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REVIEW

Cholesterol in end-stage renal disease: the good, the bad or the ugly?

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ABSTRACT

The incidence of cardiovascular disease is markedly increased in patients with end-stage renal disease (ESRD). High serum cholesterol is widely recognised as a cardiovascular risk factor in the general population. However, in patients with ESRD high concentrations of cholesterol are associated with a better survival. This reverse epidemiology is, amongst others, caused by confounding due to malnutrition and chronic inflammation. In this population, treatment with statins to lower the serum cholesterol remains a matter of debate. In ESRD, LDL cholesterol is modified by increased oxidative stress. These altered LDL particles play a pivotal role in the development of atherosclerosis. Treatment with the antioxidant vitamin E has not equivocally been shown to be beneficial in this population. This review tries to put data from literature on dyslipidaemia and oxidative stress in ESRD in perspective.

KEYWORDS

Cholesterol, end-stage renal disease, oxidative stress, statins, vitamin E

INTRODUCTION

Patients with chronic renal failure (CRF) are at increased risk for developing cardiovascular disease (CVD). A decreased glomerular filtration rate (GFR) is recognised as an independent cardiovascular risk factor. The increased cardiovascular risk is already apparent in patients with moderate renal insufficiency (GFR <60 ml/min/1.73m^2), and is most prominent in patients with end-stage renal disease (ESRD).[1-3]

High concentration of serum cholesterol is one of the most widely recognised cardiovascular risk factors. There is overwhelming evidence to support serum cholesterol lowering treatment in patients with increased cardiovascular risk.[4-9] It therefore seems logical to extrapolate these findings of the 'bad' effects of cholesterol to patients with ESRD as well. However, there is some evidence to suggest that higher cholesterol *per se* may not be such an important risk factor in patients with ESRD compared with other subjects with an increased cardiovascular risk. In fact, in some studies in ESRD a low serum cholesterol was associated with increased mortality, suggesting 'good' effects of higher cholesterol levels on survival rate.[10,11] Furthermore, a recent randomised trial reported no benefit from therapy lowering serum cholesterol in diabetic haemodialysis patient.[12]

The dispute on cholesterol in patients with ESRD has become even more complicated since low-density lipoprotein (LDL) particles in these patients may be altered, and become 'ugly' through increased oxidative stress, which is characteristic for dialysis patients. This results in the formation of small, dense, oxidised LDL particles that are considered to be highly atherogenic and therefore play an important role in the development of atherosclerosis.[13,14]

In this review, we summarise the data on serum cholesterol as a possible cardiovascular risk factor and the effect of treatment with statins on cardiovascular outcome in patients with ESRD. We put these data in perspective and discuss increased oxidative stress in more detail as a potentially important modifier.

CARDIOVASCULAR RISK PROFILE IN ESRD

Cardiovascular morbidity and mortality in ESRD

Despite the availability of sophisticated techniques for renal replacement therapy (haemodialysis, peritoneal dialysis,

and renal transplantation), life expectancy of patients with ESRD on haemodialysis (HD) and peritoneal dialysis (PD) remains poor, with only a moderate amelioration after renal transplantation. The annual mortality rate in the dialysis population is about 20%. Approximately 50% of these deaths are caused by CVD. This makes cardiovascular mortality 10 to 30 times more prevalent in patients with ESRD compared with the general population.[15]

The poor cardiovascular outcome in patients with ESRD is attributed to an increased incidence and prevalence of CVD as well as a high case fatality rate. In patients treated with HD or PD, the prevalence of overt coronary artery disease (CAD) is approximately 40%.[15] After a cardiovascular event, survival in ESRD is poor: in patients with ESRD mortality rates after a myocardial infarction have been reported to be 59 and 90% after one and five years respectively.[16]

The increased prevalence of CVD is not restricted to patients with ESRD, but is already apparent in patients with mild to moderate renal insufficiency.[17-21] Thus, the process of atherosclerotic CVD starts long before patients reach ESRD. Moreover, it is important to realise that the arterial lesions in patients with ESRD differ from those observed in patients with classical coronary artery disease.[22,23] In patients with classical atherosclerotic disease, the vascular plaques have the typical aspects of atheromatous or fibroatheromatous plaques, with a prominent presence of lipid accumulation. In contrast, patients with ESRD have typical calcified plaques, predominantly composed of fibrous tissue and calcium deposits.[23] Furthermore, thickening of intima and media of the vessel wall, with subsequent narrowing of the lumen, is more prominent in ESRD. In addition to atherosclerotic or calcified vascular disease, patients with ESRD are more prone to the development of left ventricular hypertrophy (LVH) as a result of hypertension and anaemia. Both tissue calcification and LVH contribute to the development of myocardial fibrosis, diastolic dysfunction and left ventricular conduction abnormalities. This not only leads to heart failure, but more importantly may predispose to potentially lethal primary cardiac rhythm disturbances.[22-24] Notably, although mortality in patients with ESRD is often attributed to CVD, many patients die suddenly with presumed cardiac arrest, and only a minority die from typical atherosclerotic diseases such as myocardial infarction or stroke. This is reflected by data from the recent USRDS registry, showing that in 2005, 7.2% of dialysis patients died from cardiac arrest or cardiac arrhythmia whereas myocardial infarction or coronary heart disease were the cause of death in 2.9% of the patients.[25]

Cardiovascular risk factors in ESRD

In discussing cardiovascular risk factors in patients with ESRD, a distinction can be made between traditional and nontraditional risk factors. The traditional risk factors are defined by epidemiological studies such as the Framingham study and influence the development of CVD in the general population. These risk factors may also be applicable to the dialysis population. The CHOICE study showed that the majority of dialysis patients had one or more of the traditional cardiovascular risk factors: 54% of the patients had diabetes mellitus, 33% had a low serum HDL cholesterol, 96% suffered from hypertension, 22% had left ventricular hypertrophy and the average age of the patients at the start of dialysis therapy was 60 years. Of note, an increased LDL cholesterol (>4.2 mmol/l) was observed in only 11% of patients.[26] Because of the large difference in cardiovascular risk between the general population and patients with CRF and ESRD, it was postulated that in the latter patients additional 'nontraditional' cardiovascular risk factors must be present. Examples of these nontraditional risk factors include calcium, phosphorus, PTH, vitamin D, and CRP.[3,27-30] It has been postulated that these nontraditional risk factors could (partly) explain the large difference in cardiovascular disease between the general and the renal population. Little attention is given to alterations in lipid composition in ESRD.

SERUM CHOLESTEROL IN ESRD

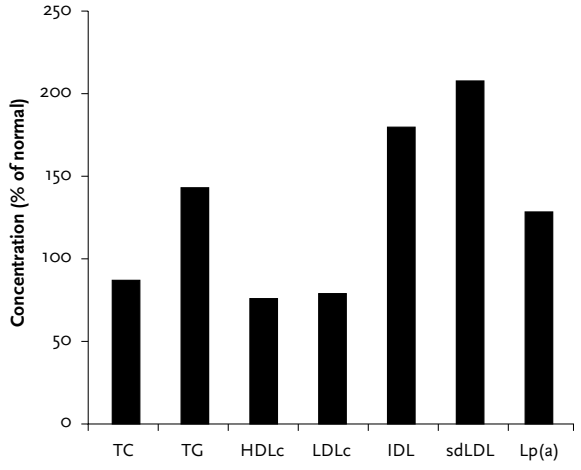
Characteristics of the lipid profile in ESRD

In patients with ESRD, dyslipidaemia is a common finding. This is caused by alterations in the metabolism and the composition of the plasma lipoproteins. The typical, traditional lipid profile in patients with ESRD is characterised by normal or low concentrations of LDL cholesterol, increased concentrations of triglycerides (TG) due to elevated levels of very-low-density lipoprotein (VLDL) and intermediate-density lipoprotein (IDL) and decreased high-density lipoprotein cholesterol (HDL). The LDL composition is abnormal and characterised by the presence of small dense LDL particles (*figure 1*). There are slight differences between patients treated with haemodialysis and those treated with peritoneal dialysis: levels of LDL cholesterol and small dense LDL are higher and levels of HDL cholesterol are lower in patients on peritoneal dialysis compared with patients on haemodialysis.[27,31-33] Most studies which describe the abnormalities in lipoproteins in ESRD focus on the 'absolute' levels of lipoproteins but do not mention possible alterations in the 'state' of these lipoproteins (e.g. oxidised or carbamylated), which may affect early onset of atherosclerosis.

Impact of dyslipidaemia on cardiovascular disease in ESRD

Several studies reported an association between dyslipidaemia and surrogate cardiovascular endpoints. Tamashiro *et al.* described that in chronic haemodialysis patients the progression of coronary arteries calcification

Figure 1. *Lipid abnormalities in patients with end-stage renal disease*[27,31-33]



TC = total cholesterol; TG = triglycerides; HDLc = high-density lipoprotein cholesterol; LDLc = low-density lipoprotein cholesterol; IDL = intermediate-density lipoprotein; sdLDL = small dense LDL; Lp(a) = lipoprotein (a).

was related to high concentrations of TG and low concentrations of HDL.[34] These data were confirmed in peritoneal dialysis patients.[35] Although these studies suggested that dyslipidaemia may affect cardiovascular outcome in patients with ESRD, many studies have failed to find a positive association between the traditional lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides) and cardiovascular endpoints in patients with ESRD.[36-39] In fact, these studies often noted a seemingly inverse relationship, low cholesterol levels being associated with higher mortality rates.[10] Although these observations have been used as arguments against a contributory role of cholesterol in cardiovascular disease in patients with ESRD, it is now clear that this 'reverse epidemiology' is explained by the confounding effects of malnutrition and inflammation.

Many patients with ESRD have evidence of malnourishment and chronic inflammation. Clinically these patients are characterised by lower body weight, lower blood pressure, low cholesterol, low serum albumin and elevated CRP. Survival rates are low in these patients. With this in mind it is no surprise that in patients with ESRD the presence of this chronic inflammatory state confounds normal associations and causes reverse epidemiology. Recent studies demonstrate this clearly. Liu *et al.* observed a higher cardiovascular event rate in ESRD patients with low serum cholesterol. However, when restricting the analysis to patients without inflammation and malnutrition they observed the 'normal' positive association between serum cholesterol and CVD mortality.[40] Iseki *et al.* confirmed this by showing that high concentrations of cholesterol were associated with a higher mortality risk in patients with normal serum albumin levels.[10] These studies suggest that in well-nourished, noninflammatory dialysis patients, hypercholesterolaemia is a cardiovascular risk factor.

Reverse epidemiology is only one part of the story. The lack of an association between LDL cholesterol and cardiovascular risk may also be explained by the contributions of other lipoproteins. As mentioned above, in patients with ESRD levels of IDL, small dense LDL and Lp(a) are increased. Several studies have reported a positive association between some of these lipoproteins and cardiovascular disease.

In patients with elevated levels of IDL there is evidence of atherosclerotic disease. Moreover, Shoji *et al.* showed that IDL is an independent risk factor for aortic sclerosis in HD patients.[41] In patients with ESRD Lp(a) is a risk factor for disease and mortality.[42-45] Finally, the highly atherogenic LDL subclass, small dense LDL, is present in HD patients.[32] In ESRD, these 'alternative' lipoproteins may fulfil a more important role in the development of cardiovascular disease than LDL. Therefore, it may be important to also focus on these nontraditional lipid parameters.

Moreover, biochemical modifications of LDL, not reflected by total and LDL cholesterol levels, may offer another explanation for the increased cardiovascular risk in patients with ESRD. The most important process involves the oxidation of lipids (discussed below in more detail).

Effect of treatment of dyslipidaemia in CRF and ESRD with statins

In the general population, treatment with HMG CoA reductase inhibitors or statins is one of the cornerstones in the strategies to reduce cardiovascular risk, both in primary and secondary prevention.[4-9] Since patients with CRF are at a high risk to develop CVD, treatment of all risk factors including serum cholesterol seems warranted. Indeed, most guidelines recommend aggressive treatment of LDL cholesterol. However, treatment with HMG CoA reductase inhibitors in patients with CRF is still open for debate, since for this subgroup the data on effect of treatment are scarce, as most trials excluded patients with severe renal insufficiency. Posthoc subgroup analysis of the Heart Protection Study (HPS) and the Cholesterol Recurrent Events Trial (CARE) indicated that cholesterol lowering was beneficial in patients with moderate renal insufficiency (GFR 30-60 ml/min.[6,46,47] However, few data are available to allow conclusions for patients with GFR <30 ml/min.

What is known about treatment of serum cholesterol in patients with ESRD?

A Cochrane review, published in 2004, concluded that statins decreased serum cholesterol in dialysis patients as effectively as in the general population. With respect

to the effects of statins on (cardiovascular) mortality no conclusions could be drawn because of the lack of studies with hard clinical endpoints.[48]

The effects of lipid-lowering therapy with statins on surrogate endpoints suggested potential benefits. Achenbach *et al*. demonstrated that treatment with cerivastatin reduced the progression of coronary calcium deposition.[49] Few studies have evaluated the effects of statin therapy on cardiovascular endpoints in patients with ESRD. Two uncontrolled studies reported a reduced cardiovascular mortality in patients who had been treated with statins.[50,51] This benefit was limited to patients with a previous history of cardiovascular disease. Although appealing, these data do not allow firm conclusions. Although the authors used multivariate analysis to adjust for known risk factors, confounding could not be excluded. In fact, only 10% of the ESRD patients used a statin, and those patients had higher cholesterol levels and less signs of malnourishment. Thus, the above-mentioned reverse epidemiology might explain the relationship between survival and statin use in these studies

The ongoing Study of Heart and Renal Protection (SHARP) is designed to study the effects of treatment with simvastatin and ezetimibe on cardiovascular disease in patients with chronic renal failure. Biochemical safety and efficacy have been shown.[52,53] The more interesting and important results of this study can be expected after 2007. The AURORA (Assessment of Survival and Cardiovascular Events) study is an ongoing randomised controlled trial, which will evaluate the efficacy of rosuvastatin in preventing cardiovascular events in HD patients.[54] Results of this study can be expected in the coming years.

So far, only one randomised controlled trial has evaluated the effect of treatment with a statin on clinical endpoints in haemodialysis patients.[55] Results of Die Deutsche Diabetes Dialysis study (4D study) were reported in 2005.

The 4D study included 1255 patients with type 2 diabetes mellitus on maintenance haemodialysis therapy. Patients with serum LDL-cholesterol levels between 2.1 mmol/l and 4.9 mmol/l were randomised for treatment with atorvastatin 20 mg or placebo. Primary endpoint was a composite of death from cardiac causes, nonfatal myocardial infarction and stroke. Secondary endpoints included death from all causes and all cardiac and cerebrovascular events combined. Atorvastatin effectively lowered serum cholesterol, was safe and well tolerated. Obviously, a reduction in cardiovascular endpoints was expected in view of the high cardiovascular risk profile of these patients. Disappointingly, treatment with atorvastatin did not significantly reduce the incidence of primary endpoints. The results of this study are often quoted and used as an argument against cholesterol lowering in patients with ESRD. However, it is important to take a closer look at the data. *Table 1* provides data on specific causes of death reported in the 4D study. Mortality was very high in the study population. It is evident that sudden death was more frequent than death from coronary heart disease. Atorvastatin lowered the incidence of death due to coronary heart disease, but had no effect on sudden death. As for the prevention of coronary death, treatment with atorvastatin was associated with an absolute risk reduction (ARR) of 2.2%, with a calculated number needed to treat (NNT) of 45. Admittedly, there was no overall statistically significant survival advantage in the atorvastatin-treated group, which is readily explained by the high incidence of death from nonatherosclerotic disease. Still, the analysis may suggest that also in patients with ESRD statins are able to modify the process of classical atheromatous disease and lower the incidence of classical, atherosclerotic coronary heart disease. In contrast, cholesterol lowering is unlikely to influence myocardial fibrosis and prevent death from cardiac arrhythmias.

Another interesting way of putting the results of the 4D study in perspective is a comparison between the 4D study and the Cholesterol Treatment Trialists' study (CTT), a meta-analysis of 14 randomised controlled trials (RCTs) of statins (*table 2*).[56] Specifically, when focusing on overall mortality and mortality due to coronary heart disease, it can be expected that cholesterol lowering is primarily beneficial by reducing the risk of an ischaemic atherosclerotic cardiovascular event. When calculating the absolute risk reduction of coronary deaths, the results of the 4D study appear comparable with the other studies with an ARR of 2.3% as compared with 0.4 to 3.5% in other studies.

Table 1. *Coronary mortality and sudden death in the Deutsche Diabetes Dialysis study*[12]

		Placebo (n=636)	Atorvastatin (n=619)	ARR	NNT
Cardiac death due to atherosclerotic disease	Death due to CHD	5 (0.8%)	1 (0.2%)		
	Death due to intervention for CHD	4 (0.6%)	3 (0.5%)		
	Fatal MI	33 (5.2%)	23 (3.7%)		
	Subtotal	42 (6.6%)	27 (4.4%)	2.2%	45
Nonatherosclerotic death	Sudden death	83 (13.1%)	77 (12.4)	0.6%	164
Subgroup 1 + 2	Total	125 (19.7%)	104 (16.8%)	2.9%	35

ARR = absolute risk reduction; NNT = numbers needed to treat; CHD = coronary heart disease; MI = myocardial infarction.

Table 2. *A comparison of the mortality due to coronary heart (CTT) disease and any death between the Deutsche Diabetes Dialysis (4D) study[12] and the Cholesterol Treatment Trialists' study[56]*

CTT	**Placebo (n=45,002)**	**Statin (n=45,054)**	**ARR**	**NNT**
Death due to CHD	1960 (4.4%)	1548 (3.4%)	0.9%	109
Any death	4354 (9.7%)	3832 (8.5%)	1.1%	89
4D	**Placebo (n=636)**	**Atorvastatin (n=619)**	**ARR**	**NNT**
Death due to CHD	42 (6.6%)	27 (4.4%)	2.2%	45
Any death	320 (50.3%)	297 (48.0%)	2.3%	43

ARR = absolute risk reduction; NNT = numbers needed to treat; CHD = coronary heart disease.

However, coronary death rate was only a small fraction of total mortality in the 4D study (11%). The overall mortality in the 4D study as well as the percentage of sudden deaths is impressive, whereas the absolute coronary event rate is rather low. One may thus conclude that, with respect to coronary events, the 4D study was clearly underpowered.

Furthermore, benefits of cholesterol lowering may not be expected in patients with the highest risk, i.e. patients with chronic inflammation and malnutrition on dialysis. As mentioned earlier, based on the data of Liu and Iseki, cholesterol lowering might be of benefit in patients with absent inflammation and no signs of chronic inflammation, most likely patients with a higher life expectancy.[10,40] In this respect the survival curve depicted in the CTT is interesting for the reported timeframe of protection. Although benefits of cholesterol lowering were evident within the first year, the effects were greater in subsequent years. Short-term mortality rate is high in patients with ESRD and in particular in patients with diabetic disease or patients with malnutrition and inflammation. Any benefit of statin treatment in patients with ESRD will thus only become apparent after many years, in patients who are well nourished, not inflamed and have a reasonable life expectancy. In this respect, analysis of the survival curves in the 4D study is notable. The survival curves of the placebo and the active treatment groups start to deviate after four years follow-up, indeed suggesting that differences might become evident with longer follow-up. It would be informative to know the state of inflammation and nutrition of the patients included in 4D and its relation with mortality. At baseline 58.6 % of the included patients had LDL cholesterol below 3.4 mmol/l. This is quite low and might be indicative of malnutrition.

Thus, we feel that the data of the 4D study do not allow the general conclusion that ESRD patients do not benefit from statin treatment. It will be important to select patients who will benefit from such therapy. We propose that this selection will include patients with pre-existing CVD and patients with a long life expectance (absence of inflammation and malnutrition). Ongoing large randomised controlled trials such as AURORA and SHARP will hopefully provide some answers and allow a more precise way of decision making in this high risk population.[54,57]

OXIDATIVE STRESS IN ESRD

Background of oxidative stress

Since increased oxidative stress is characteristic for patients on HD and may play an important role in the progression of atherosclerosis in ESRD, we will discuss this topic in more detail.

Oxidative stress can be defined as the result of an imbalance between the production of reactive oxygen species (ROS)/free radicals (FR) and antioxidant defences.[58] Oxidative injury can change the function and structure of biomolecules such as lipids, proteins, carbohydrates and nucleic acids. Oxidised lipids may be involved in the initiation and acceleration of atherosclerosis. Interventions directed at preventing lipid oxidation may have therapeutic potential.

Is oxidation present in ESRD?

In patients with CRF, the balance between pro-oxidant and antioxidant capacity is shifted towards an increased oxidative stress. The pro-oxidant effects are caused by factors that are characteristic for the CRF population, e.g. advanced age, diabetes mellitus, uraemic toxins, chronic inflammation, malnutrition and treatment with dialysis. Moreover, both the intracellular and extracellular antioxidant capacity is decreased because of depletion of selenium, vitamin C, vitamin E and decreased activity of super oxide dismutase and glutathione peroxidase.[59-62]

For a long time, reliable assessment of oxidative stress in CRF has been problematic and the results of different studies were inconsistent. These inconsistencies were most likely caused by the lack of standardised methods to determine the level of oxidative stress.

We assessed oxidative stress in ESRD patients using different methods.[63] First, we measured the susceptibility of circulating LDL particles to copper-induced oxidative stress *in vitro* as described by Esterbauer *et al.*[64] We observed that LDL particles of ESRD patients were not more susceptible for oxidation *in vitro* compared with matched controls. Our findings are in agreement with the observations of other authors.[65,66] Although these findings argue against increased oxidative stress in ESRD, this *in vitro* assay has several drawbacks. The test results may be

influenced by the blood composition of unsaturated fatty acids. In patients with ESRD, levels of monounsaturated fatty acids (MUFAs) but not polyunsaturated fatty acids (PUFAs) are higher than in controls.[65] Since MUFAs are less susceptible to copper oxidation, the increased amounts of MUFAs in ESRD might explain the measured decreased oxidisability in these patients. Furthermore, the test is influenced by several factors such as the blood temperature after collection, the storage temperature, and the levels of triglycerides, and vitamin C and E in the blood. Moreover, the 'oxidative' situation in this *in vitro* assay might not be representative for the situation *in vivo* in the subendothelial space, where the process of atherosclerosis takes place.
We also evaluated oxidation using a more recently developed monoclonal antibody against oxidised LDL. Increased antibody levels are accepted as markers of oxidative stress. We indeed noted increased antibody concentrations suggesting a higher LDL oxidation level in patients with ESRD.[63] Other markers have also been proposed for the assessment of oxidation such as plasma F2-isoprostanes and advanced oxidation protein products (AOPP). Recent studies all provided evidence for increased oxidative stress in CRF.[67-73]

Is there an association between increased oxidative stress and cardiovascular disease in ESRD?
Oxidised LDL particles play a pivotal role in the development of atherosclerosis: these particles are incorporated without restriction by macrophages through scavenger receptors. This promotes accelerated formation of foam cells, which will gradually transform and degrade into plaques, thus contributing to vascular stenoses.[13,74-77] An environment in which enhanced oxidative stress is present will therefore add to the development of atherosclerosis and cardiovascular disease.

In nonrenal patients, Holvoet *et al*. showed that a high level of circulating oxidised LDL particles is a sensitive marker of coronary artery disease.[70] Similar data were found in CRF patients. HD patients with a positive history of atherosclerotic disease have higher oxidised LDL concentrations than patients without a cardiovascular history.[78] Shoji *et al*. investigated the association between antibodies against oxidised LDL and the intima media thickness (IMT) in the carotid and femoral artery. They found that antioxidised LDL antibodies were positively correlated with IMT of the carotid artery.[79] The same authors described that the antioxidised LDL antibody titre is an independent predictor of cardiovascular mortality in patients with ESRD.[80]

Treatment of oxidative stress with vitamin E
Vitamin E refers to a group of eight, fat soluble, naturally occurring compounds, α-,- