also remains to be established but most studies have used 1.8 g of EPA and 1.2 g of DHA daily (~12 g of fish oil per day) for at least 2 years. (Level III evidence – one small study, weak effect)**
- **Ongoing therapy *ad infinitum* may provide greater benefits than intermittent therapy. In the Mayo study,[1] patients who continued taking fish oil were less likely to reach end-stage kidney disease (ESKD) or increase their creatinine by 50% than those who had discontinued fish oil treatment. (Level III evidence – one small study, weak effect)**
- **No data have been published on the utility of fish oil supplements in children**.

BACKGROUND

IgA nephropathy is the most common glomerular disease in Australia and New Zealand. Although the natural history of IgA nephropathy is variable, many patients develop progressive loss of renal function over many years. ESKD is said to develop in 20% of patients after 10 years and in 30% after 20 years, whereas another 30% show some decline in renal function.[2] In addition to non-specific renal interventions (control of hypertension, ACE inhibition, etc.) there is evidence that interventions to specifically treat IgA nephropathy may also slow the progression to ESKD.

Deficiencies of essential fatty acids have been detected in IgA nephropathy. Fish oil is rich in long-chain omega-3-polyunsaturated fatty acids, eicosapentanoic acid, and docosahexanoic acid. Repletion of n-3 fatty acids is thought to lead to the production of less potent prostaglandins and leukotrienes than those produced through the n-6 fatty acid substrate, arachidonic acid.[3] N-3 fatty acids can also suppress inflammatory and/or immunological responses through eicosanoid-independent mechanisms. The objective of this guideline is to evaluate the available clinical evidence pertaining to the impact of fish oil supplementation on renal functional decline in IgA nephropathy.

SEARCH STRATEGY

Databases searched: MeSH terms and text words for IgA nephropathy were combined with MeSH terms and text words for fish oil. This search was carried out in Medline (1966 to September Week 2, 2004). The Cochrane Renal Group Trials Register was also searched for trials not indexed in Medline.
Date of searches: 17 September 2004.

WHAT IS THE EVIDENCE?

Three prospective randomised controlled trials (RCTs) have been published:

- Pettersson *et al*[4] reported a short-term prospective, randomised study in 32 patients with non-nephrotic proteinuria and normal- to moderately-impaired renal function. Fifteen patients were assigned to fish oil with a high percentage of [omega]-3-polyunsaturated fatty acids and 17 to corn oil. By 6 months, fish oil administration resulted in a slight but significant reduction in creatinine clearance (63–59 mL/min), whereas no change occurred in the control group. The proteinuria remained unchanged.
- Bennett *et al*[5] published a 2-year prospective trial in 37 patients with normal- to severely-impaired renal function, randomly allocated to receive either fish oil or supportive treatment for 2 years. At the end of the trial, the glomerular filtration rate (GFR) in 17 treated patients declined from 80 to 57 mL/min, and in 20 untreated patients, it went from 76 to 55 mL/min. There was also no significant effect on proteinuria.

• Collaborators with the Mayo clinic performed a multicentre, placebo-controlled, randomised trial in 106 patients with normal- to moderately-impaired renal function, and nephrotic range proteinuria. Fifty-five patients were treated with 12 g of fish oil daily and 51 controls received olive oil placebo.[1] Six per cent in the fish oil group and 33% in the placebo group experienced an increase of 50% or more in the baseline serum creatinine at 2 years (P = 0.002). The cumulative percentage of patients who died or developed ESKD after 4 years was 10% in the fish oil group and 40% in the placebo group (P = 0.006). Fish oil also slowed the rate of decline in GFR. There was no effect on the level of proteinuria. In a follow-up study of the original 106 patients, now beyond 6 years, progression to ESKD remained substantially lower in the fish oil group and those who continued fish oil therapy.[6] However, results were not improved by the use of higher doses of fish oil.[7]

Two meta-analyses[8,9] have been performed, both of which concluded that a clear beneficial effect could not be demonstrated. When all studies were combined the mean effect was not statistically significant, although the probability of at least a minor beneficial effect was 75%. Mixed-effects regression suggested that fish oil therapy may have been slightly more effective among individuals with greater levels of proteinuria.

No data have been published on the use of fish oil supplements in children with IgA nephropathy.

SUMMARY OF THE EVIDENCE

Some, but not all studies, have shown that early and prolonged treatment with fish oil may retard the rate of decline in renal function in patients with progressive IgA nephropathy. However, fish oil has no significant effect on proteinuria in patients with IgA nephropathy. Overall, there is currently insufficient data to confirm the efficacy of fish oil supplementation in patients with IgA nephropathy.

WHAT DO THE OTHER GUIDELINES SAY?

Kidney Disease Outcomes Quality Initiative: No recommendation.
UK Renal Association: No recommendation.
Canadian Society of Nephrology: In patients with a slow progressive decline in creatinine clearance (less than 70 mL/min), fish oil should be given.[10]
European Best Practice Guidelines: No recommendation.
International Guidelines: No recommendation.

IMPLEMENTATION AND AUDIT

No recommendation.

SUGGESTIONS FOR FUTURE RESEARCH

No recommendation.

REFERENCES

1. Donadio JV Jr, Berkstralh EJ, Offord KP *et al*. Mayo Nephrology Collaborative Group. A controlled trial of fish oil in IgA nephropathy. *N Engl. J. Med*. 1994; **331**: 1194–9.
2. Rekola S, Bergstrand A, Bucht H. Deterioration of GFR in IgA nephropathy as measured by 51Cr-EDTA clearance. *Kidney Int*. 1991; **40**: 1050–4.
3. Donadio JV Jr. Use of fish oil to treat patients with immunoglobulin A nephropathy. *Am. J. Clin. Nutr* 2000; **71** (**1** Suppl.): S373–S375.
4. Pettersson EE, Rekola S, Berglund L *et al*. Treatment of IgA nephropathy with omega-3-polyunsaturated fatty acids: a prospective, double-blind, randomized study. *Clin. Nephrol*. 1994; **41**: 183–90.
5. Bennett WM, Walker RG, Kincaid-Smith P. Treatment of IgA nephropathy with eicosapentanoic acid (EPA): a two-year prospective trial. *Clin. Nephrol*. 1989; **31**: 128–31.
6. Donadio JV Jr, Larson TS, Bergstralh EJ *et al*. A randomized trial of high-dose compared with low-dose omega-3 fatty acids in severe IgA nephropathy. *J. Am. Soc. Nephrol*. 2001; **12**: 791–9.
7. Donadio JV Jr, Grande JP, Bergstralh EJ *et al*. The long-term outcome of patients with IgA nephropathy treated with fish oil in a controlled trial. Mayo Nephrology Collaborative Group. *J. Am. Soc. Nephrol*. 1999; **10**: 1772–7.
8. Strippoli GF, Manno C, Schena FP. An 'evidence-based' survey of therapeutic options for IgA nephropathy: assessment and criticism. *Am. J. Kidney Dis* 2003; **41**: 1129–39.
9. Dillon JJ. Fish oil therapy for IgA nephropathy: efficacy and inter-study variability. *J. Am. Soc. Nephrol*. 1997; **8**: 1739–44.
10. Nolin L, Courteau M. Management of IgA nephropathy: evidence-base recommendations. *Kidney Int. Suppl*. 1999; **70**: S56–S62.

APPENDICES

Table 1 Characteristics of included studies

Study ID (author, year)	N	Study design	Setting	Participants	Intervention (experimental group)	Intervention (control group)	Follow up (months)	Comments
Bennet *et al*, 1989	37	Randomised controlled clinical trial	Hospital, Melbourne	37 patients with biopsy-proven mesangial IgA nephropathy	Eicosapentanoic acid (EPA) 10 g/d	No treatment	24	Group A serum Cr > 0.12 mmol/L; Group B serum Cr < 0.12 mmol/L
Donadio *et al*, 2001	73	Randomised controlled clinical trial	14 centres of the Mayo Nephrology Collaborative Group	73 patients with severe IgA nephropathy	High dose fatty acids (EPA 3.76 g, DHA 2.94 g)	Low dose fatty acids (EPA 1.88 g, DHA 1.47 g)	24	
Donadio *et al*, 1994	106	Randomised controlled clinical trial	21 centres making up the Mayo Nephrology Collaborative Group, US	106 patients with IgA nephropathy who had persistent proteinuria	Fish oil 12 g/d	Placebo olive oil 12 g/d	36	
Pettersson *et al*, 1994	34	Randomised controlled clinical trial	University hospital, Sweden	34 adult patients with biopsy-proven IgA nephropathy	Fish oil (55% eicosapentanoic and 30% docosahexanoic acid)	Placebo corn oil	6	

Table 2 Quality of randomised trials

Study ID (author, year)	Method of allocation concealment	Blinding			Intention-to-treat analysis	Loss to follow up (%)
		(participants)	(investigators)	(outcome assessors)		
Bennet *et al*, 1989	Not specified	No	No	No	Unclear	0.0
Donadio *et al*, 2001	Not specified	No	No	No	No	42.5
Donadio *et al*, 1994	Not specified	Yes	Yes	Yes	No	29.2
Pettersson *et al*, 1994	Not specified	Yes	Yes	Yes	No	5.9

Table 3 Results for continuous outcomes

Study ID (author, year)	Outcomes	Intervention group (mean [SD])	Control group (mean [SD])	Difference in means [95% CI]
Bennet *et al,* 1989	Group A serum Cr (nmol/L) compared to baseline	0.19 (0.14)	0.22 (0.08)	–0.03 (95%CI: –0.14, 0.08)
	Group B serum Cr (nmol/L) compared to baseline	0.07 (0.20)	0.01 (0.03)	0.06 (95%CI: –0.07, 0.19)
Donadio *et al,* 2001	SBP (mmHg) at 2 yrs	136 (13)	136 (17)	0.00 (95%CI: –8.04, 8.04)
	DBP (mmHg) at 2 yrs	83 (8)	81 (8.9)	2.00 (95%CI: –2.51, 6.51)
	Cholesterol (mg/dL)	212 (57)	206 (50)	6.00 (95%CI: –22.69, 34.69)
Donadio *et al,* 1994	Change in SBP (mmHg) in hypertensive patients at 1 yr	–11 (19)	–9 (21)	–2.00 (95%CI: –13.02, 9.02)
	Change in SBP (mmHg) in normotensive patients at 1 yr	4 (14)	–1 (15)	5.00 (95%CI: –4.79, 14.79)
	Change in DBP (mmHg) in hypertensive patients at 1 yr	–6 (9)	–3 (11)	–3.00 (95%CI: –8.56, 2.56)
	Change in DBP (mmHg) in normotensive patients at 1 yr	–1 (9)	0.1 (8)	–1.10 (95%CI: –6.81, 4.61)
Pettersson *et al,* 1994	SBP (mmHg) at 6 mo	136 (15)	142 (19)	–6.00 (95%CI: –17.80, 5.80)
	SDP (mmHg) at 6 mo	81 (7)	82 (9)	–1.00 (95%CI: –6.55, 4.55)
	Mean increase in body weight at 6 mo (kg)	2.1 (2.7)	0.2 (2.9)	1.90 (95%CI: –0.04, 3.84)

Table 4 Results for dichotomous outcomes

Study ID (author, year)	Outcomes	Intervention group (number of patients with events/ number of patients exposed)	Control group (number of patients with events/ number of patients not exposed)	Relative risk (RR) [95% CI]	Risk difference (RD) [95% CI]
Bennet *et al,* 1989	ESRD	2/17	2/20	1.18 (95%CI: 0.18, 7.48)	0.02 (95%CI: –0.18, 0.22)
Donadio *et al,* 2001	Death	0/36	0/37	Not estimable	0.00 (95%CI: –0.05, 0.05)
	Adverse events	4/36	5/37	0.81 (95%CI: 0.24, 2.82)	–0.02 (95%CI: –0.17, 0.13)
	Diverticulitis	0/36	1/37	0.34 (95%CI: 0.01, 8.14)	–0.03 (95%CI: –0.10, 0.05)
	Hyperkalaemia	0/36	1/37	0.34 (95%CI: 0.01, 8.14)	–0.03 (95%CI: –0.10, 0.05)
	ESRD	8/36	10/37	0.82 (95%CI: 0.37, 1.85)	–0.05 (95%CI: –0.25, 0.15)
Donadio *et al,* 1994	Death, repeated dialysis, transplant	14/55	5/51	2.60 (95%CI: 1.01, 6.70)	0.16 (95%CI: 0.02, 0.30)
	Increase of ≥ 50% serum Cr	3/55	14/51	0.20 (95%CI: 0.06, 0.65)	–0.22 (95%CI: –0.36, –0.08)
	ESRD	4/55	14/51	0.26 (95%CI: 0.09, 0.75)	–0.20 (95%CI: –0.34, –0.06)
Pettersson *et al,* 1994	No change in GFR	2/15	2/17	1.13 (95%CI: 0.18, 7.09)	0.02 (95%CI: –0.21, 0.25)
	Improved ^{51}Cr-EDTA clearance	2/15	6/17	0.38 (95%CI: 0.09, 1.60)	–0.22 (95%CI: –0.50, 0.07)

Specific management of IgA nephropathy: role of triple therapy and cytotoxic therapy

Date written: July 2005
Final submission: September 2005
Author: Merlin Thomas

GUIDELINES

a. Triple therapy with cyclophosphamide, dipyridamole, and warfarin has not been shown to be superior to conventional treatment as sole therapy in patients with IgA nephropathy. (Level II evidence)

b. Treatment with cyclophosphamide and prednisolone is superior to supportive treatment alone in patients with IgA nephropathy. (Level II evidence)

SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on level III and IV evidence)

- **There is currently no evidence to demonstrate that the addition of azathioprine, cyclophosphamide, dipyridamole, or warfarin, alone or in combination, with corticosteroids has any additive benefit. At the same time, these therapies expose patients to significant toxicity. Gonadal toxicity makes this treatment a concern in young patients. (Level IV evidence)**
- **The specific utility of these agents in patients with steroid-resistant nephrotic syndrome due to IgA nephropathy remains to be tested in clinical studies. However, a number of case series have shown that remission can be induced by pulse cyclophosphamide in some steroid-resistant patients. (Level IV evidence)**

BACKGROUND

IgA nephropathy is the most common glomerular disease in Australia and New Zealand. Although the natural history of IgA nephropathy is variable, many patients develop progressive loss of renal function over many years. End-stage kidney disease (ESKD) is said to develop in 20% of cases after 10 years and in 30% after 20 years, whereas another 30% show some decline in renal function.[1] In addition to non-specific renal interventions (control of hypertension, ACE inhibition, etc.) there is evidence that interventions to specifically treat IgA nephropathy may also slow the progression to ESKD.

The objective of this guideline is to evaluate the available clinical evidence pertaining to the impact of triple therapy with cyclophosphamide, dipyridamole, and warfarin on renal functional decline in chronic IgA nephropathy. While proliferative or crescentic IgA also causes renal impairment and ESKD, these guidelines only refer to chronic progressive IgA nephropathy.

SEARCH STRATEGY

Databases searched: MeSH terms and text words for IgA nephropathy were combined with MeSH terms and text words for triple therapy. This search was carried out in Medline (1966 to September Week 2, 2004). The Cochrane Renal Group Trials Register was also searched for trials of IgA nephropathy not indexed in Medline.
Date of searches: 17 September 2004.

WHAT IS THE EVIDENCE?

There have been two RCTs comparing triple therapy and no treatment in patients with IgA nephropathy and proteinuria:

- Walker *et al*[2] in a randomised prospective study of 52 patients with mesangial IgA nephropathy, allocated 25 patients to treatment with cyclophosphamide (for 6 months), and dipyridamole and warfarin (2 years). Twenty-seven patients served as controls and received no treatment. Despite reductions in urinary protein excretions with triple therapy, no significant effect on preservation of renal function could be confirmed over the 2 years of the study, either with triple therapy or when patients received warfarin and dipyridamole alone.
- Woo *et al*[3,4] demonstrated reduction of proteinuria and stabilization of renal function in a group of 52 patients treated with cyclophosphamide, dipyridamole and warfarin. However, a 5-year post-trial assessment[3,4] found no difference in renal function between the treatment and control groups. Only half of the patients in the treatment group remained on treatment with dipyridamole and low-dose warfarin at 5 years, which may have accounted for the failure to show significant difference in renal function compared to the control group. Patients who stopped treatment had significantly worse renal function and were more likely (6 of 14) to progress to ESKD compared to those who continued treatment (0 of 13).

• Murakami *et al*,[5] retrospectively evaluated renal outcome in a total of 38 children and adolescents with IgA nephropathy who were selected for 6-month therapy for clinical (proteinuria > 1 g/m^2/24 h) and pathological features (mesangial proliferation, crescent formation, and tubulo-interstitial changes) suggestive of progressive renal failure. Seventeen patients were treated with a combination of prednisolone, cyclophosphamide and dipyridamole, and the remaining 21 patients were treated with the same drugs plus warfarin. There were no untreated controls. All of the patients were followed-up for more than 2 years (range 2–10 years, mean 4.8). In both groups, the mean urinary protein excretion value was significantly reduced after the therapy, compared with that at entry into the study. The significant reduction continued for up to 6 years in group A and up to 5 years in group B. Creatinine clearance was stable until 5–6 years after the trial in both groups, but 4 patients progressed to ESKD after that period. Post-therapy biopsy was performed in 14 patients, and was compared with the pre-therapy biopsy. The activity score improved in both groups, but the chronicity score did not. These results suggest that there was a temporary effect and limited benefit with this treatment of combined drugs for children and adolescents with IgA nephropathy. The additive effect of warfarin was not substantiated.

There has been one RCT of dipyridamole and warfarin alone.

• Lee *et al*[6] looked at the effect of double therapy with warfarin and dipyridamole in a study of 21 patients with IgA nephropathy and mild renal impairment, where 10 patients were assigned to treatment with dipyridamole and low-dose warfarin and 11 patients to the control group on no treatment. At the end of the trial, renal function remained stable in patients on treatment while a significant deterioration was seen in the control group. This study used a longer duration of treatment (3 years vs. 2 years) and warfarin at lower 'anticoagulant doses' than the Walker *et al*[2] study, which had previously shown no benefit from triple therapy.

There has been one RCT comparing triple therapy with added prednisolone to anticoagulation and dypiridamole alone.

• Yoshikawa *et al*[7] randomised 78 children with Ig A nephropathy to receive prednisone (2 mg/kg/day tapered over 2 years) and azathioprine (2 mg/kg/day) and heparin/coumadin and dipyridamole (5 mg/kg/day) or to receive heparin/coumadin and dipyridamole (5 mg/kg/day) alone. After 2 years of treatment, urinary protein excretion and serum IgA concentration fell significantly in patients receiving steroid/azathioprine, but remained unchanged in patients receiving anticoagulation alone. When comparing renal biopsies taken at the study endpoint to those at baseline, the percentage of glomeruli showing sclerosis was unchanged in children receiving prednisolone, azathioprine, heparin-warfarin, and dipyridamole for 2 years but increased significantly in those receiving heparin-warfarin and dipyridamole. Although this data is promising, given the known response to steroids in this condition (see guideline titled "specific management of IgA nephropathy: role of steroid therapy") the role of azathioprine or anticoagulation in influencing renal outcomes in this study is difficult to interpret.

There have been two randomised studies of dipyridamole alone:

• Katafuchi *et al*[8] randomised 189 patients to receive prednisolone 20 mg/day × 1 month followed by tapering over 18 months, plus dipyridamole 150 mg/day or dipyridamole 300 mg/day.

• Shoji *et al*[9] studied 21 patients, randomised to receive prednisolone 0.8 mg/kg/day tapered to 10 mg for 1 year or dipyridamole 300 mg/day. After 1 year of therapy, proteinuria was reduced in patients treated with steroids, associated with improvement in renal histology. By comparison, antiplatelet therapy had no significant effect on proteinuria or renal histology.

The addition of cyclophosphamide to steroid has also slowed the progression in patients with histologically severe disease pathology (mesangial proliferation, crescent formation, and tubulo-interstitial changes) in some case series.[2] There have been a few small studies in which the use of cytotoxic therapy (in the absence of anticoagulant therapy – as triple therapy) has been studied.

• Tsuruya *et al*,[10] retrospectively reviewed 45 patients with moderate to severe histological changes (including crescents) treated with combination therapy using prednisolone and cyclophosphamide ($n = 26$) or conventional therapy ($n = 19$). In the combination therapy group, urinary protein excretion significantly decreased and the progression rate was significantly lower than in the control group.

• Ballardie *et al*[11] studied 38 patients with progressive IgA nephropathy and renal impairment (serum creatinine > 130 μmol/L) who were randomised to treatment with prednisolone 40 mg/d (reduced to 10 mg/d by 2 years) and cyclophosphamide 1.5 mg/kg per day (adjusted down to the nearest 50 mg) for the initial 3 months, then azathioprine at the same dose continued for a minimum of 2 years, or no treatment. While cumulative renal survival after 5 years was significantly improved by intervention, it remains to be established if this represents the effect of steroids, cytotoxic therapy or their combination.

• Chen *et al*[12] retrospectively analysed the medical data of 60 patients with IgA nephropathy treated with corticosteroid alone or in combination with cyclophosphamide. They found that corticosteroid and combination therapy with corticosteroid and cyclophosphamide were equally effective.

• Rasche *et al*[13] conducted a prospective, uncontrolled trial to evaluate the effect of intravenous cyclophosphamide pulse and low-dose oral prednisolone therapy in 21 patients with biopsy-proven IgA nephropathy. Overall, the loss of renal function per year was significantly slowed compared to historical data before therapy was initiated, and proteinuria decreased.

A meta-analysis performed in 2002 concluded that there was no additional benefit from using cytotoxics.[14]

SUMMARY OF THE EVIDENCE

Despite initial enthusiasm for the combination of dipyridamole, warfarin and cyclophosphamide, recent studies have shown variable benefit in patients with chronic IgA nephropathy (Level II evidence). Many of the positive studies also used corticosteroids in treatment arms, making interpretation of the specific role of triple therapy and cytotoxic therapy in improved outcomes difficult.

WHAT DO THE OTHER GUIDELINES SAY?

Kidney Disease Outcomes Quality Initiative: No recommendation.
UK Renal Association: No recommendation.
Canadian Society of Nephrology: Treatment with cyclophosphamide, dipyridamole, and warfarin should not be used.[9]
European Best Practice Guidelines: No recommendation.
International Guidelines: No recommendation.

IMPLEMENTATION AND AUDIT

No recommendation.

SUGGESTIONS FOR FUTURE RESEARCH

No recommendation.

REFERENCES

1. Rekola S, Bergstrand A, Bucht H. Deterioration of GFR in IgA nephropathy as measured by 51Cr-EDTA clearance. *Kidney Int*. 1991; **40**: 1050–4.
2. Walker RG, Yu SH, Owen JE *et al*. The treatment of mesangial IgA nephropathy with cyclophosphamide, dipyridamole and warfarin: a two-year prospective trial. *Clin. Nephrol*. 1990; **34**: 103–7.
3. Woo KT, Lee GS. The treatment of mesangial IgA nephropathy with cyclophosphamide, dipyridamole and warfarin. *Clin. Nephrol*. 1991; **35**: 184.
4. Woo KT, Lee GS, Lau YK *et al*. Effects of triple therapy in IgA nephritis: a follow-up study 5 years later. *Clin. Nephrol*. 1991; **36**: 60–6.
5. Murakami K, Yoshioka K, Akano N *et al*. Combined therapy in children and adolescents with IgA nephropathy. *Nippon Jinzo Gakkai Shi* 1994; **36**: 38–43.
6. Lee GSL, Choong HL, Chiang GSC *et al*. Three-year randomized controlled trial of dipyridamole and low-dose warfarin in patients with IgA nephropathy and renal impairment. *Nephrology* 1997; **3**: 117–21.
7. Yoshikawa N, Ito H, Sakai T *et al*. A controlled trial of combined therapy for newly diagnosed severe childhood IgA nephropathy. The Japanese Pediatric IgA Nephropathy Treatment Study Group. *J. Am. Soc. Nephrol*. 1999; **10**: 101–9.
8. Katafuchi R., Ikeda K, Mizumasa T *et al*. Controlled, prospective trial of steroid treatment in IgA nephropathy: a limitation of low-dose prednisolone therapy. *Am. J. Kidney Dis* 2003; **41**: 972–83.
9. Shoji T, Nakanishi I, Suzuki A *et al*. Early treatment with corticosteroids ameliorates proteinuria, proliferative lesions, and mesangial phenotypic modulation in adult diffuse proliferative IgA nephropathy. *Am. J. Kidney Dis* 2000; **35**: 194–201.
10. Tsuruya K, Harada A, Hirakata H *et al*. Combination therapy using prednisolone and cyclophosphamide slows the progression of moderately advanced IgA nephropathy. *Clin. Nephrol*. 2000; **53**: 1–9.
11. Ballardie FW, Roberts IS. Controlled prospective trial of prednisolone and cytotoxics in progressive IgA nephropathy. *J. Am. Soc. Nephrol*. 2002; **13**: 142–8.
12. Chen KJ, Cheng CH, Wu MJ *et al*. Effect of corticosteroid and cyclophosphamide in IgA nephropathy patients with heavy proteinuria and/or moderate-severe pathological changes. *J. Chin Med. Assoc* 2003; **66**: 263–70.
13. Rasche FM, Klotz CH, Czock D *et al*. Cyclophosphamide pulse therapy in advanced progressive IgA nephropathy. *Nephron Clin. Pract*. 2003; **93**: c131–6.
14. Samuels JA, Strippoll GFM, Craig JC *et al*. Immunosuppressive agents for treating IgA nephropathy. *The Cochrane Database of Systematic Reviews*. 2003, Issue 4.

