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Renal Dyslipidemia and Cardiovascular Mortality Over Two Decades of Follow-Up

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Abstract

Background: Cardiovascular disease (CVD) is common in patients with chronic kidney disease. With declining renal function the CKD patients develop characteristic alterations of the lipoprotein metabolism with accumulation of intact and partially metabolized triglyceride-rich lipoproproteins. These lipoproteins contain apolipoprotein C-III, which has been suggested to have a pathophysiological role in atherogenesis.

Patients and methods: Three-hundred and forty-one non-diabetic adult patients in various stages of renal insufficiency had their lipid and apolipoprotein profiles measured and other patient characteristics registered between 1975 and 2000. After determination of their profile they have been followed until kidney transplantation, death or December 31, 2012. The patient with the longest follow-up was followed for almost 24 years. Association between baseline variables and cardiovascular and overall mortality was assessed.

Results: Fifty-five per cent of the patients died from a cardiovascular cause, and 172 patients died before the end of follow-up without having had a renal transplant. Age and smoking were significantly associated with increased CVD mortality in all patients. In patients who were not on dialysis at start of follow-up GFR was inversely and serum triglyceride and total serum cholesterol were directly significantly associated with CVD mortality. Plasma lipids were not associated with CVD mortality in the dialysis patients. Of the apolipoprotein variables none was significantly associated with CVD mortality. Although there seems to be a tendency for a slightly better prognosis in patients in the lowest Apo C-III tertile there was no statistically significant difference between the three groups.

Conclusion: The present long-term observational study showed that dyslipidemia contributes to overall and cardiovascular mortality during the early stages of renal failure but not in the more advanced stage of chronic kidney disease. Other more important prognostic factors remain to be determined in patients who go on to dialysis.

Keywords: Dyslipidemia; Chronic Kidney Disease; Mortality; Cardiovascular Disease; Apolipoprotein C-III

Introduction

Renal disease leads to a characteristic dyslipidemia which is not manifested as hyperlipidemia in many patients. Previous studies have shown that this dyslipidemia is characterised by a specific apolipoprotein (apo) profile due to an accumulation of intact and partially metabolized apoB-containing lipoproteins of very low and intermediate density [1, 2]. The characteristic profile of the renal dyslipidemia is clearly atherogenic as demonstrated in several studies in non-renal patients [3, 4]. A specific role for apolipoprotein CIII in the pathogenesis of atherosclerosis has been discussed [1, 5]. This is of particular

interest in patients with advanced chronic renal insufficiency since apoC-III is one of apolipoprotein constituents of the lipoprotein particles in the VLDL- and IDL density range. Thus, the plasma concentrations of apo CIII are increased in these patients [6].

It is logical to assume that renal dyslipidemia, and particularly elevated levels of apoC-III- containing lipoproteins, have a pathogenetic role in the accelerated development of cardiovascular disease that occurs in patients with advanced chronic kidney disease [5, 7, 8]. However, studies of lipid lowering intervention in hemodialysis patients have not shown to be beneficial [9, 10, 11], whereas subgroup analyses of patients in earlier stages of renal insufficiency have shown positive effects of lipid lowering drug treatment [12].

Only a limited number of studies have performed detailed analyses of the lipoprotein metabolism in renal patients. Most studies have only measured plasma lipid levels, i.e. total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides. Thus, the prognostic impact of the specific features of renal dyslipidemia remains to be clarified.

We have performed and reported several studies of renal dyslipidemia in patients with different stages of chronic renal disease with increasingly more detailed analysis of their lipoprotein profile [6]. Altogether, these patients represent a cohort of renal patients with more than 10 years of observation.

The aim of this study was to pool all their data to analyse the predictive value of renal dyslipidemia for overall and cardiovascular (CVD) mortality with specific focus on apoB- and apoC-III triglyceride-rich lipoproteins.

