ELSEVIER

Atherosclerosis 196 (2008) 823–834

ATHEROSCLEROSIS

www.elsevier.com/locate/atherosclerosis

Dyslipidaemia and cardiorenal disease: mechanisms, therapeutic opportunities and clinical trials

Doris T. Chan [a,b], Ashley B. Irish [b], Gursharan K. Dogra [a,b], Gerald F. Watts [a,*]

[a] *Metabolic Research Centre, School of Medicine and Pharmacology, University of Western Australia, Perth, Western Australia 6000, Australia*
[b] *Department of Nephrology and Transplantation, Royal Perth Hospital, Perth, Western Australia 6000, Australia*

Received 8 August 2006; received in revised form 13 December 2006; accepted 22 January 2007
Available online 6 March 2007

Abstract

Dyslipidaemia is an important risk factor for the development of chronic kidney disease (CKD) and cardiovascular disease (CVD). CKD generates an atherogenic lipid profile, characterised by high triglycerides, low high-density lipoprotein (HDL) cholesterol and accumulation of small dense low-density lipoprotein (LDL) particles, comparable to that in the metabolic syndrome. These changes are due specifically to the effects of CKD on key enzymes, transfer proteins and receptors involved in lipid metabolism. Dyslipidaemia is further compounded by dialysis, immunosuppressive drugs, and concomitant diseases such as diabetes mellitus. Post hoc analyses from large intervention trials suggest the benefit of statins in patients with early CKD, but prospective clinical trials in haemodialysis (HD) and renal transplant recipients have not conclusively shown improvements in hard cardiovascular end-points. The lack of efficacy of statins in late-stage CKD could be a consequence of other disease processes, such as calcific arteriopathy and insulin resistance, which are not modified by lipid-lowering agents. Despite uncertainty and pending the results of ongoing statin trials such as Study of Heart and Renal Protection (SHARP) and AURORA (A study to evaluate the Use of Rosuvastatin in subjects On Regular haemodialysis: an Assessment of survival and cardiovascular events), major international guidelines continue to support statin therapy in CKD and renal transplant patients to reduce cardiovascular risk burden. Because of increased risk of toxicity, particularly myopathy, statins and other lipid-regulating agents should be used cautiously in CKD and renal transplant recipients.

Keywords: Chronic kidney disease; Dyslipidaemia; Lipoproteins

1. Introduction

The last decade has brought renewed interest into the relationship between dyslipidaemia, cardiovascular disease (CVD) and chronic kidney disease (CKD). Cardiovascular morbidity and mortality is increased in patients who reach end-stage renal disease (ESRD) [1], as well as in milder degrees of renal dysfunction [2–4]. In Australia and New Zealand, 40% of deaths in dialysis patients and 23% of deaths in those with functioning renal transplants were attributable to cardiac events such as myocardial infarction, heart failure and arrhythmias (http://www.anzdata.org.au/anzdata/AnzdataReport/28thReport/files/). Unlike the general population, the risk of sudden cardiac death is disproportionately increased in ESRD and renal transplant patients presumably from arrhythmias and uraemic cardiomyopathy [5].

The precise mechanisms for excess CVD in CKD patients have not been fully elucidated. Atherosclerosis in CKD is profoundly accelerated and characterised by more advanced, heavily calcified plaques which extends to both the intima and medial layers of the arterial wall [6]. Coronary artery vessel wall undergo concentric arterial remodelling [6], which may partly account for increased arterial stiffness reported in this population [7–9]. Furthermore, the relative contribution

* Corresponding author at: Metabolic Research Centre, School of Medicine and Pharmacology, University of Western Australia, Western Australia 6000, Australia. Tel.: +61 8 9220245; fax: +61 8 9220246.
E-mail address: gerald.watts@uwa.edu.au (G.F. Watts).

0021-9150/$ – see front matter © 2007 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.atherosclerosis.2007.01.023

Table 1
Stages of chronic kidney disease

Stage	Description	GFR (mL/min/1.73 m^2)
1	Kidney damage with normal or ↑ GFR	>90
2	Kidney damage with mild ↓ GFR	60–89
3	Moderate ↓ GFR	30–59
4	Severe ↓ GFR	15–29
5	Kidney failure	<15 or dialysis

From the kidney disease outcomes quality initiative clinical practice guidelines for chronic kidney disease: evaluation, classification and stratification (GFR: glomerular filtration rate).

of dyslipidaemia to CVD risk in CKD patients remains unclear.

In this review, we focus on the mechanisms whereby CKD induces dyslipidaemia and the consequences for CVD. Within this context, we also review the clinical evidence and recommendations for the use of lipid-regulating therapy in patients with CKD.

2. Pathogenesis of lipoprotein abnormalities in CKD

CKD is now staged according to glomerular filtration rate (GFR) and presence of structural damage (see Table 1). Regardless of the aetiology of renal disease, patients with CKD develop complex qualitative and quantitative abnormalities in lipid and lipoprotein metabolism. These changes and the underlying molecular mechanism have been the subject of a recent review [10]. In brief, classic uraemic dyslipidaemia is characterised by raised triglyceride, low high-density lipoprotein (HDL) and normal total cholesterol concentration (see Table 2). These qualitative defects become more pronounced with advancing renal failure (stages 4 and 5) and modified by renal replacement therapy, renal transplantation, co-morbid conditions (e.g. diabetes mellitus) and concurrent medications (e.g. steroids, cyclosporine).

2.1. Chronic kidney disease

Lipoprotein metabolism is a dynamic system that can be disturbed in CKD owing to alterations in apolipoproteins, lipid transfer proteins, lipolytic enzymes and lipoprotein receptors (summarised in Table 3). When GFR falls below 60 mL/min (CKD stage 3), there is a fall in the ratio of apolipoprotein AI (apoAI) to apolipoprotein CIII (apo CIII) in spite of normal cholesterol and triglyceride concentrations [11–13]. As renal function deteriorates in non-nephrotic patients with CKD, triglyceride concentrations increase while HDL concentrations declines [14] and there is accumulation of the more atherogenic, small dense low-density lipoprotein (LDL) particles [15].

In stages 4 and 5 of CKD, there is decreased concentration of apoA-containing lipoproteins, increased concentrations of triglyceride-rich apo B-containing lipoproteins and serum lipoprotein (a). Reduced catabolism and clearance of triglyceride-rich apoB-containing lipoproteins is a consequence of: (a) decreased activity of lipolytic enzymes, such as lipoprotein lipase (LPL) and hepatic lipase (HL); (b) reduced receptor-mediated uptake via the hepatic LDL-receptor related protein (LRP) and VLDL receptors [16]; (c) accumulation of certain inhibitors of LPL such as pre-β HDL [17]. Impaired clearance of triglyceride-rich lipoproteins is further compounded by reductions in apolipoprotein CII (apo CII) and apolipoprotein E (apoE). Impaired divalent ion metabolism arising from parathyroid gland hyperplasia in CKD stage 3–5 may also adversely affect lipoprotein metabolism by suppressing LPL and HL activities [18]. Postprandial lipoprotein metabolism is also impaired in CKD, resulting in accumulation of chylomicron (CM) particles and their remnants [19]. Reduction in the expression of HL and downregulation of LRP in uraemia may also account for the accumulation of remnant lipoproteins [20]. Maturation of HDLs is impaired due to decreased plasma lecithin cholesterol acyltransferase (LCAT) activity and gene expression [21]. Plasma HDL concentration also falls in uraemia due to decreased expression of both apo AI and AII.