APPENDICES

Table 1 Characteristics of included studies

Study ID (author, year)	N	Study design	Setting	Participants	Intervention (experimental group)	Intervention (control group)	Follow up (months)	Comments
Katafuchi *et al*, 2003	103	Randomised controlled clinical trial	Single hospital, Japan	103 patients diagnosed with IgA nephropathy	Low-dose prednisolone	No treatment	60	
Lee *et al*, 1997	21	Randomised controlled trial	Hospital, Singapore	21 patients with IgA nephropathy	Dipyridamole and low-dose warfarin	No treatment	36	
Shoji *et al*, 2000	21	Randomised controlled clinical trial	Hospital, Japan	21 patients with biopsy proven IgA nephropathy	Corticosteroid	Antiplatelet therapy	12	
Walker *et al*, 1990	52	Randomised controlled clinical trial	Renal clinic, Australia	52 patients with mesangial IgA nephropathy	Cyclophosphamide for 6 mo, dipyridamole and warfarin 24 mo	No treatment	24	
Yoshikawa *et al*, 1999	78	Randomised controlled clinical trial	20 Japanese paediatric renal centres	78 children with newly diagnosed IgA nephropathy showing diffuse mesangial proliferation	Prednisolone, azathioprine, heparin-warfarin, dipyridamole for 2 yrs	Heparin-warfarin and dipyridamole	24	

Table 2 Quality of randomised trials

Study ID (author, year)	Method of allocation concealment	Blinding			Intention-to-treat analysis	Loss to follow up (%)
		(participants)	(investigators)	(outcome assessors)		
Katafuchi *et al*, 2003	Not specified	No	No	No	No	12.6
Lee *et al*, 1997	Not specified	No	Unclear	Unclear	No	Unclear
Shoji *et al*, 2000	Computer generated	No	No	No	No	9.5
Walker *et al*, 1990	Not specified	No	No	No	Yes	1.9
Yoshikawa *et al*, 1999	Sealed envelopes	No	Yes	Yes	No	5.1

Table 3 Results for continuous outcomes

Study ID (author, year)	Outcomes	Intervention group (mean [SD])	Control group (mean [SD])	Difference in means [95% CI]
Katafuchi *et al*, 2003	SBP (mmHg) at 60 mo	127 (18)	124 (13)	3.00 (95%CI: –5.98, 11.99)
	DBP (mmHg) at 60 mo	78 (12)	76 (11)	2.00 (95%CI: –4.59, 8.59)
	Serum Cr (mg/dL) at 60 mo	0.99 (0.66)	1.01 (0.40)	–0.02 (95%CI: –0.33, 0.29)
	Urinary protein (mg/dL) at 60 mo	118 (143)	100 (98)	18.00 (95%CI: –52.92, 88.92)
	Change in UP-UCR from baseline	–0.84 (1.78)	0.26 (1.65)	–1.10 (95%CI: –2.10, –0.10)
Lee *et al*, 1997	Serum Cr (mg/dL) end of treatment	2.5 (1.2)	3.3 (1.1)	–0.80 (95%CI: –1.97, 0.19)
	CrCl (mL/min) end of treatment	52 (27)	31 (22)	21.00 (95%CI: –0.19, 42.19)
	Urinary protein (g/day) end of treatment	1.3 (1.1)	1.5 (1.1)	–0.20 (95%CI: –1.14, 0.74)
Shoji *et al*, 2000	Proteinuria (mg/d) at 1 yr	289.6 (234.8)	712.2 (391.7)	–422.60 (95%CI: –727.01, –118.19)
	Serum Cr (mg/dL) at 1 yr	0.77 (0.17)	0.77 (0.25)	0.00 (95%CI: –0.20, 0.20)
	GFR (mL/min/1.73m^2) at 1 yr	110.1 (26.4)	107.6 (22.3)	2.50 (95%CI: –19.46, 24.46)
	Serum IgA (mg/dL) at 1 yr	254.6 (98.8)	313.4 (86.2)	–58.80 (95%CI: –142.33, 24.73)
	SBP (mmHg) at 1 yr	109.1 (12.5)	116.1 (4.6)	–7.00 (95%CI: –15.05, 1.05)
Walker *et al*, 1990	Change in serum Cr (mmol/L)	0.02 (0.24)	0.01 (0.05)	0.01 (95%CI: –0.09, 0.11)
	Change in urine protein (g/24 h)	–0.53 (1.20)	0.13 (1.77)	–0.66 (95%CI: –1.48, 0.16)
	Change in urine erythrocytes (log rbc/mL)	0.05 (0.95)	–0.26 (0.78)	0.31 (95%CI: –0.16, 0.78)
	Change SBP (mmHg)	0.6 (17)	–3.8 (16.63)	4.40 (95%CI: –4.75, 13.55)
	Change SDP (mmHg)	1.0 (10.5)	–0.2 (19.75)	1.20 (95%CI: –7.31, 9.71)
Yoshikawa *et al*, 1999	Urinary protein excretion at end of treatment (g/d)	0.22 (0.31)	0.88 (1.34)	–0.66 (95%CI: –1.12, –0.20)
	Creatinine clearance (ml/min/1.73 m^2)	147 (33)	145 (44)	2.00 (95%CI: –15.98, 19.98)
	Serum IgA	229 (87)	281 (92)	–52.00 (95%CI: –91.78, –12.22)

UP-UCR, urine protein-creatinine ratio.

Table 4 Results for dichotomous outcomes

Study ID (author, year)	Outcomes	Intervention group (number of patients with events/ number of patients exposed)	Control group (number of patients with events/ number of patients not exposed)	Relative risk (RR) [95% CI]	Risk difference (RD) [95% CI]
Katafuchi *et al*, 2003	Improved kidney function	28/43	27/47	1.13 (95%CI: 0.82, 1.58)	0.08 (95%CI: –0.12, 0.28)
	Unimproved kidney function	15/43	20/47	0.82 (95%CI: 0.48, 1.39)	–0.08 (95%CI: –0.28, 0.12)
Lee *et al*, 1997	ESRD	1/10	4/11	0.28 (95%CI: 0.04, 2.07)	–0.26 (95%CI: –0.60, 0.08)
Walker *et al*, 1990	Amenorrhea	1/7	0/11	4.50 (95%CI: 0.21, 97.23)	0.14 (95%CI: –0.15, 0.44)
	Oligospermia	1/18	0/16	2.68 (95%CI: 0.12, 61.58)	0.06 (95%CI: –0.09, 0.20)
Yoshikawa *et al*, 1999	Developed chronic renal insufficiency	0/40	1/38	0.32 (95%CI: 0.01, 7.55)	–0.03 (95%CI: –0.10, 0.04)
	Treatment stopped due to adverse event	2/40	1/38	1.90 (95%CI: 0.18, 20.10)	0.02 (95%CI: –0.06, 0.11)

Specific management of IgA nephropathy: role of tonsillectomy

Date written: July 2005
Final submission: September 2005
Author: Merlin Thomas

GUIDELINES

No recommendation possible based on Level I or II evidence

SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on level III and IV evidence)
Numerous retrospective cohort studies and case reports have suggested that tonsillectomy may reduce proteinuria and serum total IgA concentration, decrease episodes of macroscopic haematuria and slow progression to end-stage kidney disease (ESKD) in patients with tonsillitis. In retrospective series, tonsillectomy has been associated with improved renal outcome in patients with IgA nephropathy, over and above standard therapy. However, these results have not been consistent in all studies. Moreover, these results are confounded by indication making the true role of tonsillectomy difficult to interpret.

- **Komatsu *et al*[1] examined renal outcomes in 237 patients with IgA nephropathy (aged 31 ± 14 years, mean ± SD) who had been followed-up for at least 6 months (follow-up periods, 62.3 ± 45.5 months). On univariate analysis, tonsillectomy was the only significant treatment that contributes to the maintenance of normal renal function. In addition, urinary abnormalities disappeared at a significantly higher frequency when patients were treated by tonsillectomy. However, the severity of baseline renal disease was not equivalent in all groups and the protective effect of tonsillectomy was eliminated after adjusting for other baseline variables.**
- **Rasche *et al*[2] retrospectively reviewed data on renal outcome in 55 patients with IgA nephropathy. In this study, there was no significant correlation between tonsillectomy and ESKD after 3.4 ± 4 years of follow-up, when adjusting for baseline risk factors.**
- **Xie *et al*[3] retrospectively reviewed data from over 15 years in 118 patients with idiopathic IgA nephropathy, including 48 patients who had undergone tonsillectomy and 70 who had not. After adjusting for baseline risk factors, only five (10.4%) of patients ($n = 48$) who had undergone tonsillectomy entered dialysis, whereas 18 (25.7%) of 70 patients who had not undergone tonsillectomy required dialysis ($P = 0.04$). Cox regression analysis showed that the relative risk for terminal renal failure in patients following tonsillectomy was lower compared to control patients (hazard ratio 0.22, 95%CI: 0.06–0.76, $P = 0.0164$).**
- **Iino *et al*[4] reviewed 50 patients with IgA nephropathy and chronic tonsillitis, including 35 patients with and 15 without tonsillectomy. In patients with a serum creatinine level of < 1.4 mg/dL, renal function remained normal in all subjects with tonsillectomy, but worsened in 3 of 13 patients without tonsillectomy. There was no effect seen in patients with a serum creatinine level of > 1.4 mg/dL at the time of renal biopsy. They proposed that tonsillectomy might have a role for patients with IgA nephropathy complicated by tonsillitis when the operation was performed before deterioration of renal function.**
- **Barta *et al*[5] followed 75 patients with biopsy-proven IgA nephropathy for an average of 12.2 years, including 35 patients who had undergone tonsillectomy. Although the level of microhaematuria 6 months after tonsillectomy was similar to before the procedure, tonsillectomy stopped gross haematuria appearing in the acute exacerbation of the disease in more than two-thirds of patients. ESKD was detected only in 4 of 35 patients 10 years after tonsillectomy, compared to 8 of 40 patients from a non-tonsillectomised control group with IgA nephropathy.**
- **Hotta *et al*[6] conducted a retrospective review of the renal outcome in 329 patients with IgA nephropathy, with an observation period longer than 36 months (82.3 ± 38.2 months). Their results showed that there were no significant differences between the tonsillectomy and non-tonsillectomy groups regarding the incidence of progressive renal functional loss (defined as a 50% increase in baseline serum creatinine). However, tonsillectomy had a significant impact on clinical remission by multivariate Cox regression analysis.**
- **Sato *et al*[7] retrospectively reviewed 70 patients with IgA nephropathy and renal impairment (serum creatinine >1.5 mg/dL). Steroid pulse with tonsillectomy, and conventional steroid and supportive therapy were performed in 30, 25 and 15 patients, respectively. The incidence of ESKD in the patients treated by steroid pulse with tonsillectomy was significantly lower than the incidences in the patients treated by conventional steroid and supportive therapy at a baseline creatinine level of 1.5–2 mg/dL, but no statistical difference was observed at a level of > 2 mg/dL. Like the findings of Iino *et al*,[4] the authors concluded that steroid pulse therapy combined with ton-**

sillectomy may be more effective than conventional steroid therapy in patients without moderate to severe renal impairment.

- **Akagi *et al*[8] performed a 10-year retrospective case-control study of 71 patients with IgA nephropathy to evaluate the long-term effects and prognostic factors associated with tonsillectomy. A total of 41 patients who had undergone tonsillectomy were compared with 30 patients who had not. After over 12 years of follow-up, the clinical remission rate was 24% in the tonsillectomy group and 13.3% in those not receiving tonsillectomy. Similarly, renal survival was higher in patients who had undergone tonsillectomy.**
- **Nishi and colleagues[9] reviewed long-term renal survival in 46 patients who had undergone tonsillectomy, and 74 patients with IgA nephropathy who had not. Five (10.9%) of the tonsillectomy group reached ESKD whereas 19 (25.8%) of the non-tonsillectomy group did.**

In summary, tonsillectomy could reduce proteinuria and haematuria in those patients without moderate to severe renal impairment. These studies are retrospective and potentially confounded by indication, making the clinical significance of this intervention difficult to interpret.

BACKGROUND

IgA nephropathy is the most common glomerular disease in Australia and New Zealand. Although the natural history of IgA nephropathy is variable, many patients develop progressive loss of renal function over many years. ESKD is said to develop in 20% of cases after 10 years and in 30% after 20 years, whereas another 30% show some decline in renal function.[10] In addition to non-specific renal interventions (control of hypertension, ACE inhibition, etc.) there is evidence that interventions that specifically treat IgA nephropathy may also slow the progression to ESKD.

The macroscopic haematuria seen in IgA nephropathy is commonly precipitated by a mucosal stimulation (e.g. pharyngitis) suggesting the possibility of an aberrant mucosal immunity in the pathogenesis of IgA nephropathy. The tonsils are also a significant source of under-glycosylated IgA1, implicated in the pathogenesis of IgA deposition.[11] Tonsillectomy also decreases the levels of serum IgA levels. The objective of this guideline is to evaluate the available clinical evidence pertaining to the impact of tonsillectomy on renal functional decline in IgA nephropathy. This guideline does not address the role of tonsillectomy in those patients with appropriate ENT indications.

SEARCH STRATEGY

Databases searched: MeSH terms and text words for IgA nephropathy were combined with MeSH terms and text words for tonsillectomy. This search was carried out in Medline (1966 to September Week 2, 2004). The Cochrane Renal Group Trials Register was also searched for trials of IgA nephropathy not indexed in Medline.
Date of searches: 17 September 2004.

WHAT IS THE EVIDENCE?

There have been no randomised controlled studies.

SUMMARY OF THE EVIDENCE

No recommendations can be made regarding tonsillectomy for disease progression in patients with IgA nephropathy on the basis of currently available retrospective studies and case reports. Tonsillectomy should be performed in those patients with appropriate ENT indications. Controlled trials are needed before tonsillectomy should be considered for any other group.

WHAT DO THE OTHER GUIDELINES SAY?

Kidney Disease Outcomes Quality Initiative: No recommendation.
UK Renal Association: No recommendation.
Canadian Society of Nephrology: A tonsillectomy could reduce proteinuria and hematuria in those patients with recurrent tonsillitis.[4]
European Best Practice Guidelines: No recommendation.
International Guidelines: No recommendation.

IMPLEMENTATION AND AUDIT

No recommendation.

SUGGESTIONS FOR FUTURE RESEARCH

Patients with IgA detailed in the ANZDATA database should be questioned as to whether they have undergone tonsillectomy in the past.

REFERENCES

1. Komatsu H, Fujimoto S, Hara S *et al*. Multivariate analysis of prognostic factors and effect of treatment in patients with IgA nephropathy. *Ren Fail* 2005; **27**: 45–52.
2. Rasche FM, Schwarz A, Keller F. Tonsillectomy does not prevent a progressive course in IgA nephropathy. *Clin. Nephrol.* 1999; **51**: 147–52.
3. Xie Y, Nishi S, Ueno M *et al*. The efficacy of tonsillectomy on long-term renal survival in patients with IgA nephropathy. *Kidney Int.* 2003; **63**: 1861–7.
4. Iino Y, Ambe K, Kato Y *et al*. Chronic tonsillitis and IgA nephropathy. Clinical study of patients with and without tonsillectomy. *Acta Otolaryngol. Suppl* 1993; **508**: 29–35.
5. Barta J, Kovacs T, Fazekas A *et al*. Does tonsillectomy cause any change in long-term course of IgA nephropathy? (Hungarian). *Orv Hetil* 1996; **137**: 2903–6.
6. Hotta O, Furuta T, Chiba S *et al*. Regression of IgA nephropathy: a repeat biopsy study. *Am. J. Kidney Dis* 2002; **39**: 493–502.
7. Sato M, Hotta O, Tomioka S *et al*. Cohort study of advanced IgA nephropathy: efficacy and limitations of corticosteroids with tonsillectomy. *Nephron Clin. Pract* 2003; **93**: c137–45.

8. Akagi H, Kosaka M, Hattori K *et al*. Long-term results of tonsillectomy as a treatment for IgA nephropathy. *Acta Otolaryngol. Suppl* 2004; **555**: 38–42.
9. Nishi S, Xie Y, Ueno M *et al*. A clinicopathological study on the long-term efficacy of tonsillectomy in patients with IgA nephropathy. *Acta Otolaryngol. Suppl* 2004; **555**: 49–53.
10. Rekola S, Bergstrand A, Bucht H. Deterioration of GFR in IgA nephropathy as measured by ^{51}Cr-EDTA clearance. *Kidney Int*. 1991; **40**: 1050–4.
11. Horie A, Hiki Y, Odani H *et al*. IgA1 molecules produced by tonsillar lymphocytes are under-O-glycosylated in IgA nephropathy. *Am. J. Kidney Dis* 2003; **42**: 486–96.

Specific management of IgA nephropathy: role of cyclosporin and other therapies

Date written: July 2005
Final submission: September 2005
Author: Merlin Thomas

GUIDELINES

There is currently insufficient data to support the use of cyclosporin to slow the progression of IgA nephropathy. (Level I evidence)

SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on level III and IV evidence)

- **In patients with IgA nephropathy and nephrotic syndrome that have proved resistant to conventional treatment, clinical remission in selected patients has been reported following the use of cyclosporin,[1] azathioprine,[2] mycophenolate[3] and intravenous immunoglobulin,[4] ketoconazole[5] and mizobine.[6] These anecdotal reports do not provide conclusive evidence of their efficacy in preventing disease progression in IgA nephropathy and further studies are needed before these treatments can be recommended. (Level III evidence – anecdotal reports, uncontrolled and retrospective reviews)**
- **Although their utility in preventing progressive renal impairment remains to be established, fluvastatin appears to have antiproteinuric effects in patients with IgA nephropathy. In the presence of dyslipidemia, which complicates many cases of IgA nephropathy, it seems reasonable to consider a statin as a first-line therapy.**
- **Similarly, while the clinical utility of vitamin E therapy in preventing progressive renal impairment remains to be established, its good side-effect profile means that some patients will wish to consider vitamin E supplementation in addition to other relevant supportive strategies.**

BACKGROUND

IgA nephropathy is the most common glomerular disease in Australia and New Zealand. Although the natural history of IgA nephropathy is variable, many patients develop progressive loss of renal function over many years. End-stage kidney disease (ESKD) is said to develop in 20% of cases after 10 years and in 30% after 20 years, whereas another 30% show some decline in renal function.[7] In addition to non-specific renal interventions (control of hypertension, ACE inhibition, etc.) there is evidence that interventions to specifically treat IgA nephropathy may also slow the progression to ESKD. The objective of this guideline is to summarize evidence for the utility of these agents in patients with IgA nephropathy.

SEARCH STRATEGY

Databases searched: MeSH terms and text words for IgA nephropathy were combined with MeSH terms and text words for cyclosporine, vitamin E, fluvastatin and azathioprine. This search was carried out in Medline (1966 to September Week 2, 2004). The Cochrane Renal Group Trials Register was also searched for trials of IgA nephropathy not indexed in Medline.
Date of searches: 17 September 2004.

WHAT IS THE EVIDENCE?

Cyclosporine A

There is no current evidence that treatment with cyclosporin either prevents the occurrence of IgA nephropathy (as it recurs in transplants) or retards the long-term progression of IgA nephropathy, although long-term studies have not been performed. There are only a few small studies available using cyclosporin for the treatment of IgA nephropathy.
There has been only one small short-term randomised controlled study:

- Lai *et al*[8] randomised 19 patients with IgA nephropathy and proteinuria (greater than 1.5 g/day) to receive oral cyclosporin (5 mg/kg/day) for 12 weeks ($n = 9$) and placebo ($n = 10$). Although there was a significant fall in protein excretion, this was accompanied by a rise in serum creatinine in cyclosporin-treated patients. This was despite the plasma cyclosporin concentrations being maintained within a narrow therapeutic range. However, both proteinuria and renal function returned to pretreatment levels after cessation of treatment.

In another small non-randomised open label study,[1] 6 patients with IgA nephropathy, nephrotic-range proteinuria

resistant to corticosteroids administered for 3 months and serum creatinine less than 200 mmol/L were given cyclosporin (5 mg/kg/day) titrated to a serum concentration of 70–150 ng/mg and alternate day prednisolone for 1 year tapered to discontinuation in 9 months. Cyclosporin treatment reduced proteinuria. Overall, glomerular filtration rate (GFR) decreased after 1 year of treatment, although after 2 years it was not significantly different from baseline. The variable natural history of this disease makes such uncontrolled observations difficult to interpret.

A recent meta-analysis concluded that there was no significant difference in the risk of ESKD or rate of decline of GFR between patients treated with cyclosporin and patients treated with placebo.[9]

Vitamin E

Oxidative stress is believed to be an important mediator of renal injury in IgA nephropathy. There has been one randomised controlled trial of vitamin E therapy in children with IgA nephropathy.

- Chan *et al.*[10] randomised 55 children with IgA nephropathy to received vitamin E (400–800 IU/day) ($n = 27$) or placebo ($n = 28$). Proteinuria was significantly reduced in those receiving vitamin E compared to placebo. However, there were no significant changes in the prevalence of haematuria. As these patients did not have progressive renal impairment, the effect of vitamin E in preserving renal function could not be assessed.

Mycophenolate

Humoral immunity is believed to play a role in the pathogenesis of IgA nephropathy. There have been two prospective placebo-controlled randomised studies in patients with IgA nephropathy using mycophenolate mofetil (MMF).

- Maes *et al*[11] randomised 34 patients at risk for progressive disease, to receive ACE inhibition and MMF (2 g per day, $n = 21$) or placebo ($n = 13$) for 3 years of treatment. No significant effect of MMF could be demonstrated on renal function/outcome or proteinuria.
- Chen *et al*[12] randomised 62 patients with severe IgA nephropathy and proteinuria to receive MMF or oral prednisolone. After 6, 12 and 18 months, proteinuria was reduced in both groups, although the effect was larger in patients receiving MMF. In addition, lipid parameters were significantly improved in patients receiving MMF compared with those receiving prednisolone alone.

Fluvastatin

Fluvastatin may have an antiproteinuric effect in IgA nephropathy, independent of its lipid-lowering activities.[13] There has been one prospective controlled trial of fluvastatin in patients with IgA nephropathy.

- Kano *et al*[14] randomised 30 patients with IgA nephropathy and moderate proteinuria to receive 20 mg of fluvastatin and 5 mg/kg of dipyridamole or dipyridamole alone. After 1 year, proteinuria and haematuria and creatine clearance increased in patients treated with fluvastatin compared to patients receiving dipyridamole alone.

Other agents

There are no prospective clinical trials in patients with IgA nephropathy using azathioprine, intravenous immunoglobulin, ketoconazole or mizobine.

SUMMARY OF THE EVIDENCE

At present, there is insufficient evidence to support the use of cyclosporin or MMF to prevent progression of kidney disease in patients with IgA nephropathy. Although both fluvastatin and vitamin E appear to have antiproteinuric effects, their utility in preventing progressive renal impairment remains to be established.

WHAT DO THE OTHER GUIDELINES SAY?

Kidney Disease Outcomes Quality Initiative: No recommendation.
UK Renal Association: No recommendation.
Canadian Society of Nephrology: Cyclosporin A should not be used. No recommendation regarding other therapies.[15]
European Best Practice Guidelines: No recommendation.
International Guidelines: No recommendation.

IMPLEMENTATION AND AUDIT

No recommendation.

SUGGESTIONS FOR FUTURE RESEARCH

No recommendation.

REFERENCES

1. Chabova V, Tesar V, Zabka J *et al*. Long-term treatment of IgA nephropathy with cyclosporin A: a preliminary report. *Nephrol. Dial Transplant* 1997; **12**: 2206–7.
2. Goumenos D, Ahuja M, Shortland JR *et al*. Can immunosuppressive drugs slow the progression of IgA nephropathy? *Nephrol. Dial Transplant* 1995; **10**: 1173–81.
3. Briggs WA, Choi MJ, Scheel PJ Jr. Successful mycophenolate mofetil treatment of glomerular disease. *Am. J. Kidney Dis* 1998; **31**: 213–7.
4. Rostoker G, Desvaux-Belghiti D, Pilatte Y *et al*. High-dose immunoglobulin therapy for severe IgA nephropathy and Henoch-Schonlein purpura. *Ann. Intern. Med*. 1994; **120**: 476–84.
5. Walser M, Hill S. Effect of ketoconazole plus low-dose prednisone on progression of chronic renal failure. *Am. J. Kidney Dis* 1997; **29**: 503–13.
6. Tornino Y. Immunotherapy in IgA nephropathy. *Nephrology* 1997; **3**: 113–5.
7. Rekola S, Bergstrand A, Bucht H. Deterioration of GFR in IgA nephropathy as measured by ^{51}Cr-EDTA clearance. *Kidney Int*. 1991; **40**: 1050–4.