Patients

Between 1975 and 2000 over 400 adult patients in various stages of renal insufficiency had their lipid and apolipoprotein profiles determined as participants in our studies of different aspects of renal dyslipidemia. All patients had their lipoprotein profiles determined in the same laboratory, and with the same methods of measurement. No patient was on any kind of lipid-lowering therapy at the time of determination of the lipid profile. After exclusion of patients with diabetes mellitus and with missing laboratory data the study group consisted of 341 patients of whom 222 were men and 119 were women.

One-hundred and fourteen patients (33 %) had glomerulonephritis, 62 patients (15 %) had tubulo-interstitial nephritis, and 59 patients (17 %) had adult polycystic kidney disease. Hypertensive renal disease or nephrosclerosis was the diagnosis in 44 patients (13 %), and 62 patients (18 %) had other or unknown disease. Of all patients 203 (60%) were in CKD stage II-IV and 138 patients (40 %) were on dialysis (93 patients on hemodialysis (HD) and 45 patients on peritoneal dialysis (PD)) at the time of sampling for lipid and apolipoprotein determinations.

One-hundred and thirty-six patients (40 %) received a kidney transplant during the time of follow-up. At the end of the follow-up period, December 2012, 240 of all patients (70%) had died, while 101 patients were still alive (68 of them with a kidney transplant).

Methods

The vital status was identified for all patients at the end of the observation period which ended on December 31, 2012, from data in the Swedish Renal Registry and the National Death Registry. For deceased patients the medical records were reviewed. The causes of death were classified in five categories; cardiovascular, infectious, malignancy, uremia and other. Cardiovascular death included myocardial infarction, heart failure, sudden death, stroke and peripheral vascular disease.

Hypertension was defined as ongoing treatment with antihypertensive agent(s) at start of follow-up. In patients with CKD stage II-IV, the glomerular filtration rate (GFR) was determined at time of sampling for lipid and apolipoprotein determinations by clearance measurements (using 51Cr EDTA or Iohexol) in almost all of the patients (97 %). Body mass index was calculated from body weight and height. Information on smoking habits was available in 80 % of the patients. Previous smokers were classified as smokers. No patient was treated with any immunosuppressive drug including steroids or with any type of lipid-lowering drug at the time of investigation.

Hemodialysis was performed by conventional techniques using with low-molecular heparin for anticoagulation during the whole time of follow-up. Most patients had three dialysis sessions per week. Peritoneal dialysis was generally performed with four exchanges of dialysate per 24 h.

Serum lipids and lipoprotein concentrations were determined by methods previously described [13,14,15]. Blood was drawn after an over-night fast, and the separated plasma was immediately shipped by airfreight to the Lipid and Lipoprotein Laboratory at the Oklahoma Medical Research Foundation, Oklahoma City, USA, for analysis. The methods for measuring the serum concentrations of lipids, lipoproteins and apolipoproteins were the same during the entire time period of sampling.

Statistical Methods

The patients series was divided into three categories; 1) patients without dialysis, i.e. CKD stage II-IV, 2) patients on maintenance hemodialysis, and 3) patients on peritoneal dialysis. Overall and CVD mortality was analysed using Kaplan Meyer and Cox regression both with and without censoring of patients at the date of kidney transplantation.

Ethics

The study was approved by the Regional Ethical Review Board in Gothenburg and performed in accordance with the Declaration of Helsinki, as reviewed in 1989.

Results

Patient characteristics

Demographic data are presented in Table 1. The patients were followed until December 2012 or until death. The individual follow-up ranged from 1 week to 23.8 years with an average of 3.3 years and 2.8 years for patients on hemodialysis and peritoneal dialysis, respectively. The average time of follow-up for the CKD stage II-IV patients was 7.4 years. The plasma lipid, lipoprotein and apolipoprotein concentrations are presented in Table 2. In a subsample of patients the plasma concentrations of individual apoB-containing lipoproteins were determined. As can be seen in Table 2 the lipoprotein profile in hemodialysis patients was different from the one seen in both the CKD II-IV and peritoneal dialysis patients, who had much the same pattern, with higher triglyceride and cholesterol levels but a lower apoC-III ratio. During the follow-up period 136 patients (40 %) had a renal transplant.