The dyslipidaemia of CKD has similar features to the metabolic syndrome. The metabolic syndrome, including type 2 diabetes, is known to predispose to CKD [22], which

Table 2
Changes in plasma lipid concentrations in CKD and renal replacement therapy

	Nephrotic syndrome	CKD stage 1–4	CKD stage 5	Haemodialysis	Peritoneal dialysis	Post renal transplant
Total cholesterol	↑↑	↔	↔	↔	↑↑	↑
Triglyceride	↑↑	↔ or ↑	↑	↑	↑↑↑	↔ or ↑↑
LDL-cholesterol	↑	↔ or ↑ (but ↑ small dense particles)	↔ or ↓ (but ↑ small dense particles ↑)	↔ or ↓ (but ↑ small dense particles)	↑	↔ or ↑
HDL-cholesterol	↓	↓ or ↔	↓	↓	↓	↔

Table 3
Alterations in plasma lipoprotein metabolism in CKD: in relation to effects on to apolipoproteins, enzymes, receptors and lipid transfer proteins

	Plasma lipoprotein changes	Apolipoproteins	Enzymes	Receptors	Transfer proteins
VLDL/IDL	↑ VLDL-C	↓ Apo CII	↑ DGAT in heavy proteinuria	↓ VLDL receptor	↑ CETP levels (with proteinuria)
	↓ VLDL-Tg	↓ Apo E	↓ LPL activity		
	↑ IDL	↑ Apo CIII	↓ HL activity		
		↓ Apo CII/III ratio	↑ ACAT		
LDL	↓ LDL-C		↑ HMG CoA reductase in heavy proteinuria	Acquired LDL-R deficiency in heavy proteinuria	
	↑ LDL-Tg		LDL deficiency		
	↑ Lp(a)				
	↑ Small dense LDL				
HDL	↓ HDL-C	↓ Apo A-I	↓ LCAT activity	↓ Hepatic HDL receptor (SRB-1) in heavy proteinuria	
	↑ HDL-Tg	↓ Apo A-II	↑ ACAT activity in proteinuria		
	Impaired maturation of HDL3	↓ Apo A-I/Apo CIII ratio			
Chylomicrons	↑ Chylomicron remnants		↓ HL activity	↓ Hepatic LRP	

VLDL, IDL, LDL, HDL: very low-density, intermediate density, low-density and high-density lipoprotein; Lp(a): lipoprotein a; HMG CoA reductase: 3-hydroxy-3-methylglutaryl-coenzyme A; apo: apolipoprotein; DGAT: acyl-CoA diaglycerol acyltransferase; Tg: triglyceride; LPL: lipoprotein lipase; HL: hepatic lipase; LCAT: lecithin cholesterol acyltransferase; ACAT: acyl-CoA cholesterol acyltransferase; CETP: cholesterol ester transfer protein; LRP: LDL receptor-related protein; FCR: fractional catabolic rate; CM: chylomicron.

in turn aggravates insulin resistance and promotes dyslipidaemia. Insulin resistance increases free fatty acid (FFA) supply from adipocytes to increase hepatic lipogenesis, and this stimulates hepatic secretion of apo B100 containing lipoproteins specifically large triglyceride-rich VLDL particles (S_f 60–100) [23]. Impaired insulin signalling in skeletal muscles and adipose tissue also slows the catabolism of all triglyceride-rich containing lipoproteins, including large VLDL and CM particles. Expansion in the VLDL particle pool size impacts on the remodelling of LDL and HDL in an atherogenic direction.

2.2. Nephrotic syndrome

Nephrotic syndrome is a clinical entity characterised by marked proteinuria (>3.5 g per 1.73 m^2 per 24 h), hypoalbuminaemia, peripheral oedema, hyperlipidaemia and lipiduria. It has diverse reno-specific and systemic aetiologies that damage the glomerular basement membrane. Patients with nephrotic syndrome (NS) and preserved GFR exhibit a highly atherogenic profile, with markedly elevated plasma cholesterol and triglyceride concentrations and increased VLDL, LDL, IDL and Lp(a) levels [24–28]. Depressed plasma HDL-cholesterol concentrations also accompanies the increase in triglyceride concentration [26,27].

Changes in lipoprotein concentration and composition in NS may be due to a combination of increased synthesis and decreased catabolism of lipoproteins. Hypercholesterolaemia is due to upregulation of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG CoA) reductase [29] and acquired LDL receptor deficiency [30]. Hypertriglyceridaemia arises from increased hepatic VLDL synthesis driven by upregulation of hepatic acyl-CoA diaglycerol acyltransferase (DGAT) [31]. There is decreased catabolism of triglyceride-rich lipoproteins related to reduced LPL, HL and VLDL receptor activity [26,27] and impaired cycling of apo CII [26]. The secretion of both LDL and Lp(a) may be increased in NS, and this is independent of the degree of hypoalbuminaemia [24]. Reduced activity of LCAT enzyme impairs maturation of HDL by blocking one of the initial steps of 'reverse cholesterol transport' [27]. Elevated cholesteryl-ester transfer protein (CETP) activity in nephrotic patients also decreases HDL-cholesterol concentration while reciprocally increasing HDL-triglyceride concentration, thereby remodelling the HDL particle [27].

However, despite the above lipoprotein changes, studies have not shown a consistent relationship between NS, in the absence of uraemia, and increased risk of CVD [32,33]. Although the significance of dyslipidaemia in NS alone may be questionable, the presence of other risk factors such as endothelial dysfunction, hypertension, hypercoagulability and use of corticosteroids can compound the risk of CVD in this group of patients.

2.3. Haemodialysis

With haemodialysis (HD), dyslipidaemia is typified by a marked increase in triglyceride-rich apo B-containing particles, decreased in HDL concentration and a predominance of small dense LDL particles [34]. LDL-cholesterol concentrations are often normal, but serum Lp(a) concentration is increased [34,35]. There is a persistent disturbance in the

apolipoprotein profile, with reduced apo AI and apo AII concentrations and significant increases in apoB, apoCIII and apoE concentrations [35,36].

Chronic HD increases hepatic secretion of VLDLs, which is partly related to insulin resistance [37]. Delayed catabolism of VLDL can also result from decrease in the ratio of apo CII to CIII and reduction in LPL and HL activities [34]. Repeated exposure to unfractionated heparin also depletes endothelial-bound LPL, thereby impairing the clearance of triglyceride-rich lipoproteins [11].

2.4. Peritoneal dialysis

Peritoneal dialysis (PD) induces a particularly atherogenic lipid profile, with higher cholesterol, triglyceride, IDL, VLDL, LDL and Lp(a) concentrations compared with HD [23,35,36,38]. ApoA-containing HDL particles are however, equally reduced in both forms of renal replacement therapy [36].

Increased plasma concentrations of both triglyceride-rich and cholesterol-rich apo B-containing lipoproteins in PD patients is due to overproduction and reduced clearance of VLDL particles, together with increased formation of small dense LDL particles [23]. Co-existent insulin resistance and glucose loading from peritoneal dialysate increase FFA availability and de novo lipogenesis, key triggers to VLDL secretion [23]. Increased clearance of apolipoproteins across the peritoneal membrane during PD can also trigger profound dyslipidaemia, comparable to NS.

2.5. Renal transplantation

Hyperlipidaemia with increased total cholesterol and triglyceride concentrations has been reported in 20–80% of renal transplant recipients [39,40]. Plasma HDL cholesterol concentrations are usually normal, although qualitative changes in HDL have been reported [41,42]. Serum Lp (a) level may be normal or increased following renal transplantation [43,44].

Immunosuppressive agents play a major role in post-transplant dyslipoproteinaemia. Treatment with cyclosporine (CsA) alone or in combination with azathioprine and prednisolone elevates plasma triglyceride and triglyceride-enriched VLDL, LDL and Lp (a) levels while depressing HDL-cholesterol concentration [43,45]. Another calcineurin inhibitor, tacrolimus, does not raise LDL-cholesterol and blood pressure to the same extent as CsA, and may therefore be less atherogenic [46]. Molecular target of rapamycin (mTOR) modulators, such as sirolimus and everolimus, are new generation immunosuppresants that dose-dependently exacerbate both hypercholesterolaemia and hypertriglyceridaemia, although there is attenuation of the effect over time [47].