8. Lai KN, Lai FM, Li PK *et al*. Cyclosporin treatment of IgA nephropathy: a short term controlled trial. *Br. Med. J. (Clin. Res. Ed)* 1987; **295**: 1165–8.
9. Samuels JA, Strippoli GF, Craig JC *et al*. Immunosuppressive treatments for immunoglobulin A nephropathy: a meta-analysis of randomized controlled trials. *Nephrology* 2004; **9**: 177–85.
10. Chan JC, Mahan JD, Trachtman H *et al*. Vitamin E therapy in IgA nephropathy: a double-blind, placebo-controlled study. *Pediatr Nephrol*. 2003; **18**: 1015–9.
11. Maes BD, Oyen R, Claes K *et al*. Mycophenolate mofetil in IgA nephropathy: results of a 3-year prospective placebo-controlled randomized study. *Kidney Int*. 2004; **65**: 1842–9.
12. Chen X, Chen P, Cai G *et al*. [A randomized control trial of mycophenolate mofeil treatment in severe IgA nephropathy]. [Chinese]. *Chung-Hua i Hsueh Tsa Chih [Chinese Medical Journal]* 2002; **82**: 796–801.
13. Buemi M, Allegra A, Corica F *et al*. Effect of fluvastatin on proteinuria in patients with immunoglobulin A nephropathy. *Clin. Pharmacol. Ther* 2000; **67**: 427–31.
14. Kano K, Nishikura K, Yamada Y *et al*. Effect of fluvastatin and dipyridamole on proteinuria and renal function in childhood IgA nephropathy with mild histological findings and moderate proteinuria. *Clin. Nephrol*. 2003; **60**: 85–9.
15. Nolin L, Courteau M. Management of IgA nephropathy: evidence-based recommendations. *Kidney Int. Suppl* 1999; **70**: S56–62.

APPENDICES

Table 1 Characteristics of included studies

Study ID (author, year)	N	Study design	Setting	Participants	Intervention (experimental group)	Intervention (control group)	Follow up (months)	Comments
Chan *et al*, 2003	55	Randomised controlled clinical trial	7 paediatric nephrology programs, US	55 children with biopsy-proven IgA nephropathy	Vitamin E	Placebo	12	
Kano *et al*, 2003	60	Randomised controlled clinical trial	Hospital, Japan	30 children diagnosed with normocholesterolemic IgA nephropathy	30 mg fluvastatin and 5 mg/kg dipyridamole	5 mg/kg dipyridamole	24	
Lai *et al*, 1987	19	Randomised controlled trial	University hospital, Hong Kong	19 patients with IgA nephropathy	Oral cyclosporin (5 mg/kg/day)	Placebo	3	
Maes *et al*, 2004	34	Randomised controlled clinical trial	University Hospital, Belgium	34 patients with IgA nephropathy	Salt intake restriction, ACE inhibition, MMF 2 g/day	Placebo	36	

Table 2 Quality of randomised trials

Study ID (author, year)	Method of allocation concealment	Blinding			Intention-to-treat analysis	Loss to follow up (%)
		(Participants)	(Investigators)	(Outcome assessors)		
Chan *et al*, 2003	Not specified	Yes	Yes	Yes	Unclear	31.0
Kano *et al*, 2003	Not specified	No	No	No	No	50.0
Lai *et al*, 1987	Computer-generated numbers	Yes	No	No	Unclear	0.0
Maes *et al*, 2004	Not specified	Yes	Not stated	Not stated	Yes	20.6

Table 3 Results for continuous outcomes

Study ID (author, year)	Outcomes	Intervention group (mean [SD])	Control group (mean [SD])	Difference in means [95% CI]
Chan *et al*, 2003	Cr Clearance (mL/min/1.73 m^2) end of study	127 (50)	112 (31)	15.00 (95%CI: 2.14, 27.86)
	Urinary protein/Cr (mg/mg)	0.24 (0.38)	0.61 (1.37)	–0.37 (95%CI: –0.88, 0.14)
Kano *et al*, 2003	UP (g/24 h/1.73 m^2) at 1 yr	0.5 (0.4)	0.8 (0.6)	–0.30 (95%CI: –0.66, 0.06)
	Hematuria in morning urine	1.1 (1.0)	1.3 (1.3)	–0.20 (95%CI: –1.03, 0.63)
	Serum Cr (μmol/L) at 1 yr	41.5 (12.4)	48.6 (10.6)	–7.10 (95%CI: –15.36, 1.16)
	Cr Clearance (ml/min/1.73 m^2) at 1 yr	133.1 (14.9)	110.5 (15.2)	22.50 (95%CI: 11.73, 33.27)
	Serum total protein (g/L) at 1 yr	73 (5)	69 (4)	4.00 (95%CI: 0.76, 7.24)
	Serum albumin (g/L) at 1 yr	46 (2)	42 (3)	4.00 (95%CI: 2.18, 5.82)
	Serum total cholesterol (mmol/L) at 1 yr	3.57 (0.75)	4.48 (0.67)	–0.91 (95%CI: –1.42, –0.40)
	Serum triglyceride (g/L) at 1 yr	0.72 (0.21)	1.02 (0.25)	–0.30 (95%CI: –0.47, –0.13)
	Serum LDL cholesterol (mmol/L) at 1 year	2.02 (0.60)	2.90 (0.88)	–0.88 (95%CI: –1.42, –0.34)
Maes *et al*, 2004	Hematocrit (%) at 36 mo	43 (9.17)	42 (3.61)	1.00 (95%CI: –3.39, 5.39)
	Haemoglobin (g/dL) at 36 mo	14.1 (2.75)	13.9 (2.16)	0.20 (95%CI: –1.46, 1.86)
	IgA (g/L) at 36 mo	2.6 (1.37)	2.8 (1.08)	–0.20 (95%CI: –1.03, 0.63)
	Albumin (g/L) at 36 mo	38.7 (4.58)	39.2 (3.61)	–0.50 (95%CI: –3.27, 2.27)

Table 4 Results for dichotomous outcomes

Study ID (author, year)	Outcomes	Intervention group (number of patients with events/number of patients exposed)	Control group (number of patients with events/ number of patients not exposed)	Relative risk (RR) [95% CI]	Risk difference (RD) [95% CI]
Lai *et al*, 1987	Moderate ankle oedema	2/9	1/10	2.22 (95%CI: 0.24, 20.57)	0.12 (95%CI: –0.21, 0.45)
	Hirsutism, epigastric discomfort	2/9	0/10	5.50 (95%CI: 0.30, 101.28)	0.22 (95%CI: –0.07, 0.52)
	Decrease in serum IgA concentration	7/9	0/10	16.50 (95%CI: 1.07, 253.40)	0.78 (95%CI: 0.48, 1.07)
Maes *et al*, 2004	Mortality	0/21	1/13	0.21 (95%CI: 0.01, 4.85)	–0.08 (95%CI: –0.25, 0.10)
	Stopped treatment due to adverse events	1/21	1/13	0.62 (95%CI: 0.04, 9.07)	–0.03 (95%CI: –0.20, 0.14)
	Loss of renal function (decrease > 25% in inulin clearance)	7/21	2/12	2.17 (95%CI: 0.53, 8.88)	0.18 (95%CI: –0.10, 0.46)
	GI complaints	2/21	0/13	3.18 (95%CI: 0.16, 61.49)	0.10 (95%CI: –0.07, 0.26)

Membranous nephropathy: role of alkylating agents

Date written: July 2005
Final submission: September 2005
Author: Merlin Thomas

GUIDELINES

a. Treatment with alkylating agents is associated with an increased rate of remission in patients with nephrotic syndrome and idiopathic membranous nephropathy when compared to steroid therapy alone or no therapy. (Level I evidence)

b. There is insufficient data to confirm that this effect translates into an improvement in renal outcomes. (Level I evidence)

SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on Level III and IV evidence)

Who to treat?

- **To avoid possibly unnecessary treatments and toxicity, most clinical studies have focused on individuals who are thought to be at risk for progressive disease. Consequently, at this time, the clinical use of alkylating agents in membranous nephropathy should be restricted to individuals with poor prognostic features, such as heavy proteinuria (> 3 g/24 h), impaired renal function at presentation, deteriorating renal function and/or reduced response to supportive therapy.**
- **A variety of models incorporating a range of clinical and histological features have been validated, with the ability to predict the development of chronic renal insufficiency of up to 86%, with a sensitivity of more than 60%.[1,2] Such a model could be used to target therapy by identifying individual patients at risk for progressive disease. Treatment algorithms based on these models have been proposed.[1] These have not been tested in large-scale trials.**
- **Currently, there is no evidence to support disease-specific intervention in adult patients with good prognostic features (proteinuria < 3 g/day and normal renal function), although supportive therapy including aggressive control of blood pressure and dyslipidemia and blockade of the renin angiotensin system would seem prudent. (Level IV evidence) Nonetheless, long-term follow-up is still required to monitor for the development of adverse indicators to identify additional patients at risk for progressive kidney disease. (Level IV evidence)**

When to treat

- **The possibility of spontaneous remission has led many authors to suggest that a 6-month period on conservative therapy (including aggressive control of blood pressure and dyslipidemia and blockade of the renin angiotensin system) may be valuable before embarking on cytotoxic therapy. (Level IV evidence)**
- **While most studies have dealt with early treatment of patients with adverse prognostic features (and excluded patients with established renal impairment) there have been a few small studies to suggest that even late intervention may be efficacious.[3,4] (Level III evidence)**
- **Although such studies imply that a brief delay may not be harmful, the progression of control patients over a short period in many of the trials described below should mean this course should only be conducted with cautious observation. (Level IV evidence)**

BACKGROUND

Idiopathic membranous glomerulonephritis (MGN) runs a variable course. Most patients do well, with 10-year renal survival of 70–90%.[5] Spontaneous remissions occur in up to 65% of patients,[6] sometimes months or years after the onset of nephrotic syndrome and a substantial percentage of patients never progress to renal failure. To avoid possibly unnecessary treatments, most clinical studies have focused on individuals who are thought to be at greater risk for progressive disease. The objective of this guideline is to evaluate the available clinical evidence pertaining to the impact of alkylating agents on renal functional decline in MGN with poor prognostic features, such as heavy proteinuria (> 3 g/24 h), impaired renal function at presentation, deteriorating renal function and/or reduced response to therapy.

SEARCH STRATEGY

Databases searched: MeSH terms and text words for Membranous Nephropathy were combined with MeSH terms and text words for alkylating agents. This search was carried out in Medline (1966 to September Week 1, 2004). The Cochrane Renal Group Trials Register was also searched for trials of membranous nephropathy not indexed in Medline.
Date of searches: 9 September 2004.

WHAT IS THE EVIDENCE?

There have been a number of small, prospective, randomised controlled trials (RCTs) comparing alkylating agents with no treatment.

There have been four RCTs of alkylating agents alone or in combination with steroids, which have compared treatment responses with those observed in patients receiving therapy compared to no therapy or placebo.

- In the earliest RCT, Donadio *et al*[7] conducted a prospective study of 22 patients randomised to either oral cyclophosphamide of 1.5–2.5 mg/kg daily for a period of 12 months or no specific therapy. They were unable to demonstrate in this small study any significant difference in renal function, proteinuria, or histological stage of disease in patients who received cyclophosphamide.
- Braun *et al*[8] randomised 55 patients with idiopathic MGN to receive therapy with a cyclophosphamide or supportive care. After 60 months of follow-up, treatment modality had no effect on rates of remission or doubling of serum creatinine.
- Ponticelli *et al*[9] initially studied the effect of 6 months of treatment with chlorambucil plus corticosteroids in monthly cycles vs. symptomatic therapy, in 62 patients with MGN. All patients had nephrotic range proteinuria. Patients with renal insufficiency were excluded. Twenty-three of 32 chlorambucil patients experienced a complete or partial remission compared with just 9 of 30 control patients. Ten years after initial therapy, the probability of renal survival was 0.92 for treated patients compared with 0.60 for controls. Some have criticized this study because of this apparently rapid rate of progression in this control group.
- Murphy *et al*[10] studied 40 patients with idiopathic MGN randomised to receive either no treatment or a regimen of oral cyclophosphamide for 6 months, and warfarin and dipyridamole for 2 years. During the 2 years of the trial, renal function remained unchanged in both groups, but reduced proteinuria and improved serum albumin were found in the cyclophosphamide-treated patients. When only nephrotic patients are considered, a significantly higher proportion of patients in the treatment group achieved a complete remission compared with control patients (9 of 13 vs. 4 of 13, P = 0.05). As progressive deterioration in renal function in MGN is associated with persistent heavy proteinuria, they concluded that treatment with cyclophosphamide had a beneficial effect.

Four studies have evaluated the effect of adding an alkylating agent to a steroid-based regimen in the control arm.

- Ahmed *et al*[11] examined the effect of prednisolone plus chlorambucil compared with prednisolone alone in 20 patients with idiopathic membranous nephropathy.
- Falk *et al*[12] conducted a RCT of pulse methylprednisolone, oral corticosteroids, and 6 months of intravenous cyclophosphamide compared with oral alternate-day corticosteroids alone in 26 patients with idiopathic membranous nephropathy and clinical and laboratory evidence of deteriorating renal function. There were no differences in the numbers progressing to end-stage kidney disease (ESKD) or in the creatinine levels or urinary protein excretion over a mean follow-up period of 29 months.
- Pahari *et al*[13] randomised 71 patients with idiopathic MGN to receive steroid and cyclophosphamide every other month and steroid alone. In patients receiving cyclophosphamine, 33 of 36 patients achieved complete remissions, 2 had a relapsing course with remission on further courses of therapy and only one has reached end-stage kidney failure (ESKF). In contrast, 15 of the 35 patients receiving steroids alone achieved complete remission and 7 a partial remission.
- In a second study by Ponticelli's[14] group, 92 nephrotic patients were randomised to receive the same chlorambucil/steroid regimen or steroids alone. This confirmed a net benefit effect, with 90% survival in the chlorambucil-treated group at 10 years compared to 62% in the untreated group. However, treatment with chlorambucil and methylprednisolone was less likely to induce a remission in the presence of renal insufficiency or mesangial sclerosis.

Three meta-analyses of clinical trials in idiopathic membranous nephropathy have been published.

- Imperiale, Goldfarb, and Berns'[15] analysis included the first five trials discussed above and some retrospective data. This analysis was confounded by a number of factors including heterogeneity in the doses and duration of drug therapy, mean duration of follow-up, definitions of complete and partial responses to treatment and comparison therapies used. Nonetheless, they concluded that treatment with cytotoxic agents benefited patients with idiopathic membranous nephropathy by inducing significantly more remissions than untreated groups.
- Hogan *et al*[16] conducted a larger examination of 32 studies published between 1968 and 1993. The analysis incorporated data on close to 2000 patients followed, in most cases, for more than 2 years. The meta-analysis again found that the relative chance of complete remission was improved for patients treated with alkylating agents. At 5 years, the probability of renal survival in the steroid/no-therapy group (0.80) was lower than in patients receiving alkylating agents (0.99). However, the percentage of patients in the analysis included from RCTs was small, increasing the possibility of type II error.
- In the most recent meta-analysis,[17] no beneficial effect on ESKD was observed in patients treated with alkylating agents (RR 0.56, 95%CI: 0.18–1.68, P = 0.3) when compared with placebo or no treatment. Nonetheless, alkylating agents induced more remissions than steroids (complete remission, RR 1.89, 95%CI: 1.34–2.67, P = 0.0003; complete or partial remission, RR 1.45, 95%CI: 1.16–1.81, P = 0.001). Overall, alkylating agents showed a significant effect on complete remission (RR 2.37, 95%CI: 1.32–4.25, P = 0.004) and final proteinuria (weighted mean difference, –2.36 g/24 h; 95%CI: –4.27 to –0.46; P = 0.02).

Three studies have compared the effect of two specific immunosuppressive treatments within the class of alkylating agents.

- Branten *et al*[18] randomised patients with idiopathic membranous nephropathy and renal insufficiency to

monthly cycles of steroids (1 g methylprednisolone IV on 3 consecutive days, followed by oral prednisone 0.5 mg/kg/day in months 1, 3 and 5) and chlorambucil (0.15 mg/kg/day in months 2, 4 and 6) ($n = 15$); or oral cyclophosphamide (1.5–2.0 mg/kg/day for 1 year) and steroids in a comparable dose ($n = 17$). Twelve months after starting treatment, mean serum creatinine was lower in cyclophosphamide-treated patients than in those receiving chlorambucil ($P < 0.01$). In addition, four chlorambucil-treated patients developed ESKD, and five needed a second course of therapy, whereas only one cyclophosphamide-treated patient developed ESKD ($P < 0.05$). Remissions of proteinuria occurred more frequently after cyclophosphamide treatment (15/17 vs. 5/15; $P < 0.01$).

- Ponticelli *et al*[19] compared regimens of methylprednisolone (1 g intravenously for 3 consecutive days followed by oral methylprednisolone, 0.4 mg/kg per d for 27 d) alternated every other month either with chlorambucil (0.2 mg/kg per d for 30 d) with oral cyclophosphamide (2.5 mg/kg per d for 30 d). All patients ($n = 87$) had biopsy-proven membranous nephropathy and nephrotic syndrome. Eighty-two per cent (36/44) assigned to steroid and chlorambucil developed complete or partial remission of their nephrotic syndrome, compared to 93% assigned to methylprednisolone and cyclophosphamide ($P = 0.1$). Relapse subsequently occurred in 25–30% of patients, with no differences between treatment groups. On average, renal function remained stable over the 3-year follow-up in both treatment groups.
- Reichert *et al*[20] compared oral chlorambucil and intravenous cyclophosphamide-based drug regimens in the treatment of 18 patients with membranous nephropathy and deteriorating renal function. Therapy consisted of chlorambucil (0.15 mg/kg body weight per day orally in months 2, 4, and 6) and prednisone (three intravenous pulses of 1 g of methylprednisolone followed by oral prednisone at 0.5 mg/kg per day in months 1, 3, and 5) or intravenous cyclophosphamide (750 mg/m^2 body surface area once every month for 6 months) and methylprednisolone (three intravenous 1-g pulses in months 1, 3, and 5). Renal function was better preserved in patients receiving chlorambucil with a net reduction in serum creatinine levels in the group treated with chlorambucil and an increase in the group treated with intravenous cyclophosphamide (difference between groups, $P < 0.001$). At the end of follow-up, one patient in the chlorambucil group and four patients in the cyclophosphamide group required renal replacement therapy.

A meta-analysis of these studies[17] concluded that there was no significant difference in the need for dialysis or transplantation or in the rates of complete, partial or for complete or partial remission between different alkylating agents.

Both cyclophosphamide and chlorambucil are associated with significant short- and long-term toxicity. In particular, the risk of bladder cancer is significantly increased by cyclophosphamide, many years after initiation of treatment and often well outside standard trial analysis. In one study in Wegener's granulomatosis, the bladder cancer risk was estimated to be 5% at 10 years and 16% at 16 years after first exposure to cyclophosphamide.[21] It is possible that a similar cancer incidence in membranous nephropathy may outweigh any benefit in slowing disease progression. Some have suggested that intravenous route for cyclophosphamide may reduce bladder toxicity, however, the only RCT to use pulsed cyclophosphamide plus prednisone showed no benefit compared with the use of steroids alone.[22] These risks associated with cyclophosphamide have led some to consider chlorambucil as the alkylating agent of choice for the treatment of MGN.[21] However, chlorambucil has a very narrow therapeutic index for marrow suppression. In the recent meta-analysis, cyclophosphamide treatment resulted in an overall lower rate of discontinuation due to adverse events compared to chlorambucil (RR 2.34, 95%CI: 1.25–4.39, $P = 0.008$). In particular, leukopenia was less common in cyclophosphamide-treated patients compared to chlorambucil-treated patients.

SUMMARY OF THE EVIDENCE

While there is evidence that cyclophosphamide or chlorambucil can induce remission of proteinuria in some cases of membranous nephropathy and nephrotic syndrome, the data is confounded by the inclusion in trials of patients who may have had spontaneous remission as well as by differences in study methodology. There is also currently insufficient evidence to demonstrate any benefit in terms of progressive renal impairment and ESKD. The optimal agent to use remains to be established.

Nonetheless, in patients with poor prognostic features, such as heavy proteinuria (> 3 g/24 h), impaired renal function at presentation, deteriorating renal function in whom after a period of monitoring, an inexorable decline in renal function appears likely, the possibility of inducing remission of proteinuria by using cytotoxic therapy should be balanced against the significant risk of toxicity.

WHAT DO THE OTHER GUIDELINES SAY?

Kidney Disease Outcomes Quality Initiative: No recommendation.
UK Renal Association: No recommendation.
Canadian Society of Nephrology: The alkylating agents cyclophosphamide and chlorambucil are both effective in the management of membranous nephropathy. Because of growing concern about long term toxicity, especially with cyclophosphamide, these drugs should be reserved for patients who exhibit clinical features, such as severe or prolonged nephrosis, renal insufficiency, or hypertension, that predict a high likelihood of progression to end-stage renal disease.
European Best Practice Guidelines: No recommendation.
International Guidelines: No recommendation.

IMPLEMENTATION AND AUDIT

No recommendation.

SUGGESTIONS FOR FUTURE RESEARCH

No recommendation.

REFERENCES

1. Cattran D. Predicting outcome in the idiopathic glomerulopathies. *J. Nephrol.* 1998; **11**: 57–60.
2. Cattran DC, Pei Y, Greenwood CM *et al.* Validation of a predictive model of idiopathic membranous nephropathy: its clinical and research implications. *Kidney Int.* 1997; **51**: 901–7.
3. Bruns FJ, Adler S, Fraley DS *et al.* Sustained remission of membranous glomerulonephritis after cyclophosphamide and prednisone. *Ann. Intern. Med.* 1991; **114**: 725–30.
4. Mathieson PW, Turner AN, Maidment CG *et al.* Prednisolone and chlorambucil treatment in idiopathic membranous nephropathy with deteriorating renal function. *Lancet* 1988; **2**: 869–72.
5. Schieppati A, Mosconi L, Perna A *et al.* Prognosis of untreated patients with idiopathic membranous nephropathy. *N Engl. J. Med.* 1993; **329**: 85–9.
6. Geddes CC, Cattran DC. The treatment of idiopathic membranous nephropathy. *Semin Nephrol.* 2000; **20**: 299–308.
7. Donadio JV Jr, Holley KE, Anderson CF *et al.* Controlled trial of cyclophosphamide in idiopathic membranous nephropathy. *Kidney Int.* 1974; **6**: 431–9.
8. Braun N, Erley CM, Benda N *et al.* Therapy of membranous glomerulonephritis with nephrotic syndrome. Five years follow-up of a prospective, randomized study [abstract]. *J. Am. Soc. Nephrol.* 1995; **6**: 413.
9. Ponticelli C, Zucchelli P, Passerini P *et al.* Methylprednisolone plus chlorambucil as compared with methylprednisolone alone for the treatment of idiopathic membranous nephropathy. The Italian Idiopathic Membranous Nephropathy Treatment Study Group. *N Engl. J. Med.* 1992; **327**: 599–603.
10. Murphy BF, McDonald I, Fairley KF *et al.* Randomized controlled trial of cyclophosphamide, warfarin and dipyridamole in idiopathic membranous glomerulonephritis. *Clin. Nephrol.* 1992; **37**: 229–34.
11. Ahmed S, Rahman M, Alam MR *et al.* Methylprednisolone plus chlorambucil as compared with prednisolone alone for the treatment of idiopathic membranous nephropathy. A preliminary study. *Bangladesh Renal J.* 1994; **13**: 51–4.
12. Falk RJ, Hogan SL, Muller KE *et al.* Treatment of progressive membranous glomerulopathy. A randomized trial comparing cyclophosphamide and corticosteroids with corticosteroids alone. The Glomerular Disease Collaborative Network. *Ann. Intern. Med.* 1992; **116**: 438–45.
13. Pahari DK, Das S, Dutta BN *et al.* Prognosis and management of membraneous nephropathy. *J. Assoc Physicians India* 1993; **41**: 350–1.
14. Ponticelli C, Zucchelli P, Passerini P *et al.* A 10-year follow-up of a randomized study with methylprednisolone and chlorambucil in membranous nephropathy. *Kidney Int.* 1995; **48**: 1600–4.
15. Imperiale TF, Goldfarb S, Berns JS. Are cytotoxic agents beneficial in idiopathic membranous nephropathy? a meta-analysis of the controlled trials. *J. Am. Soc. Nephrol.* 1995; **5**: 1553–8.
16. Hogan SL, Muller KE, Jennette JC *et al.* A review of therapeutic studies of idiopathic membranous glomerulopathy. *Am. J. Kidney Dis* 1995; **25**: 862–75.
17. Schieppati A, Perna A, Zamora J *et al.* Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome. *The Cochrane Database of Systematic Reviews* 2004, Issue 4.
18. Branten AJ, Reichert LJ, Koene RA *et al.* Oral cyclophosphamide versus chlorambucil in the treatment of patients with membranous nephropathy and renal insufficiency. *QJM* 1998; **91**: 359–66.
19. Ponticelli C, Altieri P, Scolari F *et al.* A randomized study comparing methylprednisolone plus chlorambucil versus methylprednisolone plus cyclophosphamide in idiopathic membranous nephropathy. *J. Am. Soc. Nephrol.* 1998; **9**: 444–50.
20. Reichert LJ, Huysmans FT, Assmann K *et al.* Preserving renal function in patients with membranous nephropathy: daily oral chlorambucil compared with intermittent monthly pulses of cyclophosphamide. *Ann. Intern. Med.* 1994; **121**: 328–33.
21. Talar-Williams C, Hijazi YM, Walther MM *et al.* Cyclophosphamide-induced cystitis and bladder cancer in patients with Wegener granulomatosis. *Ann. Intern. Med.* 1996; **124**: 477–84.
22. Muirhead N. Management of idiopathic membranous nephropathy: evidence-based recommendations. *Kidney Int. Suppl* 1999; **70**: S47–S55.