	Patients with CKD II-IV	Patients on hemodialysis	Patients with peritoneal dialysis
Number of subjects	203	93	45
Age (years)	53.3 (sd 13.2)	65.8 (sd 12.3)	59.4 (sd 15.6)
Sex (Female/Male)	71/132	38/55	Oct-35
Follow-up (years)	7 weeks to 21.5 years	1 week to 23.7 years	7 weeks to 16.6 years
Body mass index (kg/m^2)	25.6 (sd 4.9)	24.1 (sd 4.5)	23.9 (sd 3.3)
GFR (ml/min x 1.73 m^2 BSA)	23.6 (sd 18.5)	Not measured	Not measured
Hypertension (%)	89	70	77
Smokers (%)	34	40	52

Table 1. Baseline characteristics of patients with chronic kidney disease.

Mortality

Two-hundred and thirty-seven patients died during the whole follow-up period. Of these 65 were transplanted at the time of death. Thus, 172 patients died before the end of follow-up without having had a renal transplant. There was no difference in all-cause or CVD mortality between patients on hemodialysis and peritoneal dialysis, regardless whether the patients were censored at the time of renal transplantation or not. Half of all the dialysis patients had died after about three years of follow-up. As expected, the pre-dialytic patients with CKD stages II-IV, who also were more than 10 years younger than the dialysis patients at start of follow-up (Table 1), had a significantly better survival with more than half of them still alive after 13 years.

	Patients with	Patients on hemodialysis	Patients with peritoneal dialysis
Lipids (mmol/L)	**CKD II-IV**	**(n=93)**	**(n=45)**
Triglycerides	2.27 (sd 1.57)	1.83 (sd 1.37)	2.20 (sd 1.35)
Total cholesterol	6.25 (sd 1.50)	5.53 (sd 1.65)	6.59 (sd1.42)
LDL cholesterol	4.29 (sd 1.34)	3.46 (sd 1.19)	4.50 (sd 1.19)
HDL cholesterol	1.08 (sd 0.34)	1.06 (sd 0.36)	1.14 (sd 0.31)
Apolipoproteins (mg/100 ml)			
ApoA-1	112.1 (sd 25.0)	112.1 (sd 5.7)	112.1 (sd 25.7)
ApoB	126.5 (sd 41.5)	114.9 (sd 5.5)	145.3 (sd 41.7)
ApoC-III	18.9 (sd 7.3)	19.2 (sd 6.9)	20.6 (sd 8.0)
ApoC-III in HDL[i]	6.3 (sd 3.1)	9.3 (sd 3.6)	6.9 (sd 3.6)
ApoC-III in VLDL+LDL[i]	10.8 (sd 6.2)	8.2 (sd 5.8)	11.8 (sd 5.7)
ApoE	13.6 (sd 7.2)	13.6 (sd 7.2)	11.5 (sd 3.7)
Lipoprotein B particles (mg/100 ml)			
LpB	111.5 (sd 32.0)	94.8 (sd 27.5)	124.7 (sd 35.8)
LpBc	20.7 (sd 14.0)	14.4 (sd 9.2)	21.4 (sd 11.4)

Footnote:
i. Analysed after precipitation with heparin-manganese. HDL in the supernate and VLDL+LDL in the precipitate.

Table 2. Plasma lipid levels at start of follow-up in patients with chronic kidney disease.

Fifty-five per cent of the patients died from a cardiovascular cause while 10% died from infectious diseases and 11% from a malignancy. In eight per cent of the cases the dialysis treatment was withdrawn for medical reasons, and in 14% the cause of death was due to other causes or could not be determined. Figure 1 shows the Kaplan Meyer curves for cardiovascular mortality in the three patient categories. The cardiovascular mortality rates did not differ between the two different dialysis modalities.