The mechanisms for the adverse effect of immunosuppressive medications on lipids and lipoproteins are not clearly understood. Corticosteroids may exacerbate dyslipidaemia by inducing insulin resistance. While hepatic VLDL synthesis is enhanced by increase in acetyl-coenzyme A carboxylase and FFA synthase activities, there is also impaired VLDL catabolism due to inhibition of LPL activity [48]. Steroid-induced dyslipidaemia also involves downregulation of LDL receptor from increase in HMG CoA reductase activity [49] and iatrogenic ACTH deficiency [50]. CsA interferes with LDL receptor activity through suppression of hepatic cholesterol 7α-hydroxylase [51]. CsA increases VLDL-triglyceride concentrations by inhibiting LPL activity and impairs HDL maturation by decreasing LCAT activity [51]. Likewise, sirolimus can significantly increase the hepatic secretion of VLDL by increasing adipocyte hormone-sensitive lipase activity and fatty acid flux to the liver [48,52]. It can also impair the catabolism of VLDLs by decreasing LPL activity [53] and increasing the plasma concentrations of its inhibitor, apo CIII [54]. Hypercholesterolaemia with sirolimus is related to decreased catabolism of LDL [53].

Other factors that exacerbate post-transplant dyslipidaemia include pre-transplant hyperlipidaemia, increased age at transplantation, use of anti-hypertensive medications such as beta-blockers and diuretics and degree of renal dysfunction [44].

2.6. Summary

There are a plethora of defects in lipoprotein metabolism in patients with CKD stages 3–5, as well as in dialysis and renal transplant recipients. The defects result from a combination of overproduction and clearance defects in apo B-contaning lipoproteins that arise from perturbations in lipid substrates, enzymes, lipid transfer proteins and lipoprotein receptor activities. Overall, CKD is characterised by an atherogenic lipid profile, comparable but not identical, to the metabolic syndrome. Beyond the complex metabolic sequelae of uraemia in CKD, the dyslipidaemia of CKD may reflect co-existent insulin resistance, diabetes, dialysis modality, and effects of concurrent medications.

3. Clinical consequences of dyslipidaemia in CKD

3.1. Cardiovascular consequences

3.1.1. Observational data

Unlike the general population, lower plasma cholesterol has been associated with a higher cardiovascular mortality in dialysis patients, generating the concept of “reverse causality” [55–57]. However, after adjusting for malnutrition and inflammation, there is a positive correlation between elevated cholesterol and death from CVD similar to non-renal populations [56,57]. Thus, “reverse causality” more likely reflects malnutrition and chronic inflammation rather than a protective effect of high cholesterol on CVD [56].

Several studies linking non-HDL cholesterol [58], HDL cholesterol [59] and IDL cholesterol [60] with surrogate markers of cardiovascular disease such as common carotid

artery intima media thickness (CCA-IMT) and aortic stiffness lend further support for a causal role for dyslipidaemia in uraemic CVD.

3.1.2. Interventional data

Large-scale primary and secondary prevention trials in non-renal populations clearly show that statins decrease the incidence of cardiovascular morbidity and mortality [61,62]. Furthermore, recent clinical trials suggest greater clinical benefit with more intensive LDL lowering (<70 mg/dL or 1.8 mmol/L) in high risk patients with coronary artery disease [63–65]. The specific nature of atherosclerotic vascular disease in CKD does not however, strictly allow extrapolation of the results of the clinical statin trials to renal populations.

Table 4 summarises clinical trials (post hoc and prospective data) specifically in CKD and renal transplant patients. Post-hoc analysis of large clinical trials [66–68] and pooled data from The Pravastatin Pooling Project [69] show that lipid-regulating therapy lowers all-cause mortality and CV events in patients with stages 1–3 CKD. Disappointingly, the benefit of statins has not been replicated in prospective trials of patients with more advanced CKD. The Die Deutsche Diabetes Dialyse (4D) study, a randomised placebo controlled trial of HD patients with type 2 diabetes, reported a non-significant 8% decrease over 4 years in the primary composite endpoint (death from cardiac causes, fatal stroke, nonfatal myocardial infarction or nonfatal stroke) with atorvastatin 20 mg daily [70]. Consistent with these findings, a small but well-conducted trial in CKD stages 4–5 and HD patients showed that intensive multiple risk factor modifications, including a 30% reduction in LDL-cholesterol with statins, was not associated with improvements in CCA-IMT and endothelial function [71].

The addition of ezetimibe, a selective inhibitor of cholesterol absorption, to simvastatin has been shown in a pilot study of predialysis and dialysis patients to result in a 21% further reduction in LDL-cholesterol compared with simvastatin monotherapy [72]. Whether more intensive LDL-cholesterol lowering in CKD translates into improved cardiovascular outcomes will hopefully be answered by the ongoing SHARP study.

In the Assessment of Lescol in Renal Transplantation (ALERT) trial, a randomised trial of over 2000 renal transplant recipients, fluvastatin was associated with a significant 35% reduction in the incidence of myocardial infarction (MI) and cardiac death and a non-significant 13% reduction in the primary composite endpoint of major adverse cardiovascular event (MACE), cardiac death, MI, or coronary intervention procedure [73]. Lipid levels predicted the risk for nonfatal MI but not sudden cardiac death in a post hoc analysis of the ALERT study [74]. In the ALERT extension study, there was a significant reduction in MACE in the fluvastatin-treated patients after a mean follow-up of 6.7 years, suggesting a delayed cardiovascular benefit with statin therapy post-transplantation [75]. There is also evidence for greater reduction in cardiovascular events with early, aggressive use of fluvastatin in this group [76]. However, reduction in all-cause and cardiovascular mortality in CKD and renal transplant recipients remains to be proven.

Hypertriglyceridaemia and low HDL concentrations are common lipoprotein abnormalities in patients with CKD. Fibrates effectively lower triglycerides and elevate HDL-cholesterol concentrations which could match or complement the cardiovascular benefits of statins. Post hoc analysis of the Veterans' Affairs High Density Lipoprotein Intervention Trial (VA-HIT) demonstrated lower cardiovascular events with gemfibrozil in patients with creatinine clearance (CrCl) less than 75 ml/min [68]. One specific concern is that fenofibrate may increase serum creatinine [77], but this may not reflect a true reduction in GFR. Further study is required to determine the role of fibrates in patients with renal impairment.

3.2. Progression of CKD

Slowing the progression of renal disease by lipid-regulating agents could indirectly lead to reduction in CVD in this population. The contribution of dyslipidaemia to progression of CKD is supported by animal studies. Two meta-analyses [78,79] and several post hoc analyses of large interventional studies [66,69] provide further evidence that statins slow decline in GFR. The Greek Atorvastatin and Coronary Heart Disease Evalutation (GREACE) trial reported that atorvastatin prevented decline in CrCl over 3 years in coronary patients with normal renal function at baseline [80]. Intensive lipid lowering with 80 mg of atorvastatin for 5 years was also associated with attenuation in decline in renal function compared with 10 mg of atorvastatin, in a post hoc analysis in the Treating to New Targets (TNT) Trial [81]. However, the most recent systematic review which evaluated up to 40,000 participants revealed that statins only had a modest effect on slowing decline in GFR and was significant only in those with known CVD [79].

Statins may have a protective effect on graft survival in hypertriglyceridaemic patients following transplantation [82], although the ALERT study failed to show a beneficial effect of fluvastatin on graft function post-transplantation [83]. However, a recent retrospective analysis reported that early introduction of a statin improved functional and histological graft outcome 1-year following renal transplantation [84]. This suggests a role for early institution of statin therapy in renal transplant recipients [76].