APPENDICES

Table 1 Characteristics of included studies

Study ID (author, year)	N	Study design	Setting	Participants	Intervention (experimental group)	Intervention (control group)	Follow up (months)	Comments
Ahmed *et al*, 1994	20	Randomised controlled clinical trial	Hospital, Bangladesh	20 patients with nephrotic syndrome and histological diagnosis of idiopathic membranous nephropathy	IV methylprednisolone 1 g for 3 days, then oral prednisolone and chlorambucil	Prednisolone	15	
Branten *et al*, 1998	32	Randomised controlled clinical trial	Hospital, Netherlands	32 patients with biopsy-proven membranous nephropathy	Chlorambucil and corticosteroids	Oral cyclophosphamide	38	Partial randomization
Donadio *et al*, 1974	22	Randomised controlled clinical trial	Renal clinic, US	22 adults with clinically- and histologically-defined idiopathic membranous nephropathy	Oral cyclosporine	No intervention	12	
Falk *et al*, 1992	26	Randomised controlled clinical trial	Multiple nephrology clinics, US	26 patients with biopsy-proven progressive membranous glomerulonephropathy	6 mo IV cyclophosphamide and pulse methylprednisolone corticosteroids	Alternate day corticosteroid alone	29	
Murphy *et al*, 1992	40	Randomised controlled clinical trial	University hospital, Australia	40 patients with idiopathic membranous glomerulonephritis	Oral cyclophosphamide at a maximum dose of 1.5 mg/kg/day; dipyridamole, sodium warfarin	No treatment	24	
Pahari *et al*, 1993	36	Randomised controlled clinical trial	Hospital, India	36 patients with idiopathic membranous nephropathy	Steroid and cyclophosphamide	Steroid only	46	
Ponticelli *et al*, 1998	95	Randomised controlled clinical trial	Multicentre, Italy	95 patients with biopsy-proven membranous nephropathy	Methylprednisolone and chlorambucil	Methylprednisolone and cyclophosphamide	At least 12	
Ponticelli *et al*, 1995	81	Randomised controlled clinical trial	Multicentre, Italy	81 patients with idiopathic membranous nephropathy	Methylprednisolone and chlorambucil	Symptomatic therapy	60	
Ponticelli *et al*, 1992	92	Randomised controlled clinical trial	Multicentre, Italy	92 patients with nephrotic syndrome caused by idiopathic membranous nephropathy	Alternating 1 month methylprednisolone and then chlorambucil for 6 months	Methylprednisolone for 6 months	54	
Reichert *et al*, 1994	20	Randomised controlled clinical trial	University hospital and teaching hospitals in Netherlands	20 patients with nephrotic syndrome and biopsy-proven membranous nephropathy	Chlorambucil methylprednisolone and corticosteroids	Cyclophosphamide and methylprednisolone	6–36	

Table 2 Quality of randomised trials

Study ID (author, year)	Method of allocation concealment	Blinding			Intention-to-treat analysis	Loss to follow up (%)
		(Participants)	(Investigators)	(Outcome assessors)		
Ahmed *et al*, 1994	Not specified	Not stated	Not stated	Not stated	Unclear	0.0
Branten *et al*, 1998	Not specified	Not stated	Not stated	Not stated	Yes	0.0
Donadio *et al*, 1974	Random number table	No	No	No	No	13.6
Falk *et al*, 1992	Computer generated	No	No	No	Unclear	7.7
Murphy *et al*, 1992	Sealed envelopes	No	No	No	No	2.5
Pahari *et al*, 1993	Not specified	No	No	Not stated	No	14.1
Ponticelli *et al*, 1998	Centre stratified random order	No	No	Not stated	No	8.4
Ponticelli *et al*, 1995	Central	No	No	Not stated	Yes	23.5
Ponticelli *et al*, 1992	Central	No	No	Yes	Yes	1.1
Reichert *et al*, 1994	Not specified	Not stated	Not stated	Not stated	No	0.0

Table 3 Results for continuous outcomes

Study ID (author, year)	Outcomes	Intervention group (mean [SD])	Control group (mean [SD])	Difference in means [95% CI]
Ahmed *et al*, 1994	Urinary total protein excretion (g/day) after treatment	1.8 (3.14)	2.6 (2.2)	0.80 (95%CI: −3.18, 1.58)
	Serum Cr after treatment (g/d)	1.45 (0.35)	2.38 (2.28)	−0.93 (95%CI: −2.36, 0.50)
Branten *et al*, 1998	Serum creatinine (μmol/L) at 12 mo	216 (99)	174 (78)	42.00 (95%CI: −20.33, 0.50)
	Serum albumin (g/L) at 12 mo	32 (6.8)	40 (4.7)	−8.00 (95%CI: −12.10, −3.90)
	Proteinuria (g/10 mmol creatinine) at 12 mo	6.8 (4.4)	2.0 (3.0)	4.80 (95%CI: 2.16, 7.44)
Donadio *et al*, 1974	Decrease in protein excretion (g/24 h)	4.7 (3.2)	2.6 (3.5)	2.10 (95%CI: −0.91, 5.11)
Ponticelli *et al*, 1998	Mean proteinuria (g/d) at follow up	2.11 (2.87)	1.69 (2.36)	0.42 (95%CI: −0.68, 1.52)
	Mean plasma Cr (mg/dL) at follow up	1.25 (1.37)	1.32 (1.72)	−0.07 (95%CI: −0.72, 0.58)
Reichert *et al*, 1994	Creatinine (μmol/L)	260 (112)	218 (85)	42.00 (95%CI: −49.86, 133.86)

Table 4 Results for dichotomous outcomes

Study ID (author, year)	Outcomes	Intervention group (number of patients with events/number of patients exposed)	Control group (number of patients with events/number of patients not exposed)	Relative risk (RR) [95% CI]	Risk difference (RD) [95% CI]
Ahmed *et al*, 1994	Complete remission	5/10	3/10	1.67 (95%CI: 0.54, 5.17)	0.20 (95%CI: –0.22, 0.62)
	Partial remission	3/10	3/10	1.00 (95%CI: 0.26, 3.81)	0.00 (95%CI: –0.40, 0.40)
	No response	2/10	4/10	0.50 (95%CI: 0.12, 2.14)	–0.20 (95%CI: –0.59, 0.19)
	Developed renal insufficiency	1/10	2/10	0.50 (95%CI: 0.05, 4.67)	–0.10 (95%CI: –0.41, 0.21)
Branten *et al*, 1998	ESRD	4/15	1/17	4.53 (95%CI: 0.57, 36.23)	0.21 (95%CI: –0.04, 0.46)
	Remission of proteinuria	5/15	15/17	0.38 (95%CI: 0.18, 0.79)	–0.55 (95%CI: –0.83, –0.27)
	Side effects causing interruption to treatment	11/15	6/17	2.08 (95%CI: 1.02, 4.24)	0.38 (95%CI: 0.06, 0.70)
Donadio *et al*, 1974	Decrease in renal function	1/7	2/8	0.57 (95%CI: 03.06, 5.03)	–0.11 (95%CI: –0.50, 0.29)
	Partial remission	6/9	4/10	1.67 (95%CI: 0.69, 4.05)	0.27 (95%CI: –0.17, 0.70)
	Progressed to next stage of renal lesion	5/9	5/8	0.89 (95%CI: 0.40, 1.97)	–0.07 (95%CI: –0.54, 0.40)
	Leukepenia	5/9	0/8	9.90 (95%CI: 0.63, 155.08)	0.56 (95%CI: 0.21, 0.90)
Falk *et al*, 1992	ESRD	4/13	4/13	1.00 (95%CI: 0.32, 3.17)	0.00 (95%CI: –0.35, 0.35)
	Glaucoma	0/13	1/13	0.33 (95%CI: 0.01, 7.50)	–0.08 (95%CI: –0.27, 0.11)
	Improved/stabilization of serum Cr	5/13	6/13	0.83 (95%CI: 0.34, 2.06)	–0.08 (95%CI: –0.46, 0.30)
Murphy *et al*, 1992	Mortality	1/19	0/21	3.30 (95%CI: 0.14, 76.46)	0.05 (95%CI: –0.08, 0.18)
	Complete remission of nephrotic syndrome	1/13	2/13	0.50 (95%CI: 0.05, 4.86)	–0.08 (95%CI: –0.32, 0.17)
	Partial remission of nephrotic syndrome	3/13	7/13	0.43 (95%CI: 0.14, 1.30)	–0.31 (95%CI: –0.66, 0.05)
Pahari *et al*, 1993	Complete remission	33/36	15/35	2.14 (95%CI: 1.44, 3.18)	0.49 (95%CI: 0.30, 0.68)
	Partial remission	0/36	4/35	0.11 (95%CI: 0.01, 1.94)	–0.11 (95%CI: –0.23, 0.00)
	No response	0/36	5/35	0.09 (95%CI: 0.01, 1.54)	–0.14 (95%CI: –0.27, –0.02)
	Relapse	2/36	3/35	0.65 (95%CI: 0.12, 3.65)	–0.03 (95%CI: –0.15, 0.09)
	Renal function deterioration and ESRF	1/36	5/35	0.19 (95%CI: 0.02, 1.58)	–0.12 (95%CI: –0.24, 0.01)

Ponticelli *et al*, 1998	Side effects causing interruption to treatment	6/50	2/45	2.70 (95%CI: 0.57, 12.71)	0.08 (95%CI: –0.03, 0.18)
	Herpes zoster	4/50	0/45	8.12 (95%CI: 0.45, 146.71)	0.08 (95%CI: 0.00, 0.16)
	Glucose intolerance	1/50	1/45	0.90 (95%CI: 0.06, 13.97)	0.00 (95%CI: –0.06, 0.06)
	Complete remission	12/44	16/43	0.73 (95%CI: 0.39, 1.36)	–0.10 (95%CI: –0.29, 0.10)
	Partial remission	24/44	24/43	0.98 (95%CI: 0.67, 1.43)	–0.01 (95%CI: –0.22, 0.20)
	Stable	7/44	1/43	6.84 (95%CI: 0.88, 53.28)	0.14 (95%CI: 0.02, 0.25)
	Worsened	1/44	2/43	0.49 (95%CI: 0.05, 5.19)	–0.02 (95%CI: –0.10, 0.05)
Ponticelli *et al*, 1995	Complete remission	17/42	2/39	7.98 (95%CI: 1.95, 31.97)	0.35 (95%CI: 0.19, 0.52)
	Partial remission	9/42	11/39	0.76 (95%CI: 0.35, 1.63)	–0.07 (95%CI: –0.26, 0.12)
	Nephrotic syndrome	9/42	6/39	1.39 (95%CI: 0.55, 3.55)	0.06 (95%CI: –0.11, 0.23)
	Renal dysfunction	4/42	8/39	0.46 (95%CI: 0.15, 1.42)	–0.11 (95%CI: –0.26, 0.04)
	Dialysis	2/42	9/39	0.21 (95%CI: 0.05, 0.90)	–0.18 (95%CI: –0.33, –0.04)
	Mortality	1/42	3/39	0.31 (95%CI: 0.03, 2.85)	–0.05 (95%CI: –0.15, 0.04)
	Stopped treatment due to side effects	4/42	0/39	8.37 (95%CI: 0.47, 150.62)	0.10 (95%CI: 0.00, 0.19)
Ponticelli *et al*, 1992	Mortality	1/45	1/47	1.04 (95%CI: 0.07, 16.20)	0.00 (95%CI: –0.06, 0.06)
	Stopped treatment due to side effects	4/45	1/47	4.18 (95%CI: 0.49, 35.97)	0.07 (95%CI: –0.03, 0.16)
	Complete remission at end of follow up	14/45	14/47	1.04 (95%CI: 0.56, 1.94)	0.01 (95%CI: –0.17, 0.20)
	Partial remission at end of follow up	10/45	8/47	1.31 (95%CI: 0.57, 3.01)	0.05 (95%CI: –0.11, 0.21)
Reichert *et al*, 1994	Complete remission	1/9	2/9	0.50 (95%CI: 0.05, 4.58)	–0.11 (95%CI: –0.45, 0.23)
	Partial remission	3/9	1/9	3.00 (95%CI: 0.38, 23.68)	0.22 (95%CI: –0.15, 0.59)
	ESRD	1/9	4/9	0.25 (95%CI: 0.03, 1.82)	–0.33 (95%CI: –0.72, 0.05)
	Mortality	0/9	1/9	0.33 (95%CI: 0.02, 7.24)	–0.11 (95%CI: –0.37, 0.15)
	Infectious complication	3/9	0/9	7.00 (95%CI: 0.41, 118.69)	0.33 (95%CI: 0.01, 0.66)
	Leukopenia	3/9	0/9	7.00 (95%CI: 0.41, 118.69)	0.33 (95%CI: 0.01, 0.66)
	Nausea and anorexia	3/9	7/9	0.43 (95%CI: 0.16, 1.15)	–0.44 (95%CI: –0.86, –0.03)

ESRD, end-stage renal disease.

Membranous nephropathy: role of steroids

Date written: July 2005
Final submission: September 2005
Author: Merlin Thomas

GUIDELINES

There is currently no data to support the use of short-term courses of steroids as the sole therapy to prevent progressive kidney disease in patients with membranous glomerulonephritis (MGN). (Level I evidence)

SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on level III and IV evidence)

- **This guideline refers to the use of steroids as sole therapy for patients with membranous glomerulonephropathy. Most studies that have successfully used alkylating agents or cyclosporin to induce remission have used them in combination with steroids delivered either as 2-monthly pulses of methylprednisolone, oral prednisone 0.5 mg/kg per 48 h, or sequential combinations therein. The optimal route remains to be established in clinical studies.**

BACKGROUND

Idiopathic MGN runs a variable course. Most patients do well, with 10-year renal survival of 70–90%.[1] Spontaneous remissions occur in up to 65% of patients,[2] sometimes months or years after the onset of nephrotic syndrome and a substantial percentage of patients never progress to kidney failure. To avoid possibly unnecessary treatments, most clinical studies have focused on patients thought to be at greater risk for progressive disease. The objective of this guideline is to evaluate the available clinical evidence pertaining to the impact of steroid therapy on renal functional decline in MGN with poor prognostic features.

SEARCH STRATEGY

Databases searched: MeSH terms and text words for Membranous Nephropathy were combined with MeSH terms and text words for steroids. The search was carried out in Medline (1966 to September Week 1, 2004). The Cochrane Renal Group Trials Register was also searched for trials of membranous nephropathy not indexed in Medline.
Date of searches: 9 September 2004.

WHAT IS THE EVIDENCE?

There have been three large, prospective, randomised, placebo-controlled clinical trials ($n = 333$) using corticosteroid as sole therapy for MGN.

- The U.S. Collaborative Study of Adult Idiopathic Nephrotic Syndrome,[3] reported in a controlled trial of 72 adult patients with MGN, randomised to receive 8 weeks of alternate-day prednisone (100–150 mg) or placebo. Patients receiving steroids had less proteinuria and a reduction in the rate of progression to renal failure. Deterioration of glomerular filtration rate was significantly more rapid in placebo-treated than in prednisone-treated patients, and ultimately 10 of 38 given placebo but only one of 34 given prednisone were in kidney failure (defined by a creatinine > 440 μmol/L). However, patients in the placebo group had a relatively short follow-up and their outcome was substantially worse than non-treated patients in other studies, leading many to criticize this study.
- The British Medical Research Trial[4] used a similar protocol, except that the study also included patients with impaired renal function (< 30 mL/min). Prednisone was also abruptly discontinued at 8 weeks rather than tapered (as in the US trial). A total of 107 adult patients who had not previously received immunosuppressive treatment were followed for a longer period of at least 3 years from treatment. An additional 160 patients, excluded from the trial, but with membranous nephropathy were identified, followed and assessed retrospectively at the end of the trial as a comparison group. Although there was a modest early beneficial effect on urinary protein excretion and serum albumin noted at 3 to 6 months, they were unable to demonstrate significant benefit in creatinine clearance from steroid treatment.
- The Toronto Glomerulonephritis Study Group[5] assigned patients to receive either a 6-month course of prednisone (45 mg/m^2) ($n = 81$) or no specific treatment ($n = 77$). After a median follow-up of 48 months, like the British study, renal outcomes were similar in the two groups with respect to progression to kidney disease.

Two meta-analyses of these randomised trials confirmed both a lack of beneficial effect on total mortality or end-stage kidney disease (ESKD) in patients treated with glucocorticoids (RR 0.88, 95%CI: 0.39–1.97, P = 0.75).[6,7] In addition, glucocorticoids had no effect on partial or complete remission.

Each of the three studies that make up the bulk of patients in the meta-analysis used a relatively brief course of

steroids to treat a disease with a slow and indolent course. This has led some to question the conclusions based on short-term interventions.

• A recent small trial has looked specifically at the outcome of long-term steroid treatment. Polenakovik *et al*[8] studied patients with stage II to III membranous nephropathy with proteinuria more than 2.5 g/d, without hypertension and kidney failure. Ten patients were not treated, 13 were treated with only steroids, 13 with alternate-day steroids and chlorambucil. The follow-up period was 5–10 years. A significant decrease in proteinuria was noted both in patients treated with steroids alone and in patients treated with steroids and chlorambucil. Compared with patients treated with steroids (15.3%) and patients treated with steroids and chlorambucil (15.3%), untreated patients had a high frequency of chronic kidney failure after 5 years of follow-up (70%) and had a significant increase in mean serum creatinine.

This data remains to be reproduced in larger trials. Prolonged treatment also carries the risk of significant toxicity, including change in appearance, weight gain, diabetes and bone loss, even when delivered as alternate-day therapy.

SUMMARY OF THE EVIDENCE

There is no data to support the short-term use of steroids on their own for the treatment of patients with nephrotic syndrome and idiopathic membranous MGN.

WHAT DO THE OTHER GUIDELINES SAY?

Kidney Disease Outcomes Quality Initiative: No recommendation.
UK Renal Association: No recommendation.
Canadian Society of Nephrology: There is no benefit of either a short or prolonged course of oral, alternate-day steroids for either inducing remission of nephrotic syndrome or preserving renal function in patients with membranous nephropathy. Corticosteroids should not be used as sole therapy.[9]
European Best Practice Guidelines: No recommendation.
International Guidelines: No recommendation.

IMPLEMENTATION AND AUDIT

No recommendation.

SUGGESTIONS FOR FUTURE RESEARCH

No recommendation.

REFERENCES

1. Schieppati A, Mosconi L, Perna A *et al*. Prognosis of untreated patients with idiopathic membranous nephropathy. *N Engl. J. Med.* 1993; **329**: 85–9.
2. Geddes CC, Cattran DC. The treatment of idiopathic membranous nephropathy. *Semin Nephrol.* 2000; **20**: 299–308.
3. AINS Collaborative. A controlled study of short-term prednisone treatment in adults with membranous nephropathy. Collaborative Study of the Adult Idiopathic Nephrotic Syndrome. *N Engl. J. Med.* 1979; **301**: 1301–6.
4. Cameron JS, Healy MJ, Adu D. The Medical Research Council trial of short-term high-dose alternate day prednisolone in idiopathic membranous nephropathy with nephrotic syndrome in adults. The MRC Glomerulonephritis Working Party. *Q J. Med.* 1990; **74**: 133–56.
5. Cattran DC, Delmore T, Roscoe J *et al*. A randomized controlled trial of prednisone in patients with idiopathic membranous nephropathy. *N Engl. J. Med.* 1989; **320**: 210–5.
6. Hogan SL, Muller KE, Jennette JC *et al*. A review of therapeutic studies of idiopathic membranous glomerulopathy. *Am. J. Kidney Dis* 1995; **25**: 862–75.
7. Schieppati A, Perna A, Zamora J *et al*. Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome. *The Cochrane Database of Systematic Reviews*. 2004, Issue 4.
8. Polenakovik MH, Grcevska L. Treatment and long-term follow-up of patients with stage II to III idiopathic membranous nephropathy. *Am. J. Kidney Dis* 1999; **34**: 911–7.
9. Muirhead N. Management of idiopathic membranous nephropathy: evidence based recommendations. *Kidney Int. Suppl* 1999; **70**: S47–S55.

APPENDICES

Table 1 Characteristics of included studies

Study ID (author, year)	N	Study design	Setting	Participants	Intervention (experimental group)	Intervention (control group)	Follow up (months)	Comments
AINS Collaborative, 1979	72	Randomised controlled clinical trial	Multicentre, US	72 adults with nephrotic syndrome without renal insufficiency with membranous type of renal histology on biopsy	Alternate-day prednisolone	Placebo	23	
Cameron *et al*, 1990	103	Randomised controlled clinical trial	Multicentre, US	103 adults with histological diagnosis of membranous nephropathy	High-dose, alternate-day prednisolone	Placebo	36	
Cattran *et al*, 1989	158	Randomised controlled clinical trial	Multicentre, Canada	158 patients with biopsy-confirmed idiopathic membranous nephropathy	Alternate-day prednisolone	No treatment	48	

Table 2 Quality of randomised trials

Study ID (author, year)	Method of allocation concealment	Blinding			Intention-to-treat analysis	Loss to follow up (%)
		(participants)	(investigators)	(outcome assessors)		
AINS Collaborative, 1979	Central	Yes	Yes	Yes	No	6.9
Cameron *et al*, 1990	Central	Yes	Yes	Not stated	Yes	6.8
Cattran *et al*, 1989	Random numbers	No	No	Not stated	Yes	17.1

Table 3 Results for continuous outcomes

Study ID (author, year)	Outcomes	Intervention group (mean [SD])	Control group (mean [SD])	Difference in means [95% CI]
Cameron *et al*, 1990	Serum Cr (μmol/L) at 36 mo	251 (165.83)	203 (163.94)	48.00 (95%CI: –21.30, 117.30)
	Serum Cr (μmol/L) including those on dialysis as 1000 μmol/L plasma creatinine	317 (263.27)	297 (169.56)	20.00 (95%CI: –69.15, 109.15)
	Cr clearance (mL/min) at 36 mo	75 (41.31)	67 (43.28)	8.00 (95%CI: –9.88, 25.88)
	24-h urine protein (g/24 hr)	5.6 (4.59)	5.6 (4.59)	1.10 (95%CI: –0.84, 3.04)
	Serum albumin (g/L)	34 (8.52)	35 (5.90)	–1.00 (95%CI: –4.10, 2.10)

Table 4 Results for dichotomous outcomes

Study ID (author, year)	Outcomes	Intervention group (number of patients with events/ number of patients exposed)	Control group (number of patients with events/ number of patients not exposed)	Relative risk (RR) [95% CI]	Risk difference (RD) [95% CI]
AINS Collaborative, 1979	Complete/partial remission	22/34	11/38	2.24 (95%CI: 1.28, 3.90)	0.36 (95%CI: 0.14, 0.57)
	Complete remission	4/34	4/38	1.12 (95%CI: 0.30, 4.13)	0.01 (95%CI: –0.13, 0.16)
	Partial remission	8/34	3/38	0.01 (95%CI: –0.13, 0.16)	2.98 (95%CI: 0.86, 10.34)
	No response	22/34	31/38	0.16 (95%CI: –0.01, 0.32)	0.79 (95%CI: 0.59, 1.06)
Cameron *et al*, 1990	Mortality	1/52	4/51	0.25 (95%CI: 0.03, 2.12)	–0.06 (95%CI: –0.14, 0.02)
	In remission at 36 mo	7/52	4/51	1.72 (95%CI: 0.53, 5.51)	0.06 (95%CI: –0.06, 0.17)
	Proteinuria at 36 mo	30/52	33/51	0.89 (95%CI: 0.65, 1.21)	–0.07 (95%CI: –0.26, 0.12)
	Renal failure at 36 mo	6/52	7/51	0.84 (95%CI: 0.30, 2.33)	–0.02 (95%CI: –0.15, 0.11)
Cattran *et al*, 1989	Progression to renal failure	3/77	4/81	–0.17 (95%CI: –0.37, 0.03)	–0.01 (95%CI: –0.07, 0.05)
	Mortality	3/77	1/81	3.16 (95%CI: 0.34, 29.69)	0.03 (95%CI: –0.02, 0.08)
	Complete remission	16/77	19/81	0.89 (95%CI: 0.49, 1.59)	–0.03 (95%CI: –0.16, 0.10)

Membranous nephropathy: role of cyclosporin therapy

Date written: July 2005
Final submission: September 2005
Author: Merlin Thomas

GUIDELINES

a. The use of cyclosporin therapy alone to prevent progressive renal injury in idiopathic membranous glomerulonephritis (MGN) is not supported by current data. (Level I evidence)

b. Cyclosporin therapy in combination with steroids may be more effective than steroids alone for the induction of remission in patients with idiopathic MGN. (Level II evidence, one RCT)

SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on level III and IV evidence)

What dose should be used?