Risk factors for cardiovascular mortality

Age and smoking were significantly associated with increased CVD mortality in all patients. Glomerular filtration rate was inversely and statistically significant associated with CVD mortality in the predialytic patients (stage CKD II-IV). Both serum triglyceride and total serum cholesterol concentrations were significantly associated with CVD mortality in the patients with CKD stage II-IV, but not in the dialysis patients.

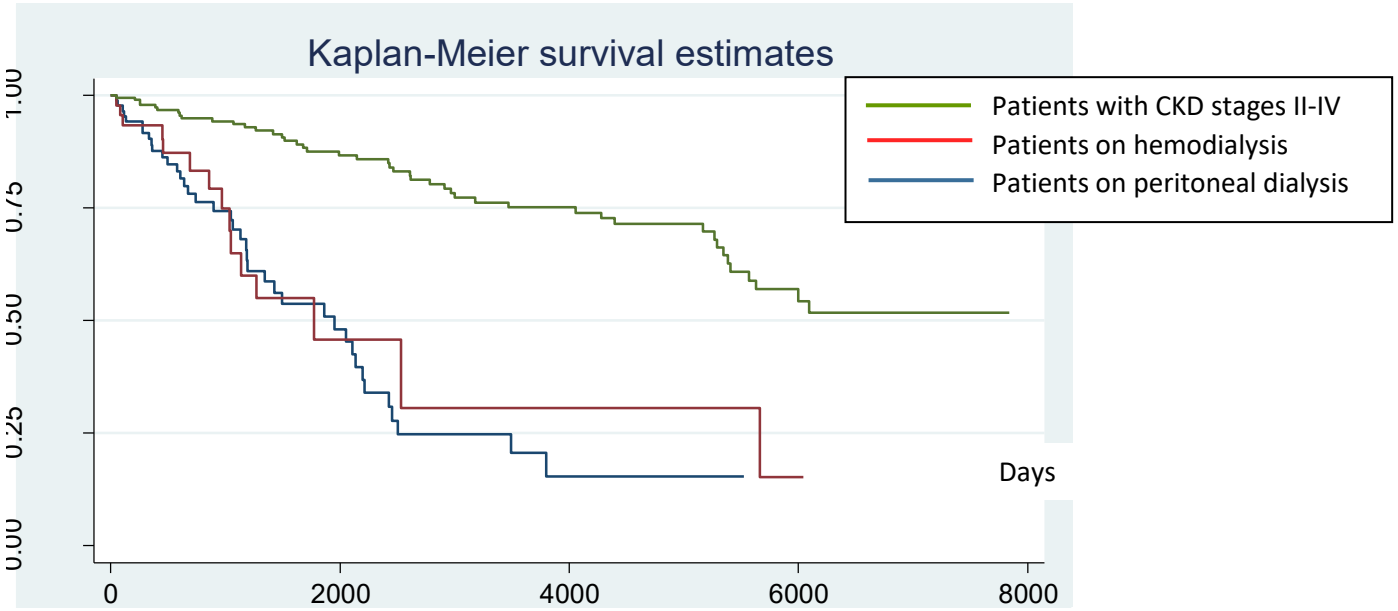

Figure 1. Cardiovascular mortality according to patient category.