Fenofibrate has been shown to decrease albuminuria in type 2 diabetes in a post-hoc analysis of a small angiographic trial [85] and the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study [77]. LDL-lowering with cholestyramine does not benefit renal function in hypercholesterolaemic subjects [86]

3.2.1. Summary

Although the post hoc analyses referred to above suggest a benefit of statins in early stage CKD, similar results have not

Table 4
Clinical trials of lipid lowering therapy in CKD and renal transplant patients

Trial	Design	Population	Size	Intervention	Duration	Outcome
PPP(69)	Post hoc subanalysis of WOSCOP, CARE, LIPID	Moderate CKD (CG-GFR 30–59 ml/min per 1.73 m^2)	$N = 4491$	Pravastatin 40 mg/day	∼5 years	↓ Risk (HR 0.77) of adjusted incidence of primary outcome (coronary mortality, nonfatal MI, coronary revascularisation) Pravastatin reduced risk (HR 0.86) of total mortality
HPS (66)	Post hoc, sub analysis	CKD (sCr > 110 μmol/L for women and >130 μmol/L for men but <200 μmol/L)	$N = 1329$	Simvastatin 40 mg/d	5 years	↓ Risk of (HR 0.72) of major vascular events
ASCOT-LLA(67)	Post hoc, sub analysis	Renal dysfunction (microalbuminuria, proteinuria)	$N = 6517$	Atorvastatin 10 mg/d	3.3 years	↓ Risk (HR 0.61) of primary end-point (combined nonfatal MI and fatal CHD)
VA-HIT(68)	Post hoc, sub analysis	Pre dialysis CKD (CrCl ≤ 75 ml/min by Cockgroft Gault)	$N = 1046$	Gemfibrozil 1200 mg/d	5.3 years	↓ Risk (HR 0.73) of primary outcome (coronary death or nonfatal MI) and ↓ risk (HR 0.74) of combined outcome of coronary death, nonfatal MI or stroke
ALERT(73)	Prospective placebo-controlled RCT	Renal transplant patients	$N = 2102$	Fluvastatin 40 mg/d	5.4 years	Non-significantly ↓ (17%) primary endpoint (cardiac death, nonfatal MI, coronary revascularisation including CABG and percutaneous coronary intervention) ↓ (35%) combined endpoint of cardiac death or definite MI
4D(70)	Randomised placebo-controlled	Diabetic HD	$N = 1255$	Atorvastatin 20 mg	4 years	Non-statistically significant 8% ↓ in composite endpoint Significant 18% ↓ in cardiac events
SHARP(95)	Prospective double-blind RCT	Pre dialysis	9000 (6000 pre dialysis and 3000 dialysis)	Simvastatin 20 mg and ezetimibe 10 mg	At least 4 years (will report in 2008)	Major vascular events (nonfatal MI or cardiac death, nonfatal or fatal stroke, or revascularisation)
		HD				Rate of progression to ESRD in pre dialysis patients
		PD				Cause of death, major cardiac events (nonfatal MI or cardiac death, stroke and hospitalisation for angina)
AURORA (96)	Prospective double-blind RCT	Chronic HD	3000 HD	Rosuvastatin 10 mg/d	Until 620 experienced major CV event	Time to major CV event (CV death, fatal MI, or nonfatal stroke) All cause mortality, CV event free survival, CV death, non-CV death, procedures as a result of stenosis or thrombosis of vascular access, and coronary or peripheral revascularisation)

PPP: Pravastatin Pooling Project; WOSCOPS: West of Scotland Coronary Prevention Study; CARE: Cholesterol and Recurrent Events; LIPID: Long-term Intervention with Pravastatin in Ischaemic Disease; HPS: Heart Protection Study MI: myocardial infarction; ASCOT-LLA: Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm; VA-HIT: Veterans' Affairs High Density Lipoprotein Intervention Trial (VA-HIT); ALERT: Assessment of Lescol in Renal Transplantation; 4D: Die Deutsche Diabetes Dialyse; SHARP: Study of Heart and Renal Protection; AURORA: A Study to Evaluate the Use of Rosuvastatin in subjects On Regular Haemodialysis: an Assessment of survival and cardiovascular events; RCT: randomised controlled trial; CKD: chronic kidney disease; sCr: serum creatinine; HD: haemodialysis; PD: peritoneal dialysis; HR: hazard ratio; MI: myocardial infarction; CHD: coronary heart disease; CABG: coronary artery bypass graft; CV: cardiovascular.

be replicated in more advanced (stages 4–5) CKD and dialysis patients. This lack of efficacy in CKD may relate to delay in initiating therapy in patients who already have an atypically severe form of atherosclerosis characterised by overwhelming calcification. Lipid-regulating therapy may not correct uraemic cardiomyopathy, an important contributor to arrhythmic death [74], and other concomitant CV risk factors such as insulin resistance, oxidative stress and hypertension.

In contrast, there is consistent evidence that statins, but not other lipid-regulating agents, slow CKD progression which may translate to lowering CVD risk. The cholesterol-lowering and pleiotropic effects of statins such as reduction in oxidative stress, inflammation and thrombogenesis and improvement in endothelial function [87], provide multiple mechanisms for specific improvement in renal outcomes.

4. Treatment guidelines for dyslipidaemia

There are several international guidelines for treating dyslipidaemia in patients with CKD and renal transplants. These are summarised in Table 5 according to the definition of dyslipidaemia, treatment goals, initial approach to therapy and pharmacotherapies.

4.1. NKF DOQI

The North American National Kidney Foundation Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines go beyond the standard recommendations for managing dyslipidaemia set in the National Cholesterol Education Program—Third Adult Treatment Panel (NCEP-ATPIII) (http://www.kidney.org/professionals/kdoqi/guidelines_lipids/index.htm) [88]. The K/DOQI considers CKD stages 1–5 and renal transplant recipients as CHD risk equivalents and provides treatment recommendations for CKD patients aged 18–20 years. It recommends statins as the optimal drug for those with high LDL-cholesterol and fibrates for managing hypertriglyceridaemia (Tg > 5.6 mmol/L or 500 mg/dL) in stage 5 CKD. Although LDL-lowering remains the focus of treatment, a markedly elevated triglyceride concentration (>5.6 mmol/L or 500 mg/dL) should be treated regardless of LDL concentration because of increased risk of pancreatitis. No specific treatment goals are given for HDL-cholesterol, although recommended targets for LDL and non-HDL cholesterol are similar to those of the NCEP-ATPIII for high risk subjects.

The management of dyslipidaemia in renal transplant recipients poses a particular clinical challenge. Achieving lipid targets with statins in this population can be difficult [89] owing to increased toxicity and drug-drug interactions with co-prescribed immunosuppressive drugs. The safety of other lipid regulating agents such as fibrates, nicotinic acid and bile acid sequestrants are also questionable and should be avoided until further studies become available.

4.2. European guidelines

The most recent Joint European Societies Guidelines broadened treatment recommendations to include prevention of all forms of CVD [90], but did not specifically mention CKD. The treatment goals for those with established CVD, diabetes or asymptomatic patients with more than 5% 10-yr risk for fatal CVD are given in Table 5 [91].

The European Best Practice Guidelines (EBPG) published by the European Renal Association, however, considers ESRD as a coronary risk equivalent that requires an appropriate management strategy [92]. It also considers an urgent need for large clinical trials to assess whether treating dyslipidaemia reduces cardiovascular outcomes in CKD and HD patients. Until results of these trials become available, HD patients should be treated according to the recommendations of the Joint European Societies or NCEP to achieve a target LDL-cholesterol of <2.6 mmol/L (100 mg/dL). Similar to the NCEP-ATPIII, the EBPG recommend treatment of high triglyceride concentrations (>2.0–5.6 mmol/L or 180–499 mg/dL) with a non-HDL cholesterol set at <3.3 mmol/L (130 mg/dL). As with K/DOQI, EBPG consider gemfibrozil of up to 600 mg daily as relatively safe in patients with CKD. The guidelines, however, caution against the use of fenofibrates in dialysis patients and the use of statins with fibrates in CKD. Again, no recommended target for HDL-cholesterol is provided.

4.3. Australian guidelines

The most recent National Heart Foundation of Australia/Cardiac Society of Australia and New Zealand (NHFA/CSANZ) Position on Lipid Management Guidelines considers all stages of CKD at high risk for CVD [93]. Pending the result of clinical trials, the Guidelines suggest individualised treatment for patients with CKD and avoidance of high dose statins because of risk of myopathy. Similar to other guidelines, LDL-cholesterol lowering is the focus, with therapeutic target set at <2.0 mmol/L (77 mg/dL). HDL-cholesterol > 1.0 mmol/L (38.7 mg/dL) and Tg < 1.5 mmol/L (133 mg/dL) are also advised, but no specific recommendations are given for use fibrates or nicotinic acid.