- **Most studies using cyclosporin have used a dose of 4–6 mg/kg/day in divided doses, aimed at achieving a trough level of 150 ng/mL.**

How long should therapy be continued?

- **The antiproteinuric response of cyclosporin is typically seen within 2 to 4 weeks, if therapy is going to be effective. (Level III evidence) Generally, if no response is seen in a patient with adequate drug levels by 3 months, therapy can be considered ineffective and discontinued.**
- **If remission is induced, most studies have continued treatment for at least 12 months, although the optimal duration of therapy remains to be established.**
- **In general, within 2 years of discontinuing cyclosporin, a relapse rate between 30 and 40% is observed. This may be responsive to reintroduction of the cyclosporin treatment or a cytotoxic/corticosteroid.**
- **It has been suggested that more prolonged therapy or long-term lower dose maintenance may be considered for patients who achieve a partial remission with cyclosporin, who are at high risk of relapse or progressive renal impairment. (Level IV, anecdotal reports) However, this practice remains to be tested in any clinical studies.**

BACKGROUND

Idiopathic MGN is the most common form of nephrotic syndrome in adults. Although many patients have a benign course or undergo spontaneous complete or partial remission, 30–40% of patients progress toward end-stage kidney disease (ESKD) within 5–15 years,[1,2] sometimes months or years after the onset of nephrotic syndrome and a substantial percentage of patients never progress to kidney failure. To avoid possibly unnecessary treatments, most clinical studies have focused on individuals who are thought to be at greater risk for progressive disease. The objective of this guideline is to evaluate the available clinical evidence pertaining to the impact of cyclosporin on renal functional decline in MGN with poor prognostic features, such as heavy proteinuria (> 3 g/24 h), impaired renal function at presentation, deteriorating renal function and/or reduced response to therapy.

SEARCH STRATEGY

Databases searched: MeSH terms and text words for Membranous Nephropathy were combined with MeSH terms and text words for cyclosporine therapy. This search was carried out in Medline (1966 to September Week 1, 2004). The Cochrane Renal Group Trials Register was also searched for trials in membranous nephropathy not indexed in Medline.
Date of searches: 9 September 2004.

WHAT IS THE EVIDENCE?

There have been three randomised controlled trials (RCTs) comparing cyclosporin vs. placebo or no treatment and one of these included adding cyclosporin to a therapy based on steroids.

- Guasch *et al*[3] identified 17 patients with MGN and persistent nephrotic range proteinuria, a rate of decline in creatinine clearance in excess of 8 mL/min/year and baseline renal impairment (creatinine clearance ~ 50 mL/min/1.73 m^2). These patients were randomised to cyclosporin ($n = 9$) or placebo. After 12 months of cyclosporin therapy, there was significant slowing of loss of glomerular filtration rate (GFR) in patients on cyclosporin compared to that of the placebo-treated patients. This improvement was maintained in 6 of 8 patients over a mean follow-up of 21 months after cyclosporin was discontinued.
- Braun *et al*[4] randomised 105 patients with MGN and persistent nephrotic range to cyclosporin and prednisone,

methyl-prednisolone/chlorambucil or symptomatic treatment (control group). There was no difference in rates of remission and doubling of serum creatinine was found in approximately 20% of patients, irrespective of treatment modality.

- Pisoni and colleagues[5] examined cyclosporin vs. conservative therapy in 21 patients with idiopathic MGN and deteriorating renal function and followed them for 12 months. In this study, there was no significant difference in any of the study outcomes.
- Cattran *et al*[6] randomised 51 patients with biopsy-proven idiopathic MGN and nephrotic-range proteinuria to 26 weeks of cyclosporin treatment plus low-dose prednisone to placebo plus prednisone. Seventy-five per cent of the treatment group vs. 22% of the control group ($P < 0.001$) had a partial or complete remission of their proteinuria by 26 weeks. Relapse occurred in 43% ($n = 9$) of the cyclosporin remission group and 40% ($n = 2$) of the placebo group by week 52. From this time until the end of the study at 78 weeks, the fraction of the total population in remission remained unchanged (cyclosporin 39%, placebo 13%, $P = 0.007$). Renal insufficiency, defined as doubling of baseline creatinine, was seen in 2 patients in each group.

In a recent meta-analysis of placebo-controlled trials of cyclosporin/prednisolone, involving 104 randomised patients, no clinically relevant beneficial effect was observed.[7] Nonetheless, partial remissions were more frequent in cyclosporin-treated patients than in those treated with alkylating agents (partial remission RR 1.68, 95%CI: 1.06–2.65, $P = 0.03$)

While some authors have suggested that cyclosporin/prednisolone treatment can be considered an alternative to therapy with alkylating agents, this assertion remains to be adequately tested.

SUMMARY OF THE EVIDENCE

Cyclosporin may induce remission in patients with idiopathic MGN. Partial remissions may be more common in patients treated with cyclosporin than in those treated with alkylating agents. However, the impact of this finding on long-term, preservation of renal function remains to be established.

Moreover, relapse is common when the drug is discontinued.

WHAT DO THE OTHER GUIDELINES SAY?

Kidney Disease Outcomes Quality Initiative: No recommendation.

UK Renal Association: No recommendation.

Canadian Society of Nephrology: Cyclosporine A therapy shows promise as an effective therapy for patients with membranous nephropathy who are at high risk for progressive renal failure. Cyclosporine A of 4 to 6 mg/kg daily for 12 months is the preferred regimen.[8]

European Best Practice Guidelines: No recommendation.

International Guidelines: No recommendation.

IMPLEMENTATION AND AUDIT

No recommendation.

SUGGESTIONS FOR FUTURE RESEARCH

The ANZSN should support participation in any multinational clinical trial of cyclopsorin/prednisolone in patients with membranous nephropathy and at high risk of progressive kidney disease.

REFERENCES

1. Schieppati A, Mosconi L, Perna A *et al*. Prognosis of untreated patients with idiopathic membranous nephropathy. *N Engl. J. Med.* 1993; **329**: 85–9.
2. Geddes CC, Cattran DC. The treatment of idiopathic membranous nephropathy. *Semin Nephrol.* 2000; **20**: 299–308.
3. Guasch A, Suranyi M, Newton L *et al*. Short-term responsiveness of membranous glomerulopathy to cyclosporine. *Am. J. Kidney Dis.* 1992; **20**: 472–81.
4. Braun N, Erley CM, Benda N *et al*. Therapy of membranous glomerulonephritis with nephrotic syndrome. Five year follow-up of a prospective, randomized study [abstract]. *J. Am. Soc. Nephrol.* 1995; **6**: 413.
5. Pisoni R., Grinyo JM, Salvadori M *et al*. Cyclosporine versus conservative therapy in patients with idiopathic membranous nephropathy (IMN) and deteriorating renal function: results of the CYCLOMEN trial [abstract]. *J. Am. Soc. Nephrol.* 2000; **11**: 95A.
6. Cattran DC, Greenwood C, Ritchie S *et al*. A controlled trial of cyclosporine in patients with progressive membranous nephropathy. Canadian Glomerulonephritis Study Group. *Kidney Int.* 1995; **47**: 1130–5.
7. Schieppati A, Perna A, Zamora J *et al*. Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome. *The Cochrane Database of Systematic Reviews*. 2004, Issue 4.
8. Muirhead N. Management of idiopathic membranous nephropathy: evidence-based recommendations. *Kidney Int. Suppl* 1999; **70**: S47–S55.

APPENDICES

Table 1 Characteristics of included studies

Study ID (author, year)	N	Study design	Setting	Participants	Intervention (experimental group)	Intervention (control group)	Follow up (months)	Comments
Braun *et al*, 1995 (abstract)	53	Randomised controlled clinical trial		Patients with idiopathic membranous nephropathy	Alkylating agents	No treatment	60	Cyclosporin
Cattran *et al*, 1995	17	Randomised controlled clinical trial	Multicentre, Canada	17 patients with biopsy-proven membranous nephropathy with proteinuria	Cyclosporine	Placebo	12	
Pisoni *et al*, 2000 (abstract)	21	Randomised controlled clinical trial		Patients with idiopathic membranous nephropathy	Cyclosporine	No treatment		

Table 2 Quality of randomised trials

Study ID (author, year)	Method of allocation concealment	Blinding			Intention-to-treat analysis	Loss to follow up (%)
		(participants)	(investigators)	(outcome assessors)		
Braun *et al*, 1995 (abstract)		No	No	No	No	18.6
Cattran *et al*, 1995	Centre stratified	No	Yes	Not stated	Unclear	0.0
Pisoni *et al*, 2000 (abstract)		No	No	No	Yes	4.8

Table 3 Results for continuous outcomes

Study ID (author, year)	Outcomes	Intervention group (mean [SD])	Control group (mean [SD])	Difference in means [95% CI]
Cattran *et al*, 1995	Proteinuria (g/day) at 12 mo	7.2 (7)	11.0 (5)	–3.80 (95%CI: –9.54, 1.94)
	Serum albumin (g/L) at 12 mo	34.8 (4)	34.6 (9)	3.20 (95%CI: –3.23, 9.63)

Table 4 Results for dichotomous outcomes

Study ID (author, year)	Outcomes	Intervention group (number of patients with events/number of patients exposed)	Control group (number of patients with events/number of patients not exposed)	Relative risk (RR) [95% CI]	Risk difference (RD) [95% CI]
Braun *et al*, 1995 (abstract)	ESRD/death (immunosuppressive vs. no treatment)	6/75	2/22	0.88 (95%CI: 0.19, 0.46)	–0.01 (95%CI: –0.15, 0.12)
	ESRD/death (alkylating agents vs. placebo/no treatment	2/31	2/22	0.71 (95%CI: 0.11, 4.66)	–0.03 (95%CI: –0.17, 0.12)
	ESRD/death (cyclosporine vs. alkylating agents)	4/44	2/31	1.41 (95%CI: 0.27, 7.22)	0.03 (95%CI: –0.09, 0.15)
	Complete remission (immunosuppressive vs. no treatment)	17/75	4/22	1.25 (95%CI: 0.47, 3.32)	0.04 (95%CI: –0.14, 0.23)
	Complete remission (alkylating agents vs. placebo/no treatment	7/31	4/22	1.24 (95%CI: 0.41, 3.73)	0.04 (95%CI: –0.17, 0.26)
	Complete remission (cyclosporine vs. placebo/no treatment)	10/44	4/22	1.25 (95%CI: 0.44, 3.54)	0.05 (95%CI: –0.16, 0.25)
	Complete remission (cyclosporine vs. alkylating agents)	10/44	7/31	1.01 (95%CI: 0.43, 2.35)	0.00 (95%CI: –0.19, 0.19)
Cattran *et al*, 1995	GI complaints	2/9	1/8	1.78 (95%CI: 0.20, 16.10)	0.10 (95%CI: –0.26, 0.45)
	Tremor	1/9	1/8	0.89 (95%CI: 0.07, 12.00)	–0.01 (95%CI: –0.32, 0.29)
	Hirsutism	1/9	1/8	0.89 (95%CI: 0.07, 12.00)	–0.01 (95%CI: –0.32, 0.29)
	Infections	1/9	3/8	0.30 (95%CI: 0.04, 2.31)	–0.26 (95%CI: –0.66, 0.13)
	ESRD	1/8	4/8	0.25 (95%CI: 0.04, 1.77)	–0.38 (95%CI: –0.79, 0.04)
Pisonni *et al*, 2000 (abstract)	ESRD/death	3/10	1/11	3.30 (95%CI: 0.41, 26.81)	0.21 (95%CI: –0.12, 0.54)
	Complete remission	0/10	1/11	0.36 (95%CI: 0.02, 8.03)	–0.09 (95%CI: –0.31, 0.13)
	Stopped treatment due to adverse effects	2/10	0/11	5.45 (95%CI: 0.29, 101.55)	0.20 (95%CI: –0.07, 0.47)

Treatment of secondary membranous nephropathy

Date written: July 2005
Final submission: September 2005
Author: Merlin Thomas

GUIDELINES

No recommendations possible based on Level I or II evidence

SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on level III and IV evidence)

- **Removal of underlying causes of membranous glomerulonephritis (MGN) has been associated with clinical remission and slowing of progression of kidney disease in some cases.[1–3] (Level IV evidence – anecdotal reports)**
- **Efforts should be made to identify and where possible eradicate underlying disease in patients with secondary MGN. (Level IV evidence, case series, variable results)**
- **While careful clinical and biological investigations may detect the underlying cause of most cases of secondary MGN, the diagnosis can be difficult in some patients. In particular, proteinuria may antedate clinical manifestations of cancer in up to 40–45% of patients with MGN secondary to malignancy. Consequently, elderly patients presenting with MGN should complete an appropriate work-up for malignancy. (Level IV evidence)**

BACKGROUND

Membranous nephropathy may occur secondary to conditions such as systemic lupus erythematosus (SLE), drug therapy (gold, penicillamine, NSAIDs, etc.), hepatitis B, malaria, schistosomiasis, syphilis and other infections, diabetes, thyroiditis and certain malignancies.[4] In one series of 82 consecutive Caucasian adults with MGN, secondary causes were identified in 17 patients (21%) including drugs, malignancy in four, thyroiditis, syphilis and hepatitis B virus infection.[5] Removal of such initiating agents can induce remission of MGN in some cases. The objective of this guideline is to evaluate the available clinical evidence pertaining to the impact of specific interventions on kidney function in patients with secondary MGN. This guideline does not address the potential advantages of diagnosing underlying conditions that may facilitate their management and treatment.

SEARCH STRATEGY

Databases searched: MeSH terms and text words for secondary membranous nephropathy. This search was carried out in Medline (1966 to September Week 1, 2004). The Cochrane Renal Group Trials Register was also searched for trials of membranous nephropathy not indexed in Medline.
Date of searches: 9 September 2004.

WHAT IS THE EVIDENCE?

There have been no randomised controlled trials (RCTs).

SUMMARY OF THE EVIDENCE

No recommendations can be made on the basis of current anecdotal evidence.

WHAT DO THE OTHER GUIDELINES SAY?

Kidney Disease Outcomes Quality Initiative: No recommendation.
UK Renal Association: No recommendation.
Canadian Society of Nephrology: No recommendation.
European Best Practice Guidelines: No recommendation.
International Guidelines: No recommendation.

IMPLEMENTATION AND AUDIT

No recommendation.

SUGGESTIONS FOR FUTURE RESEARCH

No recommendation.

REFERENCES

1. Butty H, Asfoura J, Cortese F *et al*. Chronic lymphocytic leukemia-associated membranous glomerulopathy: remission with fludarabine. *Am. J. Kidney Dis* 1999; **33**: E8.
2. Hu SL, Jaber BL. Ribavirin monotherapy for hepatitis C virus-associated membranous nephropathy. *Clin. Nephrol.* 2005; **63**: 41–5.

3. Lopes Neto EP, Lopes LV, Kirsztajn GM *et al*. alpha- Interferon therapy for HBV-related glomerulonephritis. *Rev. Paul Med.* 1998; **116**: 1823–5.
4. Brueggemeyer CD, Ramirez G. Membranous nephropathy: a concern for malignancy. *Am. J. Kidney Dis* 1987; **9**: 23–62.
5. Cahen R., Francois B, Trolliet P *et al*. Aetiology of membranous glomerulonephritis: a prospective study of 82 adult patients. *Nephrol. Dial Transplant* 1989; **4**: 172–80.

Idiopathic membranous nephropathy: use of other therapies

Date written: July 2005
Final submission: September 2005
Author: Merlin Thomas

GUIDELINES

No recommendations possible based on Level I or II evidence

SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on level III and IV evidence)

- **While there have been mixed reports of success with a number of agents, further evidence is required before they can be recommended as second line therapy in membranous glomerulonephritis (MGN).**

Azathioprine

Studies in the treatment of idiopathic MGN have found mixed benefits from using azathioprine combined with corticosteroids over steroid alone.

- **Baker *et al*[1] demonstrated that the addition of oral azathioprine to a regimen of intravenous pulse methylprednisolone and oral prednisone could reverse or stabilize progressive kidney failure in patients with membranous nephropathy.**

Most series have not shown any benefit (Brown *et al.*[2]).

- **In a small controlled trial, five patients with the nephrotic syndrome due to idiopathic MGN received azathioprine, 2.5 mg/kg/d, while four others received placebo. After 1 year of treatment there was no significant difference in creatinine clearance or 24- h excretion of protein between the two groups.[3]**
- **The Sheffield Kidney Institute reviewed 58 patients with idiopathic MGN and nephrotic-range proteinuria.[4] Thirty-eight patients were treated with prednisolone (1 mg/kg/d) and azathioprine (2 mg/kg/d) for a median period of 26 months. Twenty patients received no specific treatment for idiopathic MGN and served as a control group. Neither the level of proteinuria, the rate of renal decline nor the proportion of patients with deteriorating renal function differed significantly between the groups. In addition, adverse effects of immunosuppressive treatment were observed in 9 patients.**

Immunoglobulin

Pooled intravenous immunoglobulin in a few small series has been shown to reduce proteinuria and stabilize renal function in patients with resistant nephrotic syndrome.[5] (Level III evidence – single study, additional selected case series)

- **Palla *et al*[6] followed 9 patients with idiopathic MGN following treatment with pulse doses of IgG (0.4 g/kg body weight) for 3 consecutive days, repeated 3 times at 21-day intervals for 10 months. In 5 patients, a complete remission of proteinuria (daily proteinuria less than 0.2 g) was observed, and 3 patients showed partial remission (proteinuria 2 g/day). In responder patients, clinical and biological findings of the nephrotic syndrome disappeared and a statistically significant increase of creatinine clearance was observed.**
- **Yokoyama *et al*[7] reviewed 86 patients with primary MGN for at least 5 years. They treated 30 of these patients with 1–3 short-term courses of low-dose intravenous immune globulin (5–10 g/day) [100–150 mg/kg/day] for 6 consecutive days. There was no difference in the long term outcome in patients treated with intravenous immunoglobulin therapy compared with patients not receiving therapy with immunoglobulin. A subgroup of patients with 'homogenous type MGN with electron microscopy findings of synchronous electron-dense deposits' had earlier induction of remission.**

Fludarabine

Fludadrabine has been reported to lead to remission in some patients with MGN (Level IV evidence – anedoctal reports).

- **Treatment of refractory chronic lymphocytic leukaemia (CLL) with fludarabine, a purine nucleoside analogue, has been associated with remission of malignancy-associated MGN.[8]**
- **Boumpas *et al*[9] treated 7 patients with refractory idiopathic membranous nephropathy with 6-monthly cycles of fludarabine. Although all patients developed significant lymphopenia, proteinuria decreased by >50% in 5 of 7 patients ($P = 0.11$) and glomerular filtration rate (GFR) improved in all those with renal failure at baseline.**

Mycophenolate mofetil

Mycophenolate appears to reduce proteinuria in some patients with resistant MGN. (Level IV evidence – small case series, variable results)

• Zhao *et al*[10] treated 18 patients with refractory MGN, 13 of whom achieved remission on 1.0–2.0 g/d for 3–6 months.
• Miller *et al*[11] treated 16 nephrotic patients with MGN with mycophenolate mofetil. Fifteen patients had steroid-resistant disease; cytotoxic agents had failed in 6 patients and cyclosporin therapy had failed in 5 patients. Six patients experienced a halving of proteinuria, which occurred after a mean duration of 6 months of therapy. Partial remissions occurred in 2 patients. There were no significant changes in mean values for serum creatinine during the study.
• Briggs *et al*[12] also described reductions in proteinuria and stabilizing of creatine in 3 patients with MGN.
• Choi *et al*[13] studied 17 patients with MGN including 15 with nephrotic range proteinuria and 6 with renal insufficiency. Indications for mycophenolate mofetil treatment were steroid- (11/17), cyclosporin- (4/17) or cytotoxic (1/17) dependency. After 5–12 months of follow-up, there was a 61.1% reduction in protein excretion. Two patients (13.3%), both of whom were nephrotic, achieved a complete remission; 8 patients (60%), all of whom were nephrotic, achieved a partial remission; and 2 patients (13.3%), including 1 nephrotic, had increased proteinuria. Eight of the 15 (53.3%) nephrotic patients improved to subnephrotic proteinuria with treatment. Two patients relapsed after mycophenolate mofetil was stopped, and they both responded to re-treatment. Three of 6 patients with renal insufficiency experienced substantial improvement in excretory renal function.
• Polenakovic *et al*[14] gave mycophenolate mofetil 2 g/day for 9 months to 8 patients with stage III–IV idiopathic membranous nephropathy. Previous treatment had failed in 5 of 8 patients (three patients had received cyclosporin and steroids, one cyclosporin, steroids and cyclophosphamide and one an alternative use of steroids and chlorambucil). Proteinuria decreased significantly during the treatment ($P < 0.05$), from 4.4 g/d at the start, to 2.0 g/day after 3 months, and 1.9 g/day after 6 months and 9 months. Renal function improved slightly, but not significantly ($P > 0.05$).

Monoclonal antibodies

Monoclonal antibodies against the cell surface antigen CD20 of B cells may reduce proteinuria in some patients with idiopathic MGN.

Ruggenenti *et al*[15] followed 8 patients with idiopathic MGN and long-lasting persistent proteinuria, following an intravenous infusion of the anti-CD20 monoclonal antibody, rituximab. After 20 weeks of treatment, there was a 60% reduction in urinary proteinuria. At 12 months, proteinuria decreased to ≤0.5 g/24 h or ≤ 3.5 g/24 h in two and three patients, respectively. There was no significant loss of renal function in any patient.

Eculizumax, a humanized monoclonal antibody that prevents the cleavage of human complement component C5 into its proinflammatory elements, did not appear to have any significant effect on proteinuria or renal function in patients with membranous nephropathy, although this Phase II study was not designed to test this outcome and the dose required for efficacy testing may not have been achieved.[16]

BACKGROUND

Many patients with progressive kidney failure from MGN remain resistant to therapy with alkylating agents. There have been mixed reports of success with a number of agents. The objective of this guideline is to evaluate the available clinical evidence pertaining to the impact of specific interventions not covered in other guidelines on declining renal function in chronic kidney disease patients with idiopathic MGN. The potential utility of these agents in patients with secondary MGN is discussed in the guideline titled "Membranous nephropathy: role of cyclosporin therapy."

SEARCH STRATEGY

Databases searched: MeSH terms and text words for Membranous Nephropathy were combined with MeSH terms and text words for aziothioprine, immunoglobulin, fludarabine, mycophenolate mofetil and rituximab. This search was carried out in Medline (1966 to September Week 1, 2004). The Cochrane Renal Group Trials Register was also searched for trials in membranous nephropathy not indexed in Medline.
Date of searches: 9 September 2004.

WHAT IS THE EVIDENCE?

There have been no randomised controlled trials (RCTs) of these potential agents.

WHAT DO THE OTHER GUIDELINES SAY?

Kidney Disease Outcomes Quality Initiative: No recommendation.
UK Renal Association: No recommendation.
Canadian Society of Nephrology: No evidence for the use of azathioprine (Level C).
European Best Practice Guidelines: No recommendation.
International Guidelines: No recommendation.

IMPLEMENTATION AND AUDIT

No recommendation.

SUGGESTIONS FOR FUTURE RESEARCH

No recommendation.