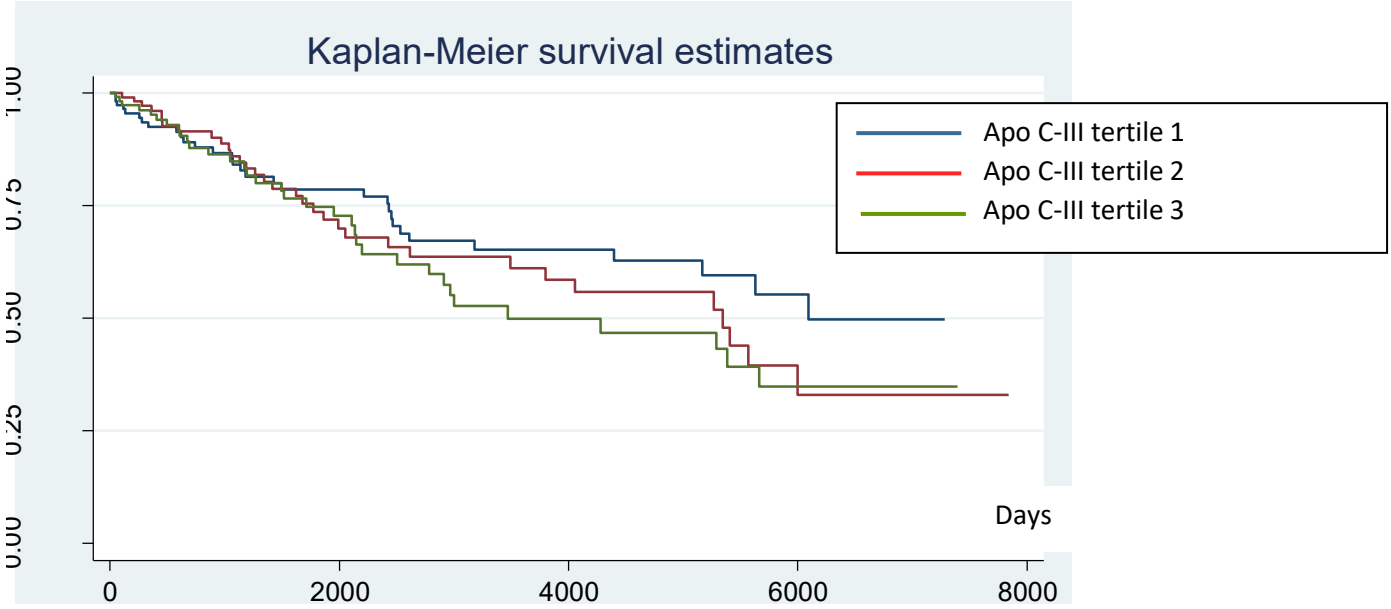

Figure 2. Cardiovascular mortality according to serum level of apoliprotein C-III.

	All patients	Patients with CKD II-IV	Patients on hemodialysis	Patients with peritoneal dialysis
	(n= 341)	(n=203)	(n=93)	(n=45)
Gender (Male vs Female)	1.21 (0.79-1.85)	1.14 (0.60-2.14)	1.26 (0.66-2.39)	2.29 (0.51-10.35)
Age (years)	**1.08 (1.06-1.10)**	**1.06 (1.03-1.09)**	**1.04 (1.01-1.08)**	**1.06 (1.02-1.16)**
Hypertension (yes/no)	0.65 (0.39-1.09)	1.14 (0.40-3.18)	0.76 (0.37-1.56)	4.07 0.51-32.63)
Smoking (yes/no)	**1.77 (1.14-2.74)**	1.73 (0.92-3.26)	1.73 (0.82-3.66)	1.46 (0.40-5.27)
BMI (kg/m^2)	1.01 (0.96-1.05)	1.04 (0.97-1.10)	1.00 (0.95-1.06)	1.02 (0.83-1.26)
GFR (ml/min)	-	**0.92 (0.90-0.95)**	-	-
Triglycerides (mmol/L)	1.00 (0.99-1.01)	**1.002 (1.00-1.01)**	0.998 (0.993-.002)	1.00 (0.99-1.017)
Total cholesterol (mmol/L)	1.00 (0.99-1.01)	**1.005 (1.00-1.01)**	0.997 (0.991-.002)	1.00 (0.99-1.01)
ApoB (mg/100 ml)	1.00 (0.99-1.01)	1.00 (0.99-1.01)	1.00 (0.99-1.01)	1.00 (0.99-1.06)
ApoC-III (mg/100 ml)	1.02 (0.99-1.05)	1.03 (0.99-1.07)	0.97 (0.93-1.03)	1.03 (0.97-1.09)
ApoC-III in HDL[i] (mg/100 ml)	**1.07 (1.01-1.12)**	1.01 (0.90-1.13)	0.97 (0.88-1.07)	1.02 (0.92-1.13)
ApoC-III in VLDL + LDL[i] (mg/100 ml)	1.01 (0.98-1.05)	1.04 (0.99-1.10)	0.97 (0.93-1.04)	1.06 (0.96-1.61)
LpB (mg/100 ml)	0.99 (0.98-1.01)	1.00 (0.99-1.02)	0.99 (0.98-1.01)	1.01 (0.99-1.02)
LpBc (mg/100 ml)	1.01 (0.98-1.02)	1.01 (0.98-1.05)	1.01 (0.98-1.05)	1.00 (0.95-1.04)