The Caring for Australians with Renal Insufficiency (CARI) Guidelines, produced by the Australia New Zealand Society of Nephrology (ANZSN) and Kidney Health Australia (KHA), emphasise the lack of robust trial evidence, which precludes specific recommendation for lipid-lowering therapy in CKD patients [94]. However, the CARI guidelines indicate that patients with mild CKD (stage 1 and 2) and established CAD may benefit from lipid-lowering therapy, while those without a history of CAD should be enrolled in a clinical trial. Unlike other guidelines, CARI paradoxically recommend the use of statins to retard the progression of renal failure.

Table 5
Comparison of guidelines for the treatment of dyslipidaemia in CKD

Recommendations	North America		Europe		Australia	
	NKF KDOQI	NCEP-ATPIII	Third Joint European societies	European best practice guidelines	NHFA/CSANZ	CARI
Overall for CKD	CKD stages 1–5 and renal transplant recipients are CHD risk equivalents	DM and MetS are high risk groups for CHD	DM and MetSyn are high risk groups for CHD	ESRD is considered a coronary risk equivalent	CKD is a high risk group for CHD	CKD stage 1–2 with established IHD may benefit from treatment. CKD patients without IHD should be in clinical trials.
CKD patients aged 18–20 years	Treatment recommendation available	No recommendation	No recommendation	No recommendation	No recommendation	No recommendation
Statins	Drug of choice for high LDL cholesterol	Drug of choice in those at moderate to high risk (eg DM with CVD)	Emphasis on lifestyle advise prior to drug therapy Statins not specifically recommended	No recommendation Warned against combination of statin and fibrate	Drug of choice but high dose must be avoided because of risk of myositis	No recommendation
Fibrates	Recommended for hyperTg > 500 mg/dL (5.6 mmol/L) in CKD stage 5	Consider adding fibrate or nicotinic acid if Tg > 200 mg/dL (2.3 mmol/L) or HDL < 40 g/dL (1.03 mmol/L) after LDL target achieved	No recommendation	Gemfibrozil (up to 600 mg/d) safe for use in CKD. Caution with use of fenofibrate in dialysis patients	No recommendation	No recommendation
Target LDL-C	LDL <100 mg/dL (2.6 mmol/L) focus of treatment	Optional target LDL of 100 mg/dL (2.6 mmol/L) or 30-40% reduction in LDL. Consider LDL threshold of 70 mg/dL (1.8 mmol/L) if high risk (i.e. DM) Non-HDL chol secondary target if Tg > 200 mg/dL (2.2 mmol/L) and MetSyn	LDL 100 mg/dL (2.6 mmol/L) for those with established CVD, DM, or more than 5% 10yr risk of fatal CVD	LDL < 100 mg/dL (2.6 mmol/L)	LDL < 100 mg/dL (2.6 mmol/L)	No recommendation
Target triglycerides	Treat isolated Tg > 500 mg/dL (5.6 mmol/L) due to high risk of pancreatitis		No recommendation	Treat isolated high Tg > 180–499 mg/dL (>2.0–5.6 mmol/L). Non-HDL of 130 mg/dL (3.7 mmol/L) secondary target. Tg marker of coronary disease	Tg < 132 mg/dL (1.5 mmol/L)	No recommendation
Target HDL-cholesterol	No recommendation	No recommendation	No recommendation	No recommendation	HDL > 34 mg/dL (1.0 mmol/L)	No recommendation
To retard progression of CKD	No recommendation	No recommendation	No recommendation	No recommendation	No recommendation	Use statins

Conversion: For total cholesterol, LDL-C, HDL-C and non-HDL: 1 mg/dL = 0.2586 mmol/L; For triglyceride 1 mg/dL = 0.01129 mmol/L; NKF DOQI: National Kidney Foundation Dialysis Outcomes; NCEP ATP III: National Cholesterol Education Program Adult Treatment Panel III; NHFA/CSANZ: National Health Foundation of Australia/Cardiac Society of Australia and New Zealand; CARI: Caring for Australians with Renal Impairment; CKD: Chronic Kidney Disease; CHD: coronary heart disease; ESRD: end-stage renal disease; MetSyn: metabolic syndrome; IHD: ischaemic heart disease; VLDL, IDL, LDL, HDL: very low-density, intermediate-density, low-density and high-density lipoprotein; Tg: triglyceride.

5. Clinical trials of statin therapy in CKD populations

There is wide variation in the international recommendations for the management of dyslipidaemia in CKD. This discordance emphasises the need for good clinical trials on the effectiveness of lipid-regulating therapy in this population. Two double-blind, placebo-controlled randomised trials are currently ongoing to address the question of whether statins and cholesterol lowering can improve cardiovascular outcomes in CKD patients.

The SHARP study is an investigator-initiated trial comparing simvastatin plus ezetimibe versus placebo in 9000 predialysis and haemodialysis patients [95]. It aims to examine the effectiveness of LDL-lowering on major vascular events over a period of 4 years, and is also powered to determine benefits on progression of renal disease. The use of ezetimibe allows for the use of a lower dose statin which may play an important role in reducing the risk of myotoxicity in CKD. SHARP will report in 2008.

The AURORA study aims to evaluate the effectiveness of rosuvastatin 10 mg daily in reducing cardiovascular events in chronic HD patients over 4 years. To date, 2750 patients have been randomised and recruitment completed. Follow-up of patients will continue until 620 patients achieve a major cardiovascular event [96].

While the above trials employ agents that predominantly regulate LDL-cholesterol, there are no trials, to our knowledge, that plan to prospectively evaluate the effectiveness of treating the atherogenic dyslipidaemia and related risk factors, such as insulin resistance in CKD, using fibrates, nicotinic acid or thiazolinediones.

6. Safety of lipid-regulating therapy in CKD

6.1. HMG CoA reductase inhibitors

Although statins are considered safe for use in patients with CKD [97], the risk of complications, particularly myopathy and rhabdomyolysis, is increased particularly when statins metabolised by the CYP3A4 system (ie lovastatin, simvastatin and atorvastatin) [98] are co-administered with CYP3A4 inhibitors (i.e. calcineurin inhibitors, non-dihydropyridine calcium channel blockers and antibiotics such as macrolides). Thus, it is prudent to commence statins at a low dose when used in combination with calcineurin inhibitors. Fluvastatin (oxidised by CYP2C9), pravastatin (metabolised by sulfation) and rosuvastatin (oxidised by CYP2C9) are likely to safer and should be used preferentially in renal transplant recipients due to decreased (proven and theoretical) risk of rhabdomyolysis and myopathy.

6.2. Fibrates

Fibrates are primarily excreted via the kidney and may also increase serum creatinine [99,100]. The rise in serum creatinine with fenofibrate use does not appear to reflect a true reduction in CrCl, but increased endogenous production of creatinine from muscle creatine, a mechanism that may also explain the increase in plasma homocysteine levels [101]. The risk of myopathy and rhabdomyolysis is greater with fibrates than with statins and increases particularly with gemfibrozil, co-administration with a statin and renal impairment. The safety of fibrates taken with statins has not been proven in CKD and in our view this combination should be avoided.

6.3. Cholesterol absorption inhibitor

Because ezetimibe is predominantly metabolised by glucoronidation and excreted in the faeces, dose adjustment is not required for patients with severe renal insufficiency [102]. In patients with CKD and stable renal transplant, ezetimibe monotherapy or in combination with a statin is well-tolerated and does not appear to increase the risk of hepatotoxicity, myopathy or renal dysfunction [72,102,103]. However, there is no room for complacency given recent reports of myopathy with ezetimibe prescribed alone or in combination with statins [104].

6.4. Other agents

Unlike statins, extended-release (ER) niacin can have a favourable global impact on dyslipidaemia of CKD, by effectively lowering triglyceride, LDL-apoB, Lp(a) and elevate HDL-cholesterol [105]. However, experience with niacin in patients with CKD is limited. Caution is required in this population not only because of drug tolerability related to flushing but also increased risk of myotoxicity, hyperuricaemia and dysglycaemia due to its predominant renal elimination [106].

