

Lipids

Date written: July 2004

Final submission: July 2004

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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 (Ravid et al 1998, Krolewski et al 1994, Yang et al 1999). Studies in experimental CKD have suggested that treatment with statins retards the progression of kidney disease in animals (Oda et al 1997). 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 Specialised 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) (Lam et al 1995, Smulders et al 1997, Thomas et al 1993, Hommel et al 1992, Olbricht et al 1999, Bianchi et al 2003, Tonelli et al 2003, Fried et al 2001, Imai et al 1999); 1 meta-analysis (Fried et al 2001); 1 prospective controlled study (Rayner et al 1996); 2 prospective crossover studies

(Tonolo et al 1997); and 3 prospective non-controlled studies (Fuiano et al 1996, Nielsen et al 1993, Scanferla et al 1991). All the available individual studies have been limited by small numbers and generally short follow-up times.

Thomas et al (1993) 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 (Bianchi et al 2003). 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 to 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 hours (-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 (2003) 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 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 m²/year slower than placebo (95% CI, -0.1 to 1.2; $P = 0.07$) in those with MDRD-GFR < 50 mL/min, and 2.5 mL/min per 1.73 m²/year slower (95% CI, 1.4 to 3.6 slower; $P = 0.0001$) in those with MDRD-GFR < 40 mL/min per 1.73 m²/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 (1999), 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 $> 40 \text{ mL/min/1.73 m}^2$. 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 (Olbricht 1997). A cholesterol-lowering efficacy paper has been published by a group in 1999 (Olbricht et al 1999), even though the primary renal outcome data have not appeared in print.

A 2-year, randomised, double-blind, placebo-controlled pilot trial of simvastatin versus placebo was conducted in 39 Type 1 diabetics without overt nephropathy (Fried et al 2001). 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, $P < .001$), 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 (1996) reported a prospective, open-label, controlled trial of simvastatin in 17 hypercholesterolaemic (cholesterol $> 6.1 \text{ mmol/L}$) 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 (1999) 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 $251.4 \pm 7.3 \text{ mg/dl}$ to $218.2 \pm 6.5 \text{ mg/dl}$, whilst no significant change was observed in the placebo group. Serum creatinine concentration rose in the placebo group from 1.6 ± 0.07 to $2.1 \pm 0.2 \text{ mg/dl}$, but did not change in the pravastatin group (1.3 ± 0.07 to $1.3 \pm 0.09 \text{ mg/dl}$). 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 (Nielsen et al 1993), or proteinuria (Lam et al 1995) 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). 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 (Tonolo et al 1997) 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 (1997) 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 (Golper et al 1989, Kasiske et al 1990, Elisaf et al 1991) or a slower decline (Gonzalo et al 1994, Chan et al 1992, Rabelink et al 1990) 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 (Hommel 1992), although a beneficial effect on albuminuria was reported for pravastatin after 9 weeks (Sasaki 1990).

Fried et al (2001) 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 to 0.285 mL/min/month, P = 0.008). There was a tendency for a favorable 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-randomised controlled trials.

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 hyper-cholesterolaemic 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 (eg the SHARP trial) should also assess the effects of such treatments on renal failure progression.

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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	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	39	Randomised double-blind placebo-controlled trial	Single centre	39 adult patients who have had insulin-dependent diabetes mellitus for at least 10 yrs; LDL cholesterol 100–160 mg/dl, AER < 200 microg/min	10 mg/day simvastatin	Placebo	24	
Hommel et al, 1992	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	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	36	Randomised single-blind placebo-	Single centre	36 Chinese NIDDM patients with mild to moderate	Lovastatin 20 mg/day as a single evening dose; increased by 20 mg/day at	Placebo	24	

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Study ID (author, year)	N	Study Design	Setting	Participants	Intervention (experimental group)	Intervention (control group)	Follow up (months)	Comments
		controlled trial		hypercholesterolaemia and proteinuria	6 wk intervals if fasting total cholesterol remained > 5.2 mmol/L.			
Olbricht et al, 1999	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	15	Randomised placebo-controlled trial	Single centre	15 normotensive NIDDM patients with hypertriglyceridaemia (> 2.5 mmol L ⁻¹) and microalbuminuria	Gemfibrozil 600 mg b.i.d	Placebo	12	
Thomas et al, 1993	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 20–40mg/day if required for 24 weeks	Placebo	6	
Tonelli et al, 2003	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	Randomly assigned in a blinded fashion	No	No	No	Unclear	0
Fried et al, 2001	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	Not specified	Yes	Yes	No	No	19.2% (5/26)
Imai et al, 1999	Not specified	No	No	No	No	8% (5/62)
Lam et al, 1995	Block randomisation	Yes	No	No	No	5.6% (2/36)
Olbricht et al, 1999	Not specified	Yes	Yes	No	No	23% (13/56) after 24 months
Smulders et al, 1997	Not specified	Yes	Unclear	No	Unclear	0
Thomas et al, 1993	Not specified	Yes	Yes	No	No	23.3% (7/30)
Tonelli et al, 2003	Computerised randomisation	Yes	Yes	No	Time-to-event analyses	Unclear