Footnote:

i. Analysed after precipitation with heparin-manganese. HDL in the supernate and VLDL+LDL in the precipitate.

Table 3. Hazard ratio and 95% confidence interval (in parenthesis) of patient characteristics and CVD mortality in patients with chronic renal disease. Variables that were significantly associated with CVD mortality in univariate analysis are presented in bold.

	Patient characteristic variables	Hazard Ratio (95% confidence interval)
Model 1 (n =197)	GFR (ml/min x 1.73 m^2 BSA)	0.93 (0.90-0.95)
	Triglycerides	1.00 (0.99-1.01)
Model 2 (n = 151)	GFR (ml/min x 1.73 m^2 BSA)	0.93 (0.90-0.95)
	ApoC-III in HDL[i] (mg/100 ml)	0.97 (0.86-1.09)
Model 3 (n = 151)	GFR (ml/min x 1.73 m^2 BSA)	0.93 (0.90-0.96)
	ApoC-III in VLDL+ LDL[i] (mg/100 ml)	1.01(0.96-1.07)
Model 4 (n = 151)	GFR (ml/min x 1.73 m^2 BSA)	0.93 (0.90-0.95)
	ApoC-III in VLDL+ LDL[i] (mg/100 ml)	0.91(0.57-1.46)

Footnote:

i. Analysed after precipitation with heparin-manganese. HDL in the supernate and VLDL+LDL in the precipitate.

Table 4. Hazard ratio and 95% confidence interval (in parenthesis) of patient characteristics and CVD mortality in patients with chronic renal disease stage II-IV. Four models of multivariate analysis.

Of the apolipoprotein variables apo C-III in HDL was significantly associated with CVD mortality when all patients were pooled together but not when the three patient categories were analysed separately. Figures 2 illustrates the CVD mortality in relation to the tertiles of apoC-III concentration. Although there seems to be a tendency for a slightly better prognosis in patients in the lowest apoC-III tertile there was no statistically significant difference between the three groups.

Following the results of the univariate analyses trivariate analyses with GFR and serum triglycerides and the apo C-III variables, respectively, were performed, Table 4. These analyses showed that when the GFR level was accounted for there were no tendency for any association between the triglyderide levels, or the apo C-III variables, and CVD mortality.

Discussion

The main finding of this long-term follow-up of patients with chronic kidney disease was that the specific lipoprotein metabolic alterations characteristic of progressive renal insufficiency and failure, i.e. renal dyslipidemia, had a very limited, if any, predictive value for overall and cardiovascular mortality in non-diabetic patients with chronic kidney disease. This was particularly pertinent for CKD patients already on dialy-

sis. Thus, other factors must be of greater importance for the further development of vascular disease in patients with advanced renal failure.

The patients in present study were representative of unselected patients who attend a nephrology department from 1975 until year 2000 treated according to conventional standard therapy with regard to both pharmacological treatment and dialysis regimens. Before the publication of the SHARP trial in 2011 [11] none of the patients with CKD II-IV were on any lipid-lowering drug treatment.

The observed overall mortality and cardiovascular mortality rates were in agreement with other studies in unselected non-diabetic populations with almost 60 % of all deaths attributable to a cardiovascular cause [16, 17, 18].