Bile acid sequestrants can lower LDL-cholesterol effectively with very low risk of systemic toxicity in CKD. However, their use is limited by their gastrointestinal side effects and interference with the absorption of other drugs. Although not specifically studied in CKD, plant sterols and stanols can lower cholesterol and enhance the effect of statins by interfering with cholesterol absorption [107]. Numerous epidemiologic and interventional studies in non-renal populations support a cardioprotective effect for omega-3 fatty acids, with reductions in CVD, CAD, fatal and nonfatal MI, stroke, sudden cardiac death and all-cause mortality [108]. In addition to its anti-atherosclerotic [109], anti-inflammatory and anti-thrombotic properties, omega-3 fatty acids lower triglycerides and blood pressure and improve endothelial function [110]. There is a need for a clinical trial on the benefit of omega-3 fatty acid supplementation in CKD.

7. Summary and conclusions

Dyslipidaemia is common in CKD and is an important risk factor for CVD in this population. Perturbations in lipoprotein metabolism occur at each stage of CKD and are reminiscent of the metabolic syndrome. Plasma lipopro-

tein transport defects involve increased hepatic secretion of apoB and decreased production of apo AI, as well as decreased catabolism of triglyceride-rich lipoproteins and with increased catabolism of HDLs. These defects are a consequence of uraemic alterations in apolipoproteins, enzymes, receptors and lipid transfer proteins, and are also the sequelae of co-existent insulin resistance.

Pro-atherogenic, qualitative defects in lipoproteins, typically triglyceride-enrichment of LDL and HDL with cholesterol enrichment of VLDL and IDL, are typically seen in CKD. These are accompanied by changes in constituent apolipoproteins, such as increase in apoE and in apo CIII/CII ratio. Identifying a strong relationship between dyslipidaemia and CVD in CKD is plagued by confounding factors such as effects of malnutrition, inflammation and endothelial dysfunction. Another inherent problem is that the conventional 'lipid profile' is a poor indicator of the true atherosclerotic burden attributed to dyslipoproteinaemia in the CKD population. There is some evidence that beyond cholesterol, remnant lipoproteins, insulin resistance and Lp(a) may predict CVD in CKD.

Post hoc analyses from large clinical trials in non-renal populations with CVD suggest that statin therapy can decrease cardiovascular events and progression of renal disease in subjects with early CKD (stages 1–3). However, these positive results have not been confirmed by larger randomised trials in renal transplant recipients and in diabetic patients on HD. It is likely, that the effectiveness of lipid-regulating therapy is maximal in patients with stages 1–4 CKD and that regulation of mineral metabolism, in particular the calcium phosphate product, plays a more important role in those with more advanced disease who exhibit calcific uraemic arteriopathy. Attention to good control of diabetes, hypertension and treatment of heart failure and adequate nutrition are equally important. However, lipoprotein changes may still contribute significantly to increased risk of CVD in those with early stage CKD. Furthermore, since CKD is associated with very high risk of cardiovascular disease and lipid-lowering therapy can be used relatively safely in CKD patients, it is reasonable to intensively manage dyslipidaemia in CKD, as suggested by most international guidelines. However, the lack of consensus among expert guidelines reflects the continuing need for further clinical trials of lipid-regulating therapy in patients with CKD.

Acknowledgement

Dr DT Chan is in receipt of PhD scholarship from the National Health and Medical Research Council (NHMRC).

References

[1] Foley RN, Parfrey PS, Sarnak MJ. Clinical epidemiology of cardiovascular disease in chronic renal disease. Am J Kidney Dis 1998;32:S112–9.

[2] Foley RN, Wang C, Collins AJ. Cardiovascular risk factor profiles and kidney function stage in the US general population: the NHANES III study. Mayo Clin Proc 2005;80:1270–7.

[3] Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med 2004;351:1296–305.

[4] Vanholder R, Massy Z, Argiles A, et al. Chronic kidney disease as cause of cardiovascular morbidity and mortality. Nephrol Dial Transplant 2005;20:1048–56.

[5] Baigent C, Burbury K, Wheeler D. Premature cardiovascular disease in chronic renal failure. Lancet 2000;356:147–52.

[6] Schwarz U, Buzello M, Ritz E, et al. Morphology of coronary atherosclerotic lesions in patients with end-stage renal failure. Nephrol Dial Transplant 2000;15:218–23.

[7] Blacher J, Guerin AP, Pannier B, Marchais SJ, London GM. Arterial calcifications, arterial stiffness, and cardiovascular risk in end-stage renal disease. Hypertension 2001;38:938–42.

[8] Blacher J, Safar ME, Guerin AP, et al. Aortic pulse wave velocity index and mortality in end-stage renal disease. Kidney Int 2003;63:1852–60.

[9] London GM. Arterial function in renal failure. Nephrol Dial Transplant 1998;13(Suppl. 4):12–5.

[10] Vaziri ND. Dyslipidemia of chronic renal failure: the nature, mechanisms, and potential consequences. Am J Physiol Renal Physiol 2006;290:F262–72.

[11] Attman PO, Samuelsson O, Johansson AC, Moberly JB, Alaupovic P. Dialysis modalities and dyslipidemia. Kidney Int Suppl 2003: S110–2.

[12] Batista MC, Welty FK, Diffenderfer MR, et al. Apolipoprotein A-I, B-100, and B-48 metabolism in subjects with chronic kidney disease, obesity, and the metabolic syndrome. Metabolism 2004;53: 1255–61.

[13] Kimak E, Solski J, Janicka L. Lipoprotein profiles at different stages of chronic renal insufficiency. Ren Fail 2000;22:63–71.

[14] Farbakhsh K, Kasiske BL. Dyslipidemias in patients who have chronic kidney disease. Med Clin North Am 2005;89:689–99.

[15] Deighan CJ, Caslake MJ, McConnell M, Boulton-Jones JM, Packard CJ. Atherogenic lipoprotein phenotype in end-stage renal failure: origin and extent of small dense low-density lipoprotein formation. Am J Kidney Dis 2000;35:852–62.

[16] Prinsen BH, De Sain-Van Der Velden MG, de Koning EJ, et al. Hypertriglyceridemia in patients with chronic renal failure: possible mechanisms. Kidney Int Suppl 2003:S121–4.

[17] Cheung AK, Parker CJ, Ren K, Iverius PH. Increased lipase inhibition in uremia: identification of pre-beta-HDL as a major inhibitor in normal and uremic plasma. Kidney Int 1996;49:1360–71.

[18] Nishizawa Y, Shoji T, Kawagishi T, Morii H. Atherosclerosis in uremia: possible roles of hyperparathyroidism and intermediate density lipoprotein accumulation. Kidney Int Suppl 1997;62:S90–2.

[19] Weintraub M, Burstein A, Rassin T, et al. Severe defect in clearing postprandial chylomicron remnants in dialysis patients. Kidney Int 1992;42:1247–52.

[20] Kim C, Vaziri ND. Down-regulation of hepatic LDL receptor-related protein (LRP) in chronic renal failure. Kidney Int 2005;67:1028–32.

[21] Vaziri ND, Liang K, Parks JS. Down-regulation of hepatic lecithin:cholesterol acyltransferase gene expression in chronic renal failure. Kidney Int 2001;59:2192–6.

[22] Kurella M, Lo JC, Chertow GM. Metabolic syndrome and the risk for chronic kidney disease among nondiabetic adults. J Am Soc Nephrol 2005;16:2134–40.

[23] Prinsen BH, Rabelink TJ, Romijn JA, et al. A broad-based metabolic approach to study VLDL apoB100 metabolism in patients with ESRD and patients treated with peritoneal dialysis. Kidney Int 2004;65:1064–75.

[24] de Sain-van der Velden M, Kaysen GA, Barrett HA, et al. Increased VLDL in nephrotic patients results from a decreased catabolism while increased LDL results from increased synthesis. Kidney Int 1998;53:994–1001.