REFERENCES

1. Baker LR, Tucker B, Macdougall IC *et al*. Treatment of progressive renal failure in idiopathic membranous nephropathy with azathioprine and prednisolone. *Nephrol. Dial. Transplant* 1998; **13**: 2704.
2. Brown JH, Douglas AF, Murphy BG *et al*. Treatment of renal failure in idiopathic membranous nephropathy with azathioprine and prednisolone. *Nephrol. Dial. Transplant* 1998; **13**: 443–8.
3. Western Canadian Glomerulonephritis Study Group. Controlled trial of azathioprine in the nephrotic syndrome secondary to idiopathic membranous glomerulonephritis. *Can Med. Assoc. J*. 1976; **115**: 1209–10.
4. Ahuja M, Goumenos D, Shortland JR *et al*. Does immunosuppression with prednisolone and azathioprine alter the progression of idiopathic membranous nephropathy? *Am. J. Kidney Dis*. 1999; **34**: 521–9.
5. Levy Y, Sherer Y, George J *et al*. Use of intravenous immunoglobulin in idiopathic membranous nephropathy. *Intern. Med*. 1999; **38**: 917.
6. Palla R., Cirami C, Bionda A *et al*. High-dose intravenous gammaglobulin for membranous nephropathy. *Clin. Nephrol*. 1986; **26**: 314.
7. Yokoyama H, Goshima S, Wada T *et al*. The short- and long-term outcomes of membranous nephropathy treated with intravenous immune globulin therapy. Kanazawa Study Group for Renal Diseases and Hypertension. *Nephrol. Dial. Transplant* 1999; **14**: 2379–86.
8. Butty H, Asfoura J, Cortese F *et al*. Chronic lymphocytic leukemia-associated membranous glomerulopathy: remission with fludarabine. *Am. J. Kidney Dis*. 1999; **33**: E8.
9. Boumpas DT, Tassiulas IO, Fleisher TA *et al*. A pilot study of low-dose fludarabine in membranous nephropathy refractory to therapy. *Clin. Nephrol*. 1999; **52**: 67–75.
10. Zhao M, Chen X, Chen Y *et al*. [Mycophenolate mofetil in the treatment of primary nephrotic syndrome]. *Zhonghua Yi Xue Za Zhi* 2001; **81**: 528–31.
11. Miller G, Zimmerman R. 3rd, Radhakrishnan J *et al*. Use of mycophenolate mofetil in resistant membranous nephropathy. *Am. J. Kidney Dis* 2000; **36**: 250–6.
12. Briggs WA, Choi MJ, Scheel PJ Jr. Successful mycophenolate mofetil treatment of glomerular disease. *Am. J. Kidney Dis*. 1998; **31**: 213–7.
13. Choi MJ, Eustace JA, Gimenez LF *et al*. Mycophenolate mofetil treatment for primary glomerular diseases. *Kidney Int*. 2002; **61**: 1098–114.
14. Polenakovic M, Grcevska L, Dzikova S. Mycophenolate mofetil in treatment of idiopathic stages III–IV membranous nephropathy. *Nephrol. Dial. Transplant* 2003; **18**: 1233–4.
15. Ruggenenti P, Chiurchiu C, Brusegan V *et al*. Rituximab in idiopathic membranous nephropathy: a one-year prospective study. *J. Am. Soc. Nephrol*. 2003; **14**: 1851–7.
16. Appel G, Nachman P, Hogan S *et al*. Eculizumab (C5 complement inhibitor) in the treatment of idiopathic membranous nephropathy [abstract]. *J. Am. Soc. Nephrol*. 2002; **13**: 668A–1857.

Reflux nephropathy

Date written: July 2005
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Author: Merlin Thomas

GUIDELINES

a. Standard surgical intervention is not superior to medical management in preventing the progression to end-stage kidney disease (ESKD) in children with severe reflux disease. (Level I evidence)

b. Antibiotic prophylaxis is not superior to supportive care in preventing urinary tract infections or renal parenchymal injury in children with vesicoureteric reflux (VUR). (Level II evidence)

SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on level III and IV evidence)

- **A rationale for any intervention is only provided by the risk for adverse outcomes resulting from non-intervention. While young children with stage I or II VUR (reflux to the ureter or renal pelvis without ureteral dilatation) occasionally form new scars despite medical therapy,[1] these children are not at risk for severe renal disease and spontaneous resolution of the reflux occurs in approximately 80% in 5 years. As a consequence, there is no indication for intervention in this setting to prevent progressive kidney impairment.**
- **The optimal treatment (surgical vs. medical) of gross reflux, with or without scarring, is uncertain. Given the general lack of direct evidence that any treatment option is superior to another, the clinician should provide parents with information about the known benefits and harms of available options and facilitate discussion regarding the intervention. At present, it is not clear whether any intervention for children with primary VUR confers any benefit. Moreover, it is not clear whether antibiotics alone or reimplantation surgery alone are most effective in reducing the risk of urinary tract infections (UTI) and renal parenchymal abnormality. Because of this data and the tendency for many cases of reflux to resolve, many patients with reflux are initially treated on an observation medical protocol including periodic urine cultures to detect asymptomatic bacteriuria. Algorithms based on parental preference have been devised[2] but not as yet tested in clinical trials.**
- **Although UTI does not appear to influence progression of reflux disease, urosepsis can account for partially reversible (acute on chronic) renal impairment. Patients with renal impairment have an increased frequency of septicaemia, complications and poor outcomes with urinary infection. Higher proportions of women with pyelonephritis have been reported to heal with renal scarring if initiation of therapy is delayed.[3] Consequently, urosepsis should be treated early and aggressively in patients with renal impairment (taking into account the toxicity of antibiotic treatments). Bacteriological clearance should also be confirmed, as relapse is also more common in patients with VUR.**

BACKGROUND

VUR is a common problem in childhood that results in urine passing, in a retrograde manner, into the ureter during voiding. In some cases, this is associated with chronic renal scarring and hypertension.[4,5] The exact mechanisms for renal damage remain to be fully delineated, although recurrent urinary infection may have a role.[6] However, some researchers[7] have suggested that renal parenchymal abnormalities instead reflect underlying renal dysplasia rather than damage following UTI.[8] Consequently, there is considerable disagreement regarding the best treatment to prevent renal scarring. The objective of this guideline is to summarize evidence for the utility of interventions to prevent chronic renal impairment in patients with primary VUR. This guideline does not address secondary VUR, which results from increased bladder pressure because of neurogenic bladder, anatomical abnormality, or outlet obstruction.

SEARCH STRATEGY

Databases searched: MeSH terms and text words for reflux nephropathy. This search was carried out in Medline (1966 to September Week 1, 2004). The Cochrane Renal Group Trials Register was also searched for reflux nephropathy trials not indexed in Medline.
Date of searches: 7 September 2004.

WHAT IS THE EVIDENCE?

Surgery vs. antibiotics

There have been 7 trials comparing long-term antibiotics and surgical correction of VUR with antibiotics in 847 children.[9–15] A recent meta-analysis of these studies assessed the

utility of these interventions in preventing UTI, renal parenchymal abnormalities, hypertension and renal function impairment.[16]

Risk of UTI by 1, 2 and 5 years was not significantly different between surgical and medical groups (by 2 years RR 1.07, 95%CI: 0.55–2.09; by 5 years RR 0.99; 95% CI: 0.79–1.26). A significant reduction in the frequency of febrile UTI was observed in the combined therapy groups of the International Reflux Study (8–10%) and antibiotic only groups (22%) (RR 0.43, 95%CI: 0.27–0.70). However, the overall incidence of symptomatic UTI (febrile and non-febrile) showed no significant difference in risk between groups.

Renal parenchymal abnormalities were examined in 5 of the 7 randomised controlled trials (RCTs) comparing long-term antibiotics and surgical correction of VUR with antibiotics.[8,9,11,13,14] As for UTIs, the frequency of new renal parenchymal abnormalities or progression of existing scan abnormalities did not differ at 4–5 years between the two groups. In addition, there was no significant difference in the rate of renal growth between study groups.

ESKD and hypertension were reported by the two UK studies.[13,14] Six children developed ESKD and 11 developed hypertension during follow-up. There was no significant difference in the risk for ESKD (RR 1.07, 95%CI: 0.23–5.04) or hypertension (RR 0.93, 95%CI: 0.25–3.42) between treatment groups. None of these studies were powered to detect these endpoints and follow up time was short, meaning that late effects cannot be excluded. Four studies[10,12–14] reported data on glomerular filtration rates (GFR). None of these studies individually reported any significant difference between groups.

Antibiotics vs. no treatment

There has been only one small RCT comparing antibiotic prophylaxis with no treatment.

- Reddy *et al*[17] randomised 43 children with newly diagnosed VUR grade to receive no treatment, daily antibiotic prophylaxis or prophylaxis given on three days each week. There was no significant difference in risk for UTI between daily antibiotic prophylaxis and no prophylaxis (RR 0.25, 95%CI: 0.03–1.83) or between intermittent prophylaxis and no prophylaxis (RR 0.46, 95% CI: 0.10–2.00). Similarly, there was no significant difference in the risk for renal parenchymal injury between daily antibiotic prophylaxis and no prophylaxis (RR 0.40, 95%CI: 0.02–9.18) or between intermittent prophylaxis and no prophylaxis (RR 0.38, 95%CI: 0.02–8.59).

SUMMARY OF THE EVIDENCE

Reflux-correction surgery has no effect on kidney size, scarring, proteinuria, or the GFR when compared with patients managed conservatively. The long-term outcome of renal status and renal function of patients with severe reflux appears to be independent of treatment modality. In addition, the clinical course of patients with established glomerulosclerosis is not altered by late surgical correction or by infection. While the severity of reflux is the single most important determinant of whether renal impairment will occur, persistent reflux or recurrent infection does not appear to be a risk factor for progressive glomerulosclerosis. At this time, there is no evidence to indicate clear superiority of either medical or surgical management for the prevention of progressive kidney disease.

WHAT DO THE OTHER GUIDELINES SAY?

Kidney Disease Outcomes Quality Initiative: No recommendation.
UK Renal Association: No recommendation.
Canadian Society of Nephrology: No recommendation.
European Best Practice Guidelines: No recommendation.
International Guidelines:

Pediatric Vesicoureteric Reflux Guidelines Panel summary report on the management of primary vesicoureteric reflux in children.[18]

Guidelines for management of children with urinary tract infection and vesicoureteric reflux. Recommendations from a Swedish state-of-the-art conference. Swedish Medical Research Council.[19]

American Academy of Pediatrics: The Diagnosis, Treatment, and Evaluation of the Initial Urinary Tract Infection in Febrile Infants and Young Children (AC9830).[20]

IMPLEMENTATION AND AUDIT

No recommendation.

SUGGESTIONS FOR FUTURE RESEARCH

No recommendation.

REFERENCES

1. Arant BS Jr. Medical management of mild and moderate vesicoureteral reflux: follow up studies of infants and young children. A preliminary report of the South-west Pediatric Nephrology Study Group. *J. Urol.* 1992; **148** (5 Part 2): 1683–7.
2. Capozza N, Lais A, Matarazzo E *et al.* Treatment of vesico-ureteric reflux: a new algorithm based on parental preference. *BJU International* 2003; **92**: 285–8.
3. Roberts JA. Management of pyelonephritis and upper urinary tract infections. *Urol Clin. North Am.* 1999; **26**: 753–63.
4. Martinell J, Lidin-Janson G, Jagenburg R *et al.* Girls prone to urinary infections followed into adulthood. Indices of renal disease. *Ped Nephrol* 1996; **10**: 139–42.
5. Wennerstrom M, Hansson S, Jodal U *et al.* Primary and acquired renal scarring in boys and girls with urinary tract infection. *J Ped* 2000; **136**: 30–4.
6. Huland H, Busch R. Pyelonephritic scarring in 213 patients with upper and lower urinary tract infections: long-term followup. *J Urol* 1984; **132**: 936–9.
7. Sreenarasimhaiah S, Hellerstein S. Urinary tract infections per se do not cause end-stage kidney disease. *Pediatr Nephrol* 1998; **12**: 210–3.

8. Hellerstein S. Long-term consequences of urinary tract infections. *Curr. Opin. Pediatr* 2000; **12**: 125–8.
9. Weiss R., Duckett J, Spitzer A. Results of a randomized clinical trial of medical versus surgical management of infants and children with grades III and IV primary vesicoureteral reflux (United States). The International Reflux Study in Children. *J. Urol.* 1992; **148** (5 Part 2): 1667–73.
10. Holland NH, Kazee M, Duff D *et al.* Antimicrobial prophylaxis in children with urinary tract infection and vesicoureteral reflux. *Rev Infect Dis* 1982; **4**: 467–74.
11. Capozza N, Caione P. Dextranomer/hyaluronic acid copolymer implantation for vesico-ureteral reflux: a randomized comparison with antibiotic prophylaxis. *J Ped* 2002; **140**: 230–4.
12. Hjalmas K, Lohr G, Tamminen-Mobius T *et al.* Surgical results in the International Reflux Study in Children (Europe). *J. Urol.* 1992; **148** (5 Part 2): 1657–61.
13. Morris MC, Rothwell DL, Paykel AD. A prospective study of vesico-ureteric reflux and renal function in children. Second CJ, Hodson Symposium on Reflux Nephropathy Christchurch, New Zealand, 1991.
14. Smellie JM, Barratt TM, Chantler C *et al.* Medical versus surgical treatment in children with severe bilateral vesicoureteric reflux and bilateral nephropathy: a randomised trial. *Lancet* 2001; **357**: 1329–33.
15. Birmingham Reflux Study Group. Prospective trial of operative versus non-operative treatment of severe vesicoureteric reflux in children: five years' observation. *Br. Med. J. (Clin. Res. Ed)* 1987; **295**: 237–41.
16. Wheeler DM, Vimalachandra D, Hodson EM *et al.* Interventions for primary vesicoureteric reflux. *The Cochrane Database of Systematic Reviews* 2004, Issue 3.
17. Reddy PP, Evans MT, Hughes PA *et al.* Antimicrobial prophylaxis in children with vesico-ureteral reflux: a randomised prospective study of continuous therapy vs. intermittent therapy vs. surveillance. *Pediatrics Suppl.* 1997; **100**: S555–S556.
18. Elder JS, Peters CA, Arant BS Jr *et al.* Pediatric Vesicoureteral Reflux Guidelines Panel summary report on the management of primary vesicoureteral reflux in children. *J. Urol.* 1997; **157**: 1846–51.
19. Jodal U, Lindberg U. Guidelines for Management of Children with Urinary Tract Infection and Vesico-Ureteric Reflux. Recommendations from a Swedish State-of-the-Art Conference Swedish Medical Research Council. *Acta Paediatr Suppl* 1999; **88**: 87–9.
20. American Academy of Pediatrics. Practice parameter: the diagnosis, treatment, and evaluation of the initial urinary tract infection in febrile infants and young children Committee on Quality Improvement. Subcommittee on Urinary Tract Infection. *Pediatrics* 1999; **103**: 843–52.

APPENDICES

Table 1 Characteristics of included studies

Study ID (author, year)	N	Study design	Setting	Participants	Intervention (experimental group)	Intervention (control group)	Follow up (months)	Comments
Birmingham Reflux Study Group, 1987	179	Randomised controlled clinical trial	GP, paediatrician referrals, hospital casualty	179 children under 15 yrs with primary reflux	Surgical reimplantation and antibiotics	Trimethoprim or nitrofurantoin 1–2 mg/kg	24	
Capozza *et al*, 2002	61	Randomised controlled clinical trial	University hospital, Italy	61 children over 1 yr with primary reflux	Subureteric implantation of Dx/HA copolymer (Deflux and antibiotics)	Antibiotic	12	
Hjalmas *et al*, 1992	321	Randomised controlled clinical trial	University teaching hospitals, Europe	321 children 6 days – 11 yrs with primary reflux	PL, Cohen, LGe and antibiotics	Nitrofurantoin or trimethoprim 1–2 mg/kg	60	
Holland *et al*, 1982	10	Randomised controlled clinical trial	US	10 children between 2 mo–10 yrs with primary reflux	Surgical reimplantation and antibiotics	Trimethoprim-sulfamethoxazole or nitrofurantoin 1 mg/kg	24	
Morris *et al*, 1991 (abstract)	138	Randomised controlled clinical trial	New Zealand	138 children 6 mo–10 yrs	Cohen reimplantation and antibiotics	Antibiotic	24	
Reddy *et al*, 1997 (abstract)	43	Randomised controlled clinical trial	University teaching hospital, US	43 children with primary reflux	Intermittent antibiotics 3 × week, daily urine nitrate testing	Antibiotic continuous prophylaxis	12	3-arm trial with third arm of no antibiotics, surveillance
Smellie *et al*, 2001	53	Randomised controlled clinical trial	University teaching hospitals in UK	53 children with primary reflux	Cohen procedure and antibiotics	Nitrofurantoin or trimethoprim or trimethoprim-sulfamethoxazole 1–2 mg/kg	48	
Weiss *et al*, 1992	142	Randomised controlled clinical trial	University teaching hospitals, US	142 children with primary reflux	PL, Cohen, or other reimplantation and antibiotics	Nitrofurantoin or trimethoprim 1–2 mg/kg	60	

Table 2 Quality of randomised trials

Study ID (author, year)	Method of allocation concealment	Blinding			Intention-to-treat analysis	Loss to follow up (%)
		(participants)	(investigators)	(outcome assessors)		
Birmingham Reflux Study Group, 1987	Sealed envelopes	No	No	Radiological outcomes only	Unclear	14.0
Capozza *et al*, 2002	Computer generated	No	No	Not stated	No	2.0
Hjalmas *et al*, 1992	Sealed envelopes	No	No	Not stated	Unclear	11.0
Holland *et al*, 1982	Not stated	No	No	Radiological outcomes only	Unclear	0.0
Morris *et al*, 1991 (abstract)	Not stated	No	No	Not stated	Unclear	10.0
Reddy *et al*, 1997 (abstract)	Not stated	No	No	Not stated	Unclear	0.0
Smellie *et al*, 2001	Sealed envelopes	No	No	Not stated	No	6.0
Weiss *et al*, 1992	Sealed envelopes	No	No	Not stated	No	9.0

Table 3 Results for dichotomous outcomes

Study ID (author, year)	Outcomes	Intervention group (number of patients with events/number of patients exposed)	Control group (number of patients with events/number of patients not exposed)	Relative risk (RR) [95% CI]	Risk difference (RD) [95% CI]
Birmingham Reflux	UTI	16/73	23/80	0.76 (95%CI: 0.44, 1.33)	–0.07 (95%CI: –0.21, 0.07)
Study Group, 1987	Renal parenchymal defects IVP at 2 yrs	4/77	5/84	0.87 (95%CI: 0.254, 3.13)	–0.01 (95%CI: –0.08, 0.06)
	ESRD	1/51	1/53	1.04 (95%CI: 0.07, 16.18)	0.00 (95%CI: –0.05, 0.05)
	Hypertension	1/51	3/53	0.35 (95%CI: 0.04, 3.22)	–0.04 (95%CI: –0.11, 0.04)
Capozza *et al*, 2002	UTI	6/39	0/21	7.15 (95%CI: 0.42, 121.04)	0.15 (95%CI: 0.02, 0.28)
	Renal parenchymal defects on DMSA scan	1/39	3/21	0.18 (95%CI: 0.02, 1.62)	–0.12 (95%CI: –0.27, 0.04)
Hjalmas *et al*, 1992	UTI	59/147	59/150	1.02 (95%CI: 0.77, 1.35)	0.01 (95%CI: –0.10, 0.12)
	Febrile UTI	15/147	33/150	0.46 (95%CI: 0.26, 0.82)	–0.12, (95%CI: –0.20, –0.04)
	Renal parenchymal defects on IVP	35/149	30/153	1.20 (95%CI: 0.78, 1.85)	0.04 (95%CI: –0.05, 0.13)
	Renal parenchymal defects on DMSA scan	23/140	25/147	0.97 (95%CI: 0.58, 1.62)	–0.01 (95%CI: –0.09, 0.08)
	Renal scarring on IVP	21/149	19/153	1.13 (95%CI: 0.64, 2.02)	0.02 (95%CI: –0.06, 0.09)
Holland *et al*, 1982	UTI	1/5	2/5	0.50 (95%CI: 0.06, 3.91)	–0.20 (95%CI: –0.75, 0.35)
	Renal parenchymal defects on IVP	1/5	0/5	3.00 (95%CI: 0.15, 59.89)	0.20 (95%CI: –0.21, 0.61)

Morris *et al*, 1991 (abstract)	UTI	13/60	8/58	1.57 (95%CI: 0.70, 3.51)	0.08 (95%CI: –0.06, 0.22)
Reddy *et al*, 1997 (abstract)	UTI (continuous vs. surveillance)	1/13	5/16	0.25 (95%CI: 0.03, 1.85)	–0.24, (95%CI: –0.50, 0.03)
	UTI (intermittent vs. surveillance)	2/14	5/16	0.46 (95%CI: 0.10, 2.00)	–0.17 (95%CI: –0.46, 0.12)
	Renal parenchymal abnormalities (continuous vs. surveillance)	0/13	1/16	0.40 (95%CI: 0.01, 9.18)	–0.06 (95%CI: –0.23, 0.10)
	Renal parenchymal abnormalities (intermittent vs. surveillance)	0/14	1/16	0.38 (95%CI: 0.02, 8.59)	–0.06 (95%CI: –0.23, 0.10)
Smellie *et al*, 2001	UTI	6/24	11/26	0.59 (95%CI: 0.26, 1.35)	–0.17 (95%CI: –0.43, 0.08)
	ESRD	2/24	2/26	1.08 (95%CI: 0.17, 7.10)	0.01 (95%CI: –0.14, 0.16)
	Hypertension	4/24	3/26	1.44 (95%CI: 0.36, 5.80)	0.05 (95%CI: –0.14, 0.24)
Weiss *et al*, 1992	UTI	21/64	20/68	1.12 (95%CI: 0.67, 1.85)	0.03 (95%CI: –0.12, 0.19)
	Febrile UTI	5/64	15/68	0.35 (95%CI: 0.14, 0.92)	–0.14 (95%CI: –0.26, –0.02)
	Renal parenchymal defects on IVP	18/51	23/65	1.00 (95%CI: 0.61, 1.64)	0.00 (95%CI: –0.18, 0.17)
	Renal scarring on IVP	16/51	14/65	1.46 (95%CI: 0.79, 2.70)	0.10 (95%CI: –0.06, 0.26)

Focal segmental glomerulosclerosis: treatment with steroids

Date written: July 2005
Final submission: September 2005
Author: Merlin Thomas

GUIDELINES

While remission may be induced in patients receiving steroids, there have been no level I or II studies confirming the efficacy of this intervention in the preservation of renal function in adults with primary focal segmental glomerulosclerosis (FSGS)

SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on Level III and IV evidence)

- **It is uncommon for patients with normal renal function and non-nephrotic proteinuria to progress to renal impairment. Consequently, steroid therapy in these patients is currently unjustified. Nonetheless, supportive therapy including aggressive control of blood pressure and dyslipidemia and blockade of the renin angiotensin system would seem prudent. In addition, long-term follow-up is still required to monitor for the development of adverse indicators including nephrotic range proteinuria and hypertension that could presage a more progressive course. (Level IV evidence)**
- **Some studies have shown that, independent of the degree of proteinuria, patients with renal dysfunction and/or interstitial fibrosis have a significantly decreased renal survival. (Level III evidence) This has led some to consider a trial of steroids in FSGS with renal impairment and non-nephrotic proteinuria in an attempt to induce remission. However, there are currently no studies to support this practice. In addition, nephrotic patients with renal dysfunction or interstitial fibrosis tend to be less responsive to therapy.[1] At least some of these patients have secondary FGS (see guideline titled "FSGS – cytotoxic therapy").**
- **Because of the desire to induce remission in patients with FGS and nephrotic range proteinuria, it has been suggested that a 6-month trial of steroid therapy may be useful. Certainly, a prolonged course of steroids (using prednisone doses of 0.5–2 mg/kg/day) can induce remission in between 30 and 60% of patients.[1–10] However, this intervention has not been tested in any randomized controlled trial (RCT), making the accurate interpretation of the utility of steroid therapy problematic. Moreover, many series of patients with nephrotic syndrome have included an unknown number of patients with steroid-reversible nephropathy apart from FSGS, including minimal change disease.**
- **The Regional Glomerulonephritis Registry Study[3] prospectively followed 95 adult and paediatric patients with biopsy-proven FSGS, for a mean of 61 months from the time of biopsy. The probability of remission with a long duration of therapy with corticosteroids (with or without cytotoxic drugs) was similar in adults (39%) and children (44%) with FSGS.**
- **Pei *et al*[3] also found remission could be induced with steroid therapy in older patients (more than 60 years of age) with FSGS. In this study, 4 of the 9 patients (44%) who received treatment with prednisone achieved complete remission for a median duration of treatment of 6 months, alone or combined with cytotoxic therapy. There were no relapses in those patients who achieved remission and none progressed to renal failure. No untreated patients had a remission and 9 of the 14 untreated or non-responders progressed. Ninety-six per cent of the patients who had a complete remission had preservation of renal function, whereas the probability of end-stage kidney disease (ESKD) was 45% in those who had not responded or who were not treated. Treatment with steroids may be effective in preserving filtration function in children with FSGS with heavy proteinuria (> 3 g/day) (Level II evidence).**
- **At least 7% of the children enrolled in the International Study of Kidney Diseases has FSGS (ISKDC).[3] In this study, children were given daily corticosteroids in a dose of 60 mg/d/m^2 (up to 80 mg/d) for 4 weeks followed by 40 mg/d/m^2 given on three consecutive days out of seven for 4 weeks and then tapered off over 4 more weeks. Many children developed remission, although many others had remission without a diagnosis of FSGS ever being made. Conclusions about the efficacy of comparative steroids in FSGS are difficult to make in the context of this study. Nonetheless, this regimen has become the standard treatment for childhood nephrotic syndrome.**
- **Korbet, Schwartz and Lewis[1] reported a 50% response rate in a study of 16 adult patients with nephrotic syndrome and FSGS. Treatment consisted of 60 mg/day of prednisone for at least 1 month. Responses occurred by an average of 3.75 months (range: 1–10 months), and complete remission occurred at 5.75–6.75 months in the three patients who had complete remission.**
- **Banfi *et al*[5] retrospectively reviewed the management of 59 patients with FSGS and nephrotic syndrome treated with corticosteroids and/or immunosuppressive drugs.**

Twenty-seven patients were initially treated with corticosteroids alone for 9.3 months; 19 patients received corticosteroids and immunosuppressive agents associated or every other month for 5.5 months; 13 patients received either azathioprine or cyclophosphamide alone for 25 months. At follow-up, 60% of patients had experienced complete or partial remission, most commonly after at least 8 weeks of treatment.