The lipoprotein profile of the patients showed the characteristic pattern of renal failure with an accumulation of intact and partially metabolized apoB-containing lipoproteins, which in addition to apoB also containing varying amounts of apoC and apoE proteins.. Several observational studies in non-renal patients have reported that apoC-III containing lipoproteins are associated with the development of atherosclerosis and CVD (7, 8), and experimental studies have indicated that apoC-III triggers a cascade of pro-inflammatory events that can result in endothelial function and vascular damage [5]. Therefore, it has been a hypothesis that the accumulation of the apoC-III-containing lipoproteins could play an important role in the accelerated atherosclerosis seen in both patients with a moderate reduction of renal function as well as in patients with advanced renal failure. However, the results in the present study do not support this. The rejection of this hypothesis is further supported by the recent post-hoc analysis of the 4D study that reported that neither HDL-cholesterol nor apolipoprotein A-I or C-III were significantly associated with cardiovascular morbidity and mortality in type II diabetics on maintenance hemodialysis [19].

The serum levels of triglyceride and of the apoB-containing cholesterol-rich lipoproteins were higher in in CKD II-IV patients and in patients on peritoneal dialysis than in the hemodialysis patients. Furthermore, both triglycerides and cholesterol were significantly associated with increased CVD mortality in patients with CKD II-IV. This complies well with the outcome of the SHARP trial [11]. The beneficial effects of statin treatment in this trial could be explained the well-known statin effect to lower the concentrations of cholesterol-rich lipoproteins. However, the apoB-containing cholesterol lipoproteins were not elevated in the hemodialysis patients and none of the lipoproteins variables were associated with CVD mortality in these patients. Thus, it is not surprising that statin treatment were of no benefit in the 4D and the Aurora trial, and in the subgroup of hemodialysis patients in the SHARP trial [9, 10, 11].

The outcome of this long-term follow-up of patients with chronic kidney disease, the recent reported findings in the 4D trial [19], and the lack of effect of statin treatment in hemodialysis patients clearly show the hazards to extrapolate findings and treatment effects from one patient category to another. It is obvious that other factors than lipoprotein alterations have a much greater impact on the development of vascular damages and CVD morbidity in patients with advance kidney disease than in non-renal patients. Such factors may include components of the inflammatory system, oxidative stress, uremic toxins and disturbances of mineral metabolism [20].

However, it appears that in the predialytic stage the dyslipidemia can contribute to further development of vascular disease, and would therefore merit therapeutic intervention. When the patient has entered the stage of CKD V and is treated with hemodialysis it is too late for lipid-lowering intervention and treatment should be directed towards other factors. The problem is that we still do not know which factors are amenable for a beneficial intervention, and what kind of intervention we should use.

This study has some strengths but also limitations. The strengths are the use of the same methods to measure the various lipoprotein variables throughout the whole period performed at one single laboratory. Furthermore, the observation period was long with some of the patients having a follow-up of almost 25 years, and lipid-lowering therapy was not used in any of the patients without a renal transplantation, and only after renal transplantation in the transplanted patients.

Although almost 70 % of all the patients died during the observation period the number of CVD deaths was still limited to 99 events, which may be too small a number to show any significant association with any characteristic of renal dyslipidemia. Another limitation is that we lack data on non-fatal CVD events. The large number of patients who received a kidney transplant reflects the treatment policies of our department and implicates a further limitation. Transplantation introduces treatment that may affect lipoprotein metabolism by itself and post-transplant morbidity and survival is influenced by the transplantation procedure and treatment and the graft function. We therefore analysed the overall and cardiovascular outcomes with and without censoring transplanted patients at time of transplantation. The censoring aims at reducing the influence of these less relevant factors for the aim of the study. However, the main results of our study remained unchanged also after censoring which indicates that the possible contribution of the renal dyslipidemia to CVD mortality was not modified by renal transplantation and immunosuppressive treatment.

In conclusion, the present study showed that the dyslipidemia contributes to overall and cardiovascular mortality during the early stages of renal failure but not in the more advanced stage

of chronic kidney disease. Other more important prognostic factors remain to be determined in patients who go on to dialysis [21]. While lipid-lowering treatment should be considered for patients in CKD stages II-IV its use in dialysis patients is not motivated.

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