[25] Joven J, Villabona C, Vilella E, et al. Abnormalities of lipoprotein metabolism in patients with the nephrotic syndrome. N Engl J Med 1990;323:579–84.
[26] Kaysen GA, de Sain-van der Velden MG. New insights into lipid metabolism in the nephrotic syndrome. Kidney Int Suppl 1999;71:S18–21.
[27] Vaziri ND. Molecular mechanisms of lipid disorders in nephrotic syndrome. Kidney Int 2003;63:1964–76.
[28] Wheeler DC, Bernard DB. Lipid abnormalities in the nephrotic syndrome: causes, consequences, and treatment. Am J Kidney Dis 1994;23:331–46.
[29] Vaziri ND, Liang KH. Hepatic HMG-CoA reductase gene expression during the course of puromycin-induced nephrosis. Kidney Int 1995;48:1979–85.
[30] Vaziri ND, Liang KH. Down-regulation of hepatic LDL receptor expression in experimental nephrosis. Kidney Int 1996;50:887–93.
[31] Vaziri ND, Kim CH, Phan D, Kim S, Liang K. Up-regulation of hepatic Acyl CoA: diacylglycerol acyltransferase-1 (DGAT-1) expression in nephrotic syndrome. Kidney Int 2004;66:262–7.
[32] Ordonez JD, Hiatt RA, Killebrew EJ, Fireman BH. The increased risk of coronary heart disease associated with nephrotic syndrome. Kidney Int 1993;44:638–42.
[33] Lechner BL, Bockenhauer D, Iragorri S, Kennedy TL, Siegel NJ. The risk of cardiovascular disease in adults who have had childhood nephrotic syndrome. Pediatr Nephrol 2004;19:744–8.
[34] Liu J, Rosner MH. Lipid abnormalities associated with end-stage renal disease. Semin Dialysis 2006;19:32–40.
[35] Fytili CI, Progia EG, Panagoutsos SA, et al. Lipoprotein abnormalities in hemodialysis and continuous ambulatory peritoneal dialysis patients. Ren Fail 2002;24:623–30.
[36] Attman PO, Samuelsson OG, Moberly J, et al. Apolipoprotein B-containing lipoproteins in renal failure: the relation to mode of dialysis. Kidney Int 1999;55:1536–42.
[37] Kolovou GD, Anagnostopoulou KK, Cokkinos DV. Pathophysiology of dyslipidaemia in the metabolic syndrome. Postgrad Med J 2005;81:358–66.
[38] Moberly JB, Attman PO, Samuelsson O, et al. Alterations in lipoprotein composition in peritoneal dialysis patients. Perit Dial Int 2002;22:220–8.
[39] Castelao AM, Barbera MJ, Blanco A, et al. Lipid metabolic abnormalities after renal transplantation under cyclosporine and prednisone immunosuppression. Transplant Proc 1992;24:96–8.
[40] Tse KC, Lam MF, Yip PS, et al. A long-term study on hyperlipidemia in stable renal transplant recipients. Clin Transplant 2004;18:274–80.
[41] Kasiske BL. Hyperlipidemia in patients with chronic renal disease. Am J Kidney Dis 1998;32:S142–56.
[42] Kimak E, Solski J. Serum lipoprotein(a) concentrations and apolipoprotein(a) phenotypes in hemodialysis, chronic ambulatory peritoneal dialysis and post-transplant patients. Ren Fail 2002;24:187–95.
[43] Brown JH, Murphy BG, Douglas AF, et al. Influence of immunosuppressive therapy on lipoprotein(a) and other lipoproteins following renal transplantation. Nephron 1997;75:277–82.
[44] Fernandez-Miranda C, de la CA, Morales JM, et al. Lipoprotein abnormalities in long-term stable liver and renal transplanted patients A comparative study. Clin Transplant 1998;12:136–41.
[45] Quaschning T, Mainka T, Nauck M, et al. Immunosuppression enhances atherogenicity of lipid profile after transplantation. Kidney Int Suppl 1999;71:S235–7.
[46] Artz MA, Boots JM, Ligtenberg G, et al. Improved cardiovascular risk profile and renal function in renal transplant patients after randomized conversion from cyclosporine to tacrolimus. J Am Soc Nephrol 2003;14:1880–8.
[47] Chueh SC, Kahan BD. Dyslipidemia in renal transplant recipients treated with a sirolimus and cyclosporine-based immunosuppressive regimen: incidence, risk factors, progression, and prognosis. Transplantation 2003;76:375–82.
[48] Morrisett JD, bdel-Fattah G, Hoogeveen R, et al. Effects of sirolimus on plasma lipids, lipoprotein levels, and fatty acid metabolism in renal transplant patients. J Lipid Res 2002;43:1170–80.
[49] Kobashigawa JA, Kasiske BL. Hyperlipidemia in solid organ transplantation. Transplantation 1997;63:331–8.
[50] Berg AL, NilssonEhle P. ACTH lowers serum lipids in steroid-treated hyperlipemic patients with kidney disease. Kidney Int 1996;50:538–42.
[51] Mathis AS, Dave N, Knipp GT, Friedman GS. Drug-related dyslipidemia after renal transplantation. Am J Health Syst Pharm 2004;61:565–85.
[52] Morrisett JD, bdel-Fattah G, Kahan BD. Sirolimus changes lipid concentrations and lipoprotein metabolism in kidney transplant recipients. Transplant Proc 2003;35:S143–50.
[53] Hoogeveen RC, Ballantyne CM, Pownall HJ, et al. Effect of sirolimus on the metabolism of apo. Transplantation 2001;72:1244–50.
[54] Tur MD, Garrigue V, Vela C, et al. Apolipoprotein CIII is upregulated by anticalcineurins and rapamycin: implications in transplantation-induced dyslipidemia. Transplant Proc 2000;32:2783–4.
[55] Degoulet P, Legrain M, Reach I, et al. Mortality risk factors in patients treated by chronic hemodialysis Report of the Diaphane collaborative study. Nephron 1982;31:103–10.
[56] Iseki K, Yamazato M, Tozawa M, Takishita S. Hypocholesterolemia is a significant predictor of death in a cohort of chronic hemodialysis patients. Kidney Int 2002;61:1887–93.
[57] Liu Y, Coresh J, Eustace JA, et al. Association between cholesterol level and mortality in dialysis patients: role of inflammation and malnutrition. JAMA 2004;291:451–9.
[58] Shoji T, Ishimura E, Inaba M, Tabata T, Nishizawa Y. Atherogenic lipoproteins in end-stage renal disease. Am J Kidney Dis 2001;38:S30–3.
[59] Preston E, Ellis MR, Kulinskaya E, Davies AH, Brown EA. Association between carotid artery intima-media thickness and cardiovascular risk factors in CKD. Am J Kidney Dis 2005;46:856–62.
[60] Jungers P, Massy Z, Khoa T, et al. Incidence and risk factors of atherosclerotic cardiovascular accidents in predialysis chronic renal failure patients: a prospective study. Nephrol Dialysis Transplant 1997;12:2597–602.
[61] Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. N Engl J Med 1996;335:1001–9.
[62] Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet 1994;344:1383–9.
[63] Briel M, Nordmann AJ, Bucher HC. Statin therapy for prevention and treatment of acute and chronic cardiovascular disease: update on recent trials and metaanalyses. Curr Opin Lipidol 2005;16:601–5.
[64] Cannon CP, Steinberg BA, Murphy SA, Mega JL, Braunwald E. Meta-analysis of cardiovascular outcomes trials comparing intensive versus moderate statin therapy. J Am Coll Cardiol 2006;48:438–45.
[65] LaRosa JC, Grundy SM, Waters DD, et al. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. N Engl J Med 2005;352:1425–35.
[66] Collins R, Armitage J, Parish S, Sleigh P, Peto R. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. Lancet 2003;361:2005–16.
[67] Sever PS, Dahlof B, Poulter NR, et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. Lancet 2003;361:1149–58.
[68] Tonelli M, Collins D, Robins S, Bloomfield H, Curhan GC. Gemfibrozil for secondary prevention of cardiovascular events in mild

to moderate chronic renal insufficiency. Kidney Int 2004;66:1123–30.
[69] Tonelli M, Isles C, Curhan GC, et al. Effect of pravastatin on cardiovascular events in people with chronic kidney disease. Circulation 2004;110:1557–63.
[70] Wanner C, Krane V, Marz W, et al. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. N Engl J Med 2005;353:238–48.
[71] Isbel NM, Haluska B, Johnson DW, et al. Increased targeting of cardiovascular risk factors in patients with chronic kidney disease does not improve atheroma burden or cardiovascular function. Am Heart J 2006;151:745–53.
[72] Landray M, Baigent C, Leaper C, et al. The second United Kingdom Heart and Renal Protection (UK-HARP-II) Study: a randomized controlled study of the biochemical safety and efficacy of adding ezetimibe to simvastatin as initial therapy among patients with CKD. Am J Kidney Dis 2006;47:385–95.
[73] Holdaas H, Fellstrom B, Jardine AG, et al. Effect of fluvastatin on cardiac outcomes in renal transplant recipients: a multicentre, randomised, placebo-controlled trial. Lancet 2003;361:2024–31.
[74] Jardine AG, Fellstrom B, Logan JO, et al. Cardiovascular risk and renal transplantation: post hoc analyses of the Assessment of Lescol in Renal Transplantation (ALERT) Study. Am J Kidney Dis 2005;46:529–36.
[75] Holdaas H, Fellstrom B, Cole E, et al. Long-term cardiac outcomes in renal transplant recipients receiving fluvastatin: The ALERT Extension Study. Am J Transplant 2005;5:2929–36.
[76] Holdaas H, Fellstrom B, Jardine AG, et al. Beneficial effect of early initiation of lipid-lowering therapy following renal transplantation. Nephrol Dialysis Transplant 2005;20:974–80.
[77] Keech A, Simes RJ, Barter P, et al. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. Lancet 2005;366:1849–61.
[78] 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.
[79] Sandhu S, Wiebe N, Fried LF, Tonelli M. Statins for improving renal outcomes: a meta-analysis. J Am Soc Nephrol 2006;17:2006–16.
[80] 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.
[81] Shepherd J, et al. Intensive lipid lowering with atorvastatin is associated with a significant improvement in renal function: the Treating to New Targets (TNT) Study. J Am Coll Cardiol 2006;47:A316.
[82] Del CD, Cruzado JM, Manel DJ, et al. The effects of hyperlipidaemia on graft and patient outcome in renal transplantation. Nephrol Dial Transplant 2004;19(Suppl. 3):iii67–71.
[83] Fellstrom B, Holdaas H, Jardine AG, et al. Effect of fluvastatin on renal end points in the Assessment of Lescol in Renal Transplant (ALERT) trial. Kidney Int 2004;66:1549–55.
[84] Masterson R, Hewitson T, Leikis M, et al. Impact of statin treatment on 1-year functional and histologic renal allograft outcome. Transplantation 2005;80:332–8.
[85] Ansquer JC, Foucher C, Rattier S, Taskinen MR, Steiner G. Fenofibrate reduces progression to microalbuminuria over 3 years in a placebo-controlled study in type 2 diabetes: results from the Diabetes Atherosclerosis Intervention Study (DAIS). Am J Kidney Dis 2005;45:485–93.
[86] Kshirsagar AV, Shoham DA, Bang H, et al. The effect of cholesterol reduction with cholestyramine on renal function. Am J Kidney Dis 2005;46:812–9.
[87] Liao JK. Effects of statins on 3-hydroxy-3-methylglutaryl coenzyme a reductase inhibition beyond low-density lipoprotein cholesterol. Am J Cardiol 2005;96:24F–33F.
[88] Kasiske B, Cosio FG, Beto J, et al. Clinical practice guidelines for managing dyslipidemias in kidney transplant patients: a report from the Managing Dyslipidemias in Chronic Kidney Disease Work Group of the National Kidney Foundation Kidney Disease Outcomes Quality Initiative. Am J Transplant 2004;4(Suppl. 7):13–53.
[89] Schonder KS, McKaveney TP, Lynch KJ. Retrospective analysis of hyperlipidemia management in a transplant population. Pharmacotherapy 2005;25:918–23.
[90] De BG, Ambrosioni E, Borch-Johnsen K, et al. European guidelines on cardiovascular disease prevention in clinical practice Third Joint Task Force of European and other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of eight societies and by invited experts). Atherosclerosis 2004;173:381–91.
[91] Erhardt LR, Gotto J. The evolution of European guidelines: changing the management of cholesterol levels. Atherosclerosis 2006;185:12–20.
[92] European best practice guidelines for renal transplantation. Section IV: Long-term management of the transplant recipient. IV.5.3. Cardiovascular risks. Hyperlipidaemia. Nephrol Dial Transplant, 2002;17(Suppl. 4):26–8.
[93] Tonkin A, Barter P, Best J, et al. National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand: position statement on lipid management—2005. Heart Lung Circ 2005;14:275–91.
[94] Walker R. Cardiovascular risk factors. Nephrology (Carlton) 2005;10(Suppl. 5):S231–4.
[95] Baigent C, Landry M. Study of Heart and Renal Protection (SHARP). Kidney Int Suppl 2003:S207–10.
[96] Fellstrom B, Zannad F, Schmieder R, et al. Effect of rosuvastatin on outcomes in chronic haemodialysis patients—design and rationale of the AURORA study. Curr Control Trials Cardiovasc Med 2005;6:9.
[97] Kasiske BL, Wanner C, O'Neill WC. An assessment of statin safety by nephrologists. Am J Cardiol 2006;97:S82–5.
[98] Bottorff MB. Statin safety and drug interactions: clinical implications. Am J Cardiol 2006;97:S27–31.
[99] Broeders N, Knoop C, Antoine M, Tielemans C, Abramowicz D. Fibrate-induced increase in blood urea and creatinine: is gemfibrozil the only innocuous agent? Nephrol. Dial Transplant 2000;15:1993–9.
[100] Lipscombe J, Lewis GF, Cattran D, Bargman JM. Deterioration in renal function associated with fibrate therapy. Clin Nephrol 2001;55:39–44.
[101] Hottelart C, El EN, Rose F, Achard JM, Fournier A. Fenofibrate increases creatininemia by increasing metabolic production of creatinine. Nephron 2002;92:536–41.
[102] Kosoglou T, Statkevich P, Johnson-Levonas AO, et al. Ezetimibe: a review of its metabolism, pharmacokinetics and drug interactions. Clin Pharmacokinet 2005;44:467–94.
[103] Buchanan C, Smith L, Corbett J, Nelson E, Shihab F. A retrospective analysis of ezetimibe treatment in renal transplant recipients. Am J Transplant 2006;6:770–4.
[104] Simard C, Poirier P. Ezetimibe-associated myopathy in monotherapy and in combination with a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor. Can J Cardiol 2006;22:141–4.
[105] Knopp RH. Drug treatment of lipid disorders. N Engl J Med 1999;341:498–511.
[106] Guyton JR. Extended-release niacin for modifying the lipoprotein profile. Expert Opin Pharmacother 2004;5:1385–98.
[107] Devaraj S, Jialal I. The role of dietary supplementation with plant sterols and stanols in the prevention of cardiovascular disease. Nutr Rev 2006;64:348–54.
[108] Psota TL, Gebauer SK, Kris-Etherton P. Dietary omega-3 fatty acid intake and cardiovascular risk. Am J Cardiol 2006;98:3–18.
[109] Davidson MH. Mechanisms for the hypotriglyceridemic effect of marine omega-3 fatty acids. Am J Cardiol 2006;98:27–33.
[110] Robinson JG, Stone NJ. Antiatherosclerotic and antithrombotic effects of omega-3 fatty acids. Am J Cardiol 2006;98:39–49.