- **Agarwal *et al*[6] followed 38 adult cases with biopsy-proven FSGS and nephrotic syndrome treated with prednisolone; 58% showed response (31% complete remission and 27% partial remission).**
- **Rydel *et al*[7] reported a retrospective assessment of 60 patients with nephrotic syndrome and FSGS. Thirty patients received prednisone, at a total dose of more than 60 mg/day for a minimum of 2 months, followed by a tapering schedule over 5–6 months. Fifteen patients (50%) achieved a remission by 3.7 months (10 complete remission and 5 partial remissions), with all patients responding within 9 months. Remission was more common in patients who received a dose of 60 mg/day or more of prednisone for a longer period of time.**
- **Miyata *et al*[8] reviewed 32 patients with nephrotic syndrome due to FSGS treated with steroids alone. Forty-four per cent had complete remission, 12% partial remission and 44% no response.**
- **Ponticelli *et al*[10] reviewed 80 nephrotic adults with FSGS and plasma creatinine lower than 3 mg/dL. Patients were given corticosteroids (53 patients) or immunosuppressive agents (27 patients) for a median of 16 and 75 weeks, respectively. Forty-two patients responded with complete remission (29 patients, 36%) or partial remission (13 patients, 16%). Twenty-six patients who did not respond were treated again. Two patients obtained complete remission and 13 a partial remission. Overall, 70% of nephrotic adults with FSGS obtained complete or partial remission and maintained stable renal function for about 10 years when given a prolonged therapy with corticosteroids or immunosuppressive drugs. Patients with collapsing glomerulopathy, a more rapidly progressive form of FSGS, were less responsive to steroids, if at all.**
- **Valeri *et al*[11] reviewed their experience with 43 patients with collapsing FSGS and found that none of the 26 patients benefited from treatment with prednisone alone.**

Some studies have suggested that patients with a glomerular tip lesion associated with FSGS may be more likely to respond to steroid therapy, than those with typical sclerosis or collapsing glomerulopathy.[12,13] However, other studies have shown that steroid-responsiveness, rather than histology predicts good prognosis.[14]

Overall, in those patients who do not receive steroid treatment or do not respond, the rates of progression to ESKD appear to be similar. Despite the lack of RCTs of corticosteroids in FSGS, it seems clear that following a prolonged course of corticosteroids some patients achieve and sustain a remission of proteinuria, that at the very least, has useful prognostic utility, whether or not it contributes to improved renal functional outcomes.

What dose should be used?

Most clinical studies have used prednisone doses of between 0.5 and 2 mg/kg/day to produce clinical remission. There is some evidence that doses of greater than 60 mg/day are more likely to induce remission than lower doses. In addition, alternate-day therapy (e.g. doses greater than or equal to 120 mg every second day) may be equally efficacious in FSGS and minimize toxicity. (Level III evidence)

What is the optimal duration of treatment?

Prolonged therapy (of at least 6 months) appears to be important both to sustain remission as well as to induce it. (Level III evidence)

How to define steroid–responsiveness?

Most steroid-responsive patients show some reduction in protein excretion within the first few months of therapy. The median time to clinical remission, when it occurs, is usually 3 to 4 months and most within 6 months of starting steroid therapy. It is therefore prudent that treatment should continue for at least 6 months before declaring the patient steroid-resistant. Although some patients will have remissions after this time, others have suggested that a lack of any decline in protein excretion at 8 weeks in children and 12 weeks in adults is generally indicative of steroid resistance. (Level IV evidence – anecdotal)

BACKGROUND

FSGS is one of the most common primary glomerular diseases that result in renal impairment and ESKD. Patients with nephrotic-range proteinuria appear to be at the greatest risk of progressing to ESKD over the course of 3–6 years. Early treatment of patients with FSGS and nephrotic syndrome may alter the progression of renal disease in some patients. In particular, patients in whom a complete remission of proteinuria can be induced, may improve or stabilize their renal function. There is also some evidence that treatments that reduce proteinuria (partial remission) may also slow disease progression.[2] The objective of this guideline is to evaluate the available clinical evidence pertaining to the impact of steroid therapy on renal functional decline in patients with idiopathic FSGS.

SEARCH STRATEGY

Databases searched: MeSH terms and text words for focal segmental glomerulosclerosis were combined with MeSH terms and text words for steroid therapy. This search was carried out in Medline (1966 to September Week 2, 2004). The Cochrane Renal Group Trials Register was also

searched for trials in focal segmental glomerulosclerosis not indexed in Medline.
Date of searches: 17 September 2004.

WHAT IS THE EVIDENCE?

There have been no RCTs of corticosteroids in FSGS.

SUMMARY OF THE EVIDENCE

While remission may be induced in patients receiving steroids, and steroid responsiveness correlates with improved outcomes, there have been no level I or II studies confirming the efficacy of this intervention in the preservation of renal function in individuals with primary FSGS.

WHAT DO THE OTHER GUIDELINES SAY?

Kidney Disease Outcomes Quality Initiative: No recommendation.
UK Renal Association: No recommendation.
Canadian Society of Nephrology: No prospective studies have specifically assessed the use of prednisone. Reports of case series support the use of prednisone at an initial dose of 60 mg/day for a minimum of four months; patients should not be considered prednisone resistant until a six-month trial of prednisone has been completed.
European Best Practice Guidelines: No recommendation.
International Guidelines: No recommendation.

IMPLEMENTATION AND AUDIT

No recommendation.

SUGGESTIONS FOR FUTURE RESEARCH

No recommendation.

REFERENCES

1. Korbet SM, Schwartz MM, Lewis EJ. Primary focal segmental glomerulosclerosis: clinical course and response to therapy. *Am. J. Kidney Dis.* 1994; **23**: 773–83.
2. Troyanov S, Wall CA, Miller JA *et al.* Focal and segmental glomerulosclerosis: definition and relevance of a partial remission. *J. Am. Soc. Nephrol.* 2005; **16**: 1061–8.
3. Pei Y, Cattran D, Delmore T *et al.* Evidence suggesting undertreatment in adults with idiopathic focal segmental glomerulosclerosis. Regional Glomerulonephritis Registry Study. *Am. J. Med.* 1987; **82**: 938–44.
4. Nagai R, Cattran DC, Pei Y. Steroid therapy and prognosis of focal segmental glomerulosclerosis in the elderly. *Clin. Nephrol.* 1994; **42**: 18–21.
5. Banfi G, Moriggi M, Sabadini E *et al.* The impact of prolonged immuno suppression on the outcome of idiopathic focal-segmental glomerulosclerosis with nephrotic syndrome in adults. A collaborative retrospective study. *Clin. Nephrol.* 1991; **36**: 53–9.
6. Agarwal SK, Dash SC, Tiwari SC *et al.* Idiopathic adult focal segmental glomerulosclerosis: a clinicopathological study and response to steroid. *Nephron.* 1993; **63**: 168–71.
7. Rydel JJ, Korbet SM, Borok RZ *et al.* Focal segmental glomerular sclerosis in adults: presentation, course, and response to treatment. *Am. J. Kidney Dis.* 1995; **25**: 534–42.
8. Miyata J, Takebayashi S, Taguchi T *et al.* Evaluation and correlation of clinical and histological features of focal segmental glomerulosclerosis. *Nephron.* 1986; **44**: 115–3.
9. Detwiler RK, Falk RJ, Hogan SL *et al.* Collapsing glomerulopathy: a clinically and pathologically distinct variant of focal segmental glomerulosclerosis. *Kidney Int.* 1994; **45**: 1416–24.
10. Ponticelli C, Villa M, Banfi G *et al.* Can prolonged treatment improve the prognosis in adults with focal segmental glomerulosclerosis? *Am. J. Kidney Dis.* 1999; **34**: 618–25.
11. Valeri A, Barisoni L, Appel GB *et al.* Idiopathic collapsing focal segmental glomerulosclerosis: a clinicopathologic study. *Kidney Int.* 1996; **50**: 1734–46.
12. Hogan-Moulton AE, Hogan SL, Falk RJ *et al.* Glomerular tip lesion (GTL): clinical features, response to corticosteroids and comparison to focal segmental glomerulosclerosis (FSGS) [abstract]. *J. Am. Soc. Nephrol.* 1997; **8**: 87A.
13. Howie AJ, Kizaki T. Glomerular tip lesion in the 1962–66 Medical Research Council trial of prednisone in the nephrotic syndrome. *Nephrol. Dial Transplant.* 1993; **8**: 1059–63.
14. Chun MJ, Korbet SM, Schwartz MM *et al.* Focal segmental glomerulosclerosis in nephrotic adults: presentation, prognosis and response to therapy of the histologic variants. *J. Am. Soc. Nephrol.* 2004; **15**: 2169–77.

Focal segmental glomerulosclerosis: use of cyclosporin A

Date written: July 2005
Final submission: September 2005
Author: Merlin Thomas

GUIDELINES

Cyclosporin may be effective in preserving filtration function in patients with steroid-resistant focal segmental glomerulosclerosis (FSGS), in those with steroid dependence or in those who frequently relapse on conventional therapy. (Level II evidence)

SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on Level III and IV evidence)
A number of open studies have shown that cyclosporin is able to induce complete and partial remission in both adults and children with steroid-resistant FSGS and steroid-dependent FSGS.[1,2] Partial or complete remission is most likely in steroid-dependent FSGS, while the response rate in steroid-resistant FSGS is variable, ranging between 20 and 70% in most studies.

Cyclosporin is also associated with significant toxicity, which means that use of this agent should be reasonably restricted to patients at high risk of end-stage kidney disease (ESKD), or in whom toxicity from steroid-dependence confers a greater danger than chronic cyclosporin therapy.

What dose should be used?

The optimal dosing and monitoring of cyclosporin in patients with FSGS has not been fully clarified. Most studies have effectively used doses of approximately 5 mg/kg/day with achieved blood concentrations of 100–200 mg/mL. (Level III evidence)

Should steroids also be used?

Most studies have also continued a low dose of steroids while using cyclosporin. There is anecdotal evidence that this approach may be more effective in achieving remission in children than cyclosporin alone.[3]

Optimal duration of therapy

A minimum effective dose of cyclosporin should be continued for at least 2 years. (Level IV evidence) Relapse is common after tapering or discontinuing the drug. Patients who are in complete remission for more than 1 year on cyclosporin appear to be more likely to remain in remission if the cyclosporin is gradually tapered and discontinued, rather than stopped suddenly. (Level IV evidence, anecdotal reports)

BACKGROUND

FSGS is one of the most common primary glomerular diseases that result in renal impairment and ultimately ESKD, and 40–80% of patients do not respond to corticosteroids. These patients are at high risk for progressive renal disease and ESKD. In these patients, the induction of a complete or partial remission by other agents may improve or stabilize their renal function.[4] The objective of this guideline is to evaluate the available clinical evidence pertaining to the impact of cyclosporin A on renal functional decline in patients with idiopathic FSGS.

SEARCH STRATEGY

Databases searched: MeSH terms and text words for focal segmental glomerulosclerosis were combined with MeSH terms and text words for cyclosporin A therapy. This search was carried out in Medline (1966 to September Week 2, 2004). The Cochrane Renal Group Trials Register was also searched for trials in focal segmental glomerulosclerosis not indexed in Medline.
Date of searches: 17 September 2004.

WHAT IS THE EVIDENCE?

There have been a number of small randomized studies of adults with idiopathic FSGS and nephrotic syndrome:
- Heering *et al*[5] randomly assigned 57 patients with idiopathic FSGS to receive steroids and cyclosporin ($n = 34$) or steroids and chlorambucil ($n = 23$) for 6 months. There were no differences in mean serum creatinine or proteinuria between the groups. In addition, switching patients receiving chlorambucil to cyclosporin failed to improve remission rates. Interpretation of this study is made difficult by the responsiveness to steroids alone (see guideline titled "FSGS: treatment with steroids") in both groups biasing the improvement in renal parameters.

• Cattran *et al*[6] studied 49 patients with steroid-resistant FSGS, comparing 26 weeks of cyclosporin treatment plus low-dose prednisone to placebo plus prednisone. Seventy per cent of the cyclosporin group had a partial (9%) or complete remission (61%) of their proteinuria by 26 weeks compared with 4% of the placebo group ($P < 0.001$). However, 60% of responders subsequently relapsed by week 78. Nonetheless, there was a decrease of 50% in baseline creatinine clearance in 25% of the cyclosporin-treated group compared with 52% of controls, independent of other baseline demographic and laboratory variables.
• Garin *et al.*[7] conducted a small randomized trial of cyclosporin that included 4 patients with FSGS. Patients were randomly allocated to a cyclosporin (5 mg/kg/d) or a control group. After 8 weeks of therapy and 1 month without cyclosporin therapy, patients in the control group were given cyclosporin for 8 weeks and those in the cyclosporin group became controls. Proteinuria remained unchanged with cyclosporin treatment, while there was a significant increase in proteinuria in the control group. Renal progression could not be tested in this brief study format or the disease-specific impact of therapy.
• Ponticelli *et al*[8] reported a prospective trial that comprised 19 patients including adults and children with probable FSGS, of whom 10 received cyclosporin, and 9 were in the control group. A biopsy diagnosis of FSGS was made if one glomerulus with segmental hyalinosis was seen. Patients were classified as steroid-resistant if they had no response after only 6 weeks of prednisone therapy. The cyclosporin dose was 5 mg/kg per day in adults and 6 mg/kg per day in children. Treatment was stopped at 6 months in non-responders. For responders, the dose was reduced by 25% every 2 months so that the drug was ultimately stopped after 12 months. Three cyclosporin-treated patients attained complete remission, and 4 had partial remissions. Three patients in the control group had partial remissions, but their diagnoses were not itemized in the report.
In addition, there has been one trial in children with FSGS:
• Tejani *et al.*[9] randomised 28 children with nephrotic syndrome to receive either cyclosporin and low-dose prednisone or high-dose prednisone alone. Thirteen of 14 children receiving combined therapy underwent remission vs. only 8 of 14 children receiving prednisone alone ($P < 0.05$). However, there was no difference between the two groups as regards the duration of remission after discontinuation of therapy. It also was not clear how many of these patients had idiopathic FSGS.

SUMMARY OF THE EVIDENCE

Small RCTs suggest that remission can be induced in some steroid-resistant patients and deterioration of renal function can be slowed.

WHAT DO THE OTHER GUIDELINES SAY?

Kidney Disease Outcomes Quality Initiative: No recommendation.
UK Renal Association: No recommendation.
Canadian Society of Nephrology:
• The use of cyclosporin at doses of approximately 5 mg/kg/day may be effective in reducing urinary protein excretion (grade B).
• Relapse after reducing the dose or stopping cyclosporin is very common (grade B).
• Long-term use of cyclosporin may be required to maintain remission (grade D).
European Best Practice Guidelines: No recommendation.
International Guidelines: No recommendation.

IMPLEMENTATION AND AUDIT

No recommendation.

SUGGESTIONS FOR FUTURE RESEARCH

No recommendation.

REFERENCES

1. Meyrier A, Noel LH, Auriche P *et al*. Long-term renal tolerance of cyclosporin A treatment in adult idiopathic nephrotic syndrome. Collaborative Group of the Societe de Nephrologie. *Kidney Int*. 1994; **45**: 1446–56.
2. Niaudet P. French Society of Pediatric Nephrology. Treatment of childhood steroid-resistant idiopathic nephrosis with a combination of cyclosporin and prednisone. *J. Pediatr* 1994; **125**: 981–6.
3. Meyrier A, Niaudet P, Brodehl J. *Optimal Use of Sandimmun in Nephrotic Syndrome*. Berlin: Springer Verlag, 1992.
4. Troyanov S, Wall CA, Miller JA *et al*. Focal and segmental glomerulosclerosis: definition and relevance of a partial remission. *J. Am. Soc. Nephrol* 2005; **16**: 1061–8.
5. Heering P, Braun N, Mullejans R *et al*. German Collaborative Glomerulonephritis Study Group. Cyclosporine A and chlorambucil in the treatment of idiopathic focal segmental glomerulosclerosis. *Am. J. Kidney Dis* 2004; **43**: 10–8.
6. Cattran DC, Appel GB, Hebert LA *et al*. A randomized trial of cyclosporin in patients with steroid-resistant focal segmental glomerulosclerosis. North America Nephrotic Syndrome Study Group. *Kidney Int*. 1999; **56**: 2220–6.
7. Garin EH, Orak JK, Hiott KL *et al*. Cyclosporin therapy for steroid-resistant nephrotic syndrome. A controlled study. *Am. J. Dis Child* 1988; **142**: 985–8.
8. Ponticelli C, Rizzoni G, Edefonti A *et al*. A randomized trial of cyclosporine in steroid–resistant idiopathic nephrotic syndrome. *Kidney Int*. 1993; **43**: 1377–84.
9. Tejani A, Suthanthiran M, Pomrantz A. A randomized controlled trial of low-dose prednisone and cyclosporin versus high-dose prednisone in nephrotic syndrome of children. *Nephron* 1991; **59**: 96–9.

APPENDICES

Table 1 Characteristics of included studies

Study ID (author, year)	*N*	Study design	Setting	Participants	Intervention (experimental group)	Intervention (control group)	Follow up (months)	Comments
Cattran *et al*, 1999	49	Randomised controlled clinical trial	12 clinical centres in North America	49 patients with steroid-resistant FSGS	Cyclosporine and low-dose prednisolone	Placebo and prednisolone	50	
Garin *et al*, 1988	8	Randomised controlled clinical cross over trial	University hospital, US	8 patients with idiopathic, steroid-resistant nephrotic syndrome	Cyclosporine 5 mg/kg/s for eight weeks	No intervention	2	
Ponticelli *et al*, 1993	45	Randomised controlled clinical trial	Multicentre, Italy	45 patients with steroid-resistant idiopathic nephrotic syndrome	Cycloporin (CsA) 5 mg/kg/day for adults, 6 mg/kg/day for children, tapered dose	Supportive therapy	18–24	

Table 2 Quality of randomised trials

Study ID (author, year)	Method of allocation concealment	Blinding			Intention-to-treat analysis	Loss to follow up (%)
		(participants)	(investigators)	(outcome assessors)		
Cattran *et al*, 1999	Central	Yes	No	No	Unclear	0.0
Garin *et al*, 1988	Not stated	No	No	Not stated	Unclear	0.0
Ponticelli *et al*, 1993	Sequentially labelled sealed envelopes	No	No	No	Yes	8.9

Table 3 Results for continuous outcomes

Study ID (author, year)	Outcomes	Intervention group (mean [SD])	Control group (mean [SD])	Difference in means [95% CI]
Cattran *et al*, 1999	Mean slope of Cr clearance (ml/min/yr) over study period	–5.5 (18)	–23 (39)	17.50 (95% CI: 0.12, 34.88)
Garin *et al*, 1988	Urinary protein excretion at 8 wks	11.7 (8.77)	17.3 (9.90)	–5.60 (95% CI: –14.76, 3.56)
	Cr clearance at 8 wks (ml/s/1.73 m^2)	1.12 (0.65)	0.87 (0.62)	0.25 (95% CI: –0.37, 0.87)
	Serum albumin at 8 wks (g/L)	24 (8.49)	18 (8.49)	6.00 (95% CI: –2.32, 14.32)
Ponticelli *et al*, 1993	Proteinuria at 12 mo (mg/m^2/hg)-(Lg)	136.1 (141.7)	157.8 (102.87)	–21.70 (95% CI: –96.67, 53.27)
	Serum Cr at 12 mo (µmol/L)-(lg)	107.9 (166.4)	95.5 (54.04)	12.40 (95% CI: –61.12, 85.92)
	Cr clearance at 12 mo (ml/min/1.73 m^2)-(Lg)	117.8 (57.69)	100.6 (48.38)	17.20 (95% CI: –15.27, 49.67)
	Serum urea at 12 mo (mmol/L)	12.5 (10.32)	13.2 (10.90)	–0.70 (95% CI: –7.23, 5.83)
	Serum protein at 12 mo (g/L)	57.1 (12.20)	51.6 (7.41)	5.50 (95% CI: –0.59, 11.59)
	Serum albumin at 12 mo (g/L)	31.2 (10.79)	27.5 (7.85)	3.70 (95% CI: –2.03, 9.43)
	Plasma cholesterol at 12 mo (mmol/L)	0.076 (0.04)	0.094 (0.41)	–0.01 (95% CI: –0.20, 0.18)

Cr, creatinine.

Table 4 Results for dichotomous outcomes

Study ID (author, year)	Outcomes	Intervention group (number of patients with events/ number of patients exposed)	Control group (number of patients with events/ number of patients not exposed)	Relative risk (RR) [95% CI]	Risk difference (RD) [95% CI]
Cattran *et al*, 1999	Complete remission	3/26	0/23	6.22 (95% CI: 0.34, 114.42)	0.12 (95% CI: –0.02, 0.25)
	Partial remission	15/26	1/23	13.27 (95% CI: 1.90, 92.79)	0.53 (95% CI: 0.33, 0.74)
	ESRD	4/26	10/23	0.35 (95% CI: 0.13, 0.98)	–0.28 (95% CI: –0.53, –0.04)
Garin *et al*, 1988	Decrease of more than 20% of their Cr clearance at end of trial	1/8	2/8	0.50 (95% CI: 0.06, 4.47)	–0.13 (95% CI: –0.50, 0.25)
Ponticelli *et al*, 1993	Remission at 1 yr	13/22	3/19	3.74 (95% CI: 1.25, 11.19)	0.43 (95% CI: 0.17, 0.70)
	Complete remission	7/22	0/19	13.04 (95% CI: 0.79, 214.34)	0.32 (95% CI: 0.11, 0.52)
	Partial remission	6/22	3/19	1.73 (95% CI: 0.50, 5.98)	0.11 (95% CI: –0.13, 0.36)
	Decrease in Cr clearance > 50% at 2 yrs	1/11	3/11	0.33 (95% CI: 0.04, 2.73)	–0.18 (95% CI: –0.50, 0.13)
	Infections	3/22	6/19	0.43 (95% CI: 0.12, 1.50)	–0.18 (95% CI: –0.43, 0.07)
	Gum hyperplasia	7/22	0/19	13.04 (95% CI: 0.79, 214.34)	0.32 (95% CI: 0.11, 0.52)
	Hypertrichosis	3/22	0/19	6.09 (95% CI: 0.33, 110.84)	0.14 (95% CI: –0.03, 0.30)
	Conjugated bilirubinemia	1/22	1/19	0.86 (95% CI: 0.06, 12.89)	–0.01 (95% CI: –0.14, 0.13)
	Headache	1/22	1/19	0.86 (95% CI: 0.06, 12.89)	–0.01 (95% CI: –0.14, 0.13)
	Bronchospasm	1/22	1/19	0.86 (95% CI: 0.06, 12.89)	–0.01 (95% CI: –0.14, 0.13)
	Parathesia	1/22	0/19	2.61 (95% CI: 0.11, 60.51)	0.05 (95% CI: –0.08, 0.17)
	Extrasystoles or anemia	0/22	1/19	0.29 (95% CI: 0.01, 6.72)	–0.05 (95% CI: –0.18, 0.08)

Focal segmental glomerulosclerosis: cytotoxic therapy

Date written: July 2005
Final submission: September 2005
Author: Merlin Thomas

GUIDELINES

No recommendations can be made due to conflicting Level I and Level II evidence.

SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on Level III and IV evidence)

Cytotoxic therapy in children with focal segmental glomerulosclerosis (FSGS)

Cytotoxic therapy with cyclophosphamide can induce remission in children with steroid–dependent nephrotic syndrome due to FSGS, or those with FSGS with steroid-related side-effects. (Level I-II evidence, conflicting)

A number of uncontrolled studies of cytotoxic therapy in children with FSGS have reported complete remission in between 32% and 65% of cases.

- **Hari *et al*[1] prospectively treated 65 children with idiopathic steroid–resistant nephrotic syndrome and FSGS with intravenous pulses of corticosteroids and oral cyclophosphamide. Dexamethasone (5 mg/kg) or methylprednisolone (30 mg/kg) were administered intravenously, initially as 6 pulses on alternate days, followed by 4 fortnightly and 8 monthly pulses. Oral cyclophosphamide therapy was given for 12 weeks and tapering doses of prednisolone were administered for 52 weeks. Of 59 patients who completed the initial alternate-day therapy, 17 experienced complete remission with a further 8 having partial remission. Thirty-four (57.6%) patients did not respond to treatment. The outcome in patients receiving intravenous dexamethasone ($n = 48$) or methylprednisolone ($n = 11$) was similar.**
- **Geary *et al*[2] described the response to cyclophosphamide in 29 steroid-resistant patients with idiopathic FSGS. Twenty of the patients were nephrotic when cyclophosphamide was started. Three of the nephrotic patients had a sustained remission of disease following treatment with cyclophosphamide. Nine nephrotic patients had partial responses. Of those responding, only one (1/9) progressed to end-stage kidney disease (ESKD). By contrast, 7 of the 8 non-responders had reached ESKD at the study completion.**
- **Tufro-McReddie *et al*[3] described the response to cyclophosphamide in 26 children presenting with idiopathic focal glomerulosclerosis, 22 of whom were steroid-resistant. Ten of these patients responded to cyclophosphamide within 16 weeks of starting therapy. Seven patients relapsed after a cyclophosphamide-induced remission, however, remission could be induced with steroid therapy in five of them, despite the fact that they were previously steroid-resistant.**
- **Tune *et al*[4] found progression to renal failure to be less frequent in children treated with cyclophosphamide.**
- **Tune and colleagues[5] reported a good response in treating steroid-resistant children with chlorambucil 0.15–0.2 mg/kg/day. Of 32 children treated with chlorambucil, 66% had a complete remission of proteinuria.**
- **Banfi *et al*[6] retrospectively reviewed the management of 59 patients of FSGS with nephrotic syndrome treated with corticosteroids and/or immunosuppressive drugs as primary therapy. Twenty-seven patients were initially treated with corticosteroids alone for 9.3 months; 19 patients received corticosteroids and immunosuppressive agents associated or every other month for 5.5 months; 13 patients received either azathioprine or cyclophosphamide alone for 25 months. Remission numbers were no different from that seen in those treated with steroid alone, although fewer relapses and more sustained remissions were noted with combination therapy.**

Cytotoxic therapy in adults with FSGS

Cytotoxic therapy with cyclophosphamide can induce remission in adults with steroid-dependent nephrotic syndrome due to FSGS, or those with steroid-related side-effects. (Level III-IV evidence, conflicting)

The potential role of cytotoxic therapy in the treatment of FSGS is controversial. Overall, there have been a number of small studies that suggest the addition of cytotoxics to prednisolone results in only an extra 10% of those who do not respond to prednisolone alone.[7] Although one study has suggested that a remission induced by prednisolone and cyclophosphamide lasts longer than one induced by prednisolone alone.[8] (Level III – IV evidence, conflicting results)

In adults who frequently relapse after steroid therapy has been discontinued or require continuous steroid therapy to sustain the remission, cytotoxic agents can induce remission. (Level III – IV evidence, conflicting results)

- **Ponticelli *et al*[8] reviewed 80 nephrotic adults with FSGS and plasma creatinine lower than 3 mg/dL. Patients were given corticosteroids (53 patients) or immunosuppressive agents (27 patients) as primary therapy for a**

median of 16 and 75 weeks, respectively. Forty-two patients responded with complete remission (29 patients, 36%) or partial remission (13 patients, 16%). There were no differences between steroid and cytotoxic groups.

• In a clinical series, Korbet *et al* reported that cyclophosphamide given at a dose of 2 mg/kg/day resulted in complete or partial remission in approximately 75% of cases.[9] However, in cases of steroid-resistance, cyclophosphamide was much less effective, with less than 25% deriving sustained benefit from an 8 to 12 week course of therapy. Similar results for treating FSGS with chlorambucil were also reported.

What dose should be used?

Where cytotoxics are to be used, therapy should be limited to a brief course only (3–4 months) because of the risk of significant toxicity, even if reduction in proteinuria is achieved. Most of the studies of cytotoxic therapy in primary FSGS have used 8 weeks of therapy. (Level IV evidence, anecdotal evidence)

Which agent, cyclophosphamide or chlorambucil?

In the absence of trials comparing cyclophosphamide with chlorambucil in patients with FSGS, experience with either agent and patient characteristics should be taken into consideration when choosing which cytotoxic agent to use. (Level IV evidence, conflicting evidence)

BACKGROUND

FSGS is one of the most common primary glomerular diseases that result in renal impairment and ultimately ESKD, and 40–80% of patients do not respond to corticosteroids. These patients are at increased risk for progressive renal disease and ESKD. In these patients, the induction of a complete or partial remission by other agents may improve or stabilize their renal function.[10] Those patients not receiving any treatment, or failing to respond to treatment, have a high risk of developing chronic renal failure.[11] The objective of this guideline is to evaluate the available clinical evidence pertaining to the impact of cytotoxic therapy used in combination with prednisone on renal functional decline in patients with idiopathic FSGS.

SEARCH STRATEGY

Databases searched: MeSH terms and text words for focal segmental glomerulosclerosis were combined with MeSH terms and text words for cyclophosphamide and antineoplastic agents. This search was carried out in Medline (1966 to September Week 2, 2004). The Cochrane Renal Group Trials Register was also searched for reflux nephropathy trials not indexed in Medline.
Date of searches: 17 September 2004.

WHAT IS THE EVIDENCE?

There are no randomised controlled studies of cytotoxic therapy alone as primary therapy in FSGS in children. There have been two studies in children with steroid–resistant nephrotic syndrome including a variable number of children with FSGS.

• In the International Study of Kidney Disease in Children,[12] 60 children with biopsy-diagnosed FSGS and with resistant nephrotic syndrome, were randomly allocated in a clinical trial comparing prednisone 40 mg/m^2 on alternate days for a period of 12 months (control group), with the same prednisone regimen plus a 90-day course of daily cyclophosphamide, 2.5 mg/kg in a single morning dose (experimental group). One-quarter of the children in each group had complete resolution of proteinuria. The proportions of children with increased, unchanged, and decreased proteinuria by the end of the study were similar in both groups. In addition, there was no significant difference in renal function between the intervention groups.

• The French Society of Pediatric Nephrology[13] conducted a randomized controlled trial (RCT) comparing the efficacy of chlorambucil (8 mg/kg) vs. a 3-month course of cyclosporin (6 mg/kg) in inducing sustained remission in 40 children with steroid–dependent idiopathic nephrotic syndrome and signs of steroid toxicity. Only one of the 20 patients treated with cyclosporin remained in remission 16 months after the end of treatment; in comparison, six of 20 receiving chlorambucil were still in remission at 27–49 months after the drug was stopped.

Two meta-analyses of children with steroid-resistant nephrotic syndrome have been performed (again including a variable percentage of patients with FSGS).

• Habashy *et al*[14] found insufficient evidence to comment on the possible effect of cytotoxic agents, although a marginal beneficial effect of oral cyclophosphamide could not be completely excluded.

• Latta *et al*[15] reviewed the effects of cyclophosphamide and chlorambucil in children with relapsing steroid–sensitive nephrotic syndrome, evaluating 38 studies comprising 1504 children and 1573 courses of cytotoxic drug therapy. They concluded that there was an overall increased rate of relapse-free survival with increasing doses of either alkylating agent, particularly in children with frequently relapsing nephrotic syndrome compared with steroid-dependent patients. In this study, chlorambucil appeared to have higher rates of severe side-effects than cyclophosphamide.

The utility of cyclophosphamide and chlorambucil has not been tested in an RCT in adults.

SUMMARY OF THE EVIDENCE

Cytotoxic therapy may be useful for inducing or maintaining remission in steroid-resistant patients or children with steroid dependence or frequent relapse. However, the data is conflicting with one large RCT demonstrating no effect. Moreover, any potential benefits must be balanced against

the significant risk of toxicity when using alkylating agents in children.

Three is no level I or II data on the efficacy of cytotoxic therapy in adults with FSGS.

WHAT DO THE OTHER GUIDELINES SAY?

Kidney Disease Outcomes Quality Initiative: No recommendation.
UK Renal Association: No recommendation.
Canadian Society of Nephrology: The use of cytotoxic therapy (cyclophosphamide and chlorambucil) may be considered as second-line therapy but the evidence is not conclusive.
European Best Practice Guidelines: No recommendation.
International Guidelines: No recommendation.

IMPLEMENTATION AND AUDIT

No recommendation.

SUGGESTIONS FOR FUTURE RESEARCH

No recommendation.

REFERENCES

1. Hari P, Bagga A, Jindal N *et al*. Treatment of focal glomerulosclerosis with pulse steroids and oral cyclophosphamide. *Pediatr Nephrol*. 2001; **16**: 901–5.
2. Geary DF, Farine M, Thorner P *et al*. Response to cyclophosphamide in steroid-resistant focal segmental glomerulosclerosis: a reappraisal. *Clin. Nephrol*. 1984; **22**: 109–13.
3. Tufro-McReddie A, Alvarez E, Arrizurieta E *et al*. Focal glomerulosclerosis in children: an Argentinian experience. *Pediatr Nephrol*. 1992; **6**: 158–61.
4. Tune BM, Kirpekar R, Sibley RK *et al*. Intravenous methylprednisolone and oral alkylating agent therapy of prednisone-resistant pediatric focal segmental glomerulosclerosis: a long-term follow-up. *Clin. Nephrol*. 1995; **43**: 84–8.
5. Tune BM, Lieberman E, Mendoza SA. Steroid-resistant nephrotic focal segmental glomerulosclerosis: a treatable disease. *Pediatr Nephrol*. 1996; **10**: 772–8.
6. Banfi G, Moriggi M, Sabadini E *et al*. The impact of prolonged immunosuppression on the outcome of idiopathic focal-segmental glomerulosclerosis with nephrotic syndrome in adults. A collaborative retrospective study. *Clin. Nephrol*. 1991; **36**: 53–9.
7. Passerini P, Ponticelli C. Treatment of focal segmental glomerulosclerosis. *Curr. Opin. Nephrol. Hypertens* 2001; **10**: 189–93.
8. Ponticelli C, Villa M, Banfi G *et al*. Can prolonged treatment improve the prognosis in adults with focal segmental glomerulosclerosis? *Am. J. Kidney Dis* 1999; **34**: 618–25.
9. Korbet SM, Schwartz MM, Lewis EJ. Primary focal segmental glomerulosclerosis: clinical course and response to therapy. *Am. J. Kidney Dis* 1994; **23**: 773–83.
10. Troyanov S, Wall CA, Miller JA *et al*. Focal and segmental glomerulosclerosis: definition and relevance of a partial remission. *J. Am. Soc. Nephrol*. 2005; **16**: 1061–8.
11. Burgess E. Management of focal segmental glomerulosclerosis: evidence-based recommendations. *Kidney Int. Suppl* 1999; **70**: S26–32.
12. Tarshish P, Tobin JN, Bernstein J *et al*. Cyclophosphamide does not benefit patients with focal segmental glomerulosclerosis. A report of the International Study of Kidney Disease in Children. *Pediatr Nephrol*. 1996; **10**: 590–3.
13. Niaudet P. Comparison of cyclosporin and chlorambucil in the treatment of steroid–dependent idiopathic nephrotic syndrome: a multicentre randomized controlled trial. The French Society of Paediatric Nephrology *Pediatr Nephrol*. 1992; **6**: 1–3.
14. Habashy D, Hodson E, Craig J. Interventions for idiopathic steroid-resistant nephrotic syndrome in children. *The Cochrane Database of Systematic Reviews*. 2004, Issue 3.
15. Latta K, von Schnakenburg C, Ehrich JH. A meta-analysis of cytotoxic treatment for frequently relapsing nephrotic syndrome in children. *Pediatr Nephrol*. 2001; **16**: 271–82.

APPENDICES

Table 1 Characteristics of included studies

Study ID (author, year)	N	Study Design	Setting	Participants	Intervention (experimental group)	Intervention (control group)	Follow up (months)	Comments
Niaudet, 1992	40	Randomised controlled clinical trial	Hospital, France	40 children with steroid-dependent idiopathic nephrotic syndrome and signs of steroid toxicity	Cyclosporine 6 mg/kg body wt per day over 3 mo, tapered dose	Chlorambucil at cumulative dose of 8 mg/kg body wt	24	
Tarshish *et al*, 1996	60	Randomised controlled clinical trial	Multicentre, US	60 children with biopsy-diagnosed FSGS	Prednisone 40 mg/m^2 on alternate days and 90-day course of daily cyclophosphamide 2.5 mg/kg	Prednisone 40 mg/m^2 on alternate days	42	

Table 2 Quality of randomised trials

Study ID (author, year)	Method of allocation concealment	Blinding			Intention-to-treat analysis	Loss to follow up (%)
		(participants)	(investigators)	(outcome assessors)		
Niaudet, 1992	Not stated	No	No	Not stated	Unclear	0.0
Tarshish *et al*, 1996	Central	No	No	Yes	Unclear	12.0

Table 3 Results for dichotomous outcomes

Study ID (author, year)	Outcomes	Intervention group (number of patients with events/number of patients exposed)	Control group (number of patients with events/number of patients not exposed)	Relative risk (RR) [95% CI]	Risk difference (RD) [95% CI]
Niaudet, 1992	Withdrawal of prednisone	18/20	16/20	1.13 (95%CI: 0.86, 1.46)	0.10 (95%CI: –0.12, 0.32)
	Minimal change in disease (renal biopsy)	17/20	19/20	0.89 (95%CI: 0.73, 1.10)	–0.10 (95%CI: –0.28, 0.08)
	FSGS	3/20	0/20	7.00 (95%CI: 0.38, 127.32)	0.15 (95%CI: –0.02, 0.32)
	Diffuse mesangial proliferation	0/20	1/20	0.33 (95%CI: 0.01, 7.72)	–0.05 (95%CI: –0.18, 0.08)
	Hypertension	1/20	0/20	3.00 (95%CI: 0.13, 69.52)	0.05 (95%CI: –0.08, 0.18)
	Hypertrichosis	8/20	0/20	17.00 (95%CI: 1.05, 276.03)	0.40 (95%CI: 0.18, 0.62)
	Gum hypertrophy	5/20	0/20	11.00 (95%CI: 0.65, 186.62)	0.25 (95%CI: 0.05, 0.45)
Tarshish *et al*, 1996	Mortality	3/35	2/25	1.07 (95%CI: 0.19, 5.95)	0.01 (95%CI: –0.14, 0.15)
	Treatment failure (≥ 30% serum Cr) or renal failure	20/35	9/25	1.59 (95%CI: 0.87, 2.88)	0.21 (95%CI: –0.04, 0.46)
	Complete resolution of proteinuria	8/35	6/25	0.95 (95%CI: 0.38, 2.40)	–0.01 (95%CI: –0.23, 0.21)
	Hypertensive seizure	1/35	1/25	0.71 (95%CI: 0.05, 10.89)	–0.01 (95%CI: –0.11, 0.08)

Focal segmental glomerulosclerosis: correction of secondary causes

Date written: July 2005
Final submission: September 2005
Author: Merlin Thomas

GUIDELINES

No recommendations possible based on Level I or II evidence

SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on Level III and IV evidence)
There are several case series documenting improvements in proteinuria and delay in progression to end-stage kidney disease (ESKD) following disease-specific interventions in patients with secondary focal segmental glomerulosclerosis (FSGS). (Level IV evidence variable response, anecdotal reports)

- **Anecdotal case reports suggest the potential for dramatic improvement in both renal function and structure in patients with HIV-FSGS with the use of HAART.[1–3] There are currently no well-controlled studies demonstrating the effect of long-term HAART on renal outcomes.**
- **Effective therapy of the malignancy may lead to remission of proteinuria in the rare patient with tumour-induced FSGS.**
- **FSGS may not regress after thymectomy in patients with thymoma.[4]**
- **FSGS does not remit on successful elimination of the living parasites in schistomosiasis-associated FSGS.[5]**
- **There are case reports where elimination of HCV infection has been associated with remission of proteinuria in patients with HCV–associated FSGS.[6]**
- **Obesity-associated FSGS may be improved by weight loss[7] and improvement of insulin sensitivity.[8]**

To be most effective, therapy needs to be given to patients with early histological lesions and mild proteinuria/renal impairment, hence the need for prompt identification of any underlying illness if patients are to be managed successfully. (Level IV evidence, anecdotal reports)

BACKGROUND

FSGS may be observed in patients with other conditions. These include a variety of immunological conditions (e.g. lymphoproliferative disorders, thymoma), chronic infections (e.g. HCV, HIV) and disorders associated with nephron depletion (e.g. vesicoureteric reflux). The objective of this guideline is to evaluate the available clinical evidence pertaining to the impact of disease-specific interventions on renal functional decline in patients with secondary FSGS. This guideline does not address the innate utility in treating these underlying disorders.

SEARCH STRATEGY

Databases searched: MeSH terms and text words for focal segmental glomerulosclerosis were combined with MeSH terms relating to secondary causes. This search was carried out in Medline (1966 to September Week 2, 2004).
Date of search: 17 September 2004.

WHAT IS THE EVIDENCE?

There have been no randomized controlled trials (RCTs).

SUMMARY OF THE EVIDENCE

No recommendations can be made.

WHAT DO THE OTHER GUIDELINES SAY?

Kidney Disease Outcomes Quality Initiative: No recommendation.
UK Renal Association: No recommendation.
Canadian Society of Nephrology: No recommendation.
European Best Practice Guidelines: No recommendation.
International Guidelines: No recommendation.

IMPLEMENTATION AND AUDIT

No recommendation.

SUGGESTIONS FOR FUTURE RESEARCH

No recommendation.

REFERENCES

1. Winston JA, Bruggeman LA, Ross MD *et al*. Nephropathy and establishment of a renal reservoir of HIV type 1 during primary infection. *N Engl. J Med* 2001; **344**: 1979–84.
2. Wali RK, Drachenberg CI, Papadimitriou JC *et al*. HIV-1-associated nephropathy and response to highly-active antiretroviral therapy. *Lancet* 1998; **352**: 783–4.
3. Levin ML, Palella F, Shah S *et al*. HIV-associated nephropathy occurring before HIV antibody seroconversion. *Am. J. Kidney Dis* 2001; **37**: E39.
4. Ishida I, Hirakata H, Kanai H *et al*. Steroid–resistant nephritic syndrome associated with malignant thymoma. *Clin. Nephrol*. 1996; **46**: 340–6.
5. Martinelli R., Pereira LJ, Brito E *et al*. Clinical course of focal segmental glomerulosclerosis associated with hepatosplenic *Schistosomiasis mansoni*. *Nephron*. 1995; **69**: 131–4.
6. Altraif IH, Abdulla AS, al Sebayel MI *et al*. Hepatitis C-associated glomerulonephritis. *Am. J. Nephrol*. 1995; **15**: 407–10.
7. Praga M, Hernandez E, Andres A *et al*. Effects of body-weight loss and captopril treatment on proteinuria associated with obesity. *Nephron*. 1995; **70**: 35–41.
8. Matsumoto H, Nakao T, Okada T *et al*. Insulin resistance contributes to obesity-related proteinuria. *Intern. Med*. 2005; **44**: 548–53.

Focal segmental glomerulosclerosis: use of other therapies

Date written: July 2005
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Author: Merlin Thomas

GUIDELINES

No recommendations possible based on Level I or II evidence

SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on Level III and IV evidence)
There have been a number of case series using mycophenolate mofetil in patients with resistant focal segmental glomerulosclerosis (FSGS). Most demonstrate that although mycophenolate mofetil can induce some reduction of proteinuria, complete remission of proteinuria is rare. No data on long-term follow-up evaluation with this drug are currently available.

- **Cattran *et al*[1] performed an open-label, 6-month trial of mycophenolate mofetil in 18 patients with biopsy-proven FSGS who were resistant to corticosteroid therapy. Seventy-five per cent had also failed to respond to a cytotoxic agent and/or a cyclosporin. A substantial improvement in proteinuria was seen in 44% (8/18) of patients by 6 months. However, no patient achieved complete remission. In addition, relapses were common after therapy was discontinued.**
- **Briggs *et al*[2] previously reported the use of mycophenolate mofetil in 7 patients, in whom a substantial improvement in proteinuria was also observed.**
- **Gellermann *et al*[3] investigated the effect of mycophenolate mofetil in 7 children with a resistant nephrotic syndrome (6 of whom had minimal change disease and one with FSGS). In this patient, mycophenolate mofetil resulted in complete remission for a follow-up of 28 months.**

Other therapies have been used in patients with FSGS who prove resistant to standard treatment:

- **Partial remission has been observed in a few case reports using tacrolimus.[4]**
- **Vincristine has also been used for the treatment of steroid- and cyclophosphamide–resistant nephrotic syndrome. In a series of eight cases presented by Goonasekera *et al*,[5] two children treated with vincristine achieved complete remission associated with preserved renal function. Another experienced transient relapses. Although studied in primary FSGS, there may be particular advantages of vincristine in secondary forms of nephrotic syndrome associated with malignancy (see Guideline titled "FSGS: cytotoxic therapy").**
- **Plasma exchange, lipid apheresis and immunoadsorption have also been reported to induce remission of proteinuria in selected patients.[6–8]**

BACKGROUND

Despite the use of steroids, cytotoxic therapy, and cyclosporin, some patients with idiopathic FSGS are unable to establish or maintain sustained clinical remission of proteinuria and progress inexorably toward end-stage kidney disease (ESKD). The objective of this guideline is to evaluate the available clinical evidence pertaining to the impact of interventions not covered in other guidelines on renal functional decline in patients with idiopathic FSGS.

SEARCH STRATEGY

Databases searched: MeSH terms and text words for focal segmental glomerulosclerosis were combined with MeSH terms and text words for mycophenolate mofetil, tacrolimus, vincristine, plasma exchange, lipid apheresis, immunoadsorption and other therapies. This search was carried out in Medline (1966 to September Week 2, 2004). The Cochrane Renal Group Trials Register was also searched for trials not indexed in Medline.
Date of searches: 17 September 2004.

WHAT IS THE EVIDENCE?

There have been no randomized controlled trials (RCTs) of these additional agents.

SUMMARY OF THE EVIDENCE

There is currently insufficent evidence for any specific benefit from other therapies in the treatment of resistant nephrotic syndrome due to focal and segmental glomerulosclerosis.

WHAT DO THE OTHER GUIDELINES SAY?

Kidney Disease Outcomes Quality Initiative: No recommendation.
UK Renal Association: No recommendation.
Canadian Society of Nephrology: No recommendation.
European Best Practice Guidelines: No recommendation.
International Guidelines: No recommendation.

IMPLEMENTATION AND AUDIT

No recommendation.

SUGGESTIONS FOR FUTURE RESEARCH

No recommendation.

REFERENCES

1. Cattran DC, Wang MM, Appel G *et al*. Mycophenolate mofetil in the treatment of focal segmental glomerulosclerosis. *Clin. Nephrol.* 2004; **62**: 405–11.
2. Briggs WA, Choi MJ, Scheel PJ Jr. Successful mycophenolate mofetil treatment of glomerular disease. *Am. J. Kidney Dis* 1998; **31**: 213–7.
3. Gellermann J, Querfeld U. Frequently relapsing nephrotic syndrome: treatment with mycophenolate mofetil. *Pediatr Nephrol.* 2004; **19**: 101–4.
4. McCauley J, Tzakis AG, Fung JJ *et al*. FK 506 in steroid-resistant focal sclerosing glomerulonephritis of childhood. *Lancet* 1990; **335**: 674.
5. Goonasekera CD, Koziell AB, Hulton SA *et al*. Vincristine and focal segmental sclerosis: do we need a multicentre trial? *Pediatr Nephrol.* 1998; **12**: 284–9.
6. Hattori M, Chikamoto H, Akioka Y *et al*. A combined low-density lipoprotein apheresis and prednisone therapy for steroid-resistant primary focal segmental glomerulosclerosis in children. *Am. J. Kidney Dis* 2003; **42**: 1121–30.
7. Haas M, Godfrin Y, Oberbauer R *et al*. Plasma immunadsorption treatment in patients with primary focal and segmental glomerulosclerosis. *Nephrol. Dial Transplant* 1998; **13**: 2013–6.
8. Mitwalli AH. Adding plasmapheresis to corticosteroids and alkylating agents: does it benefit patients with focal segmental glomerulosclerosis? *Nephrol. Dial Transplant* 1998; **13**: 1524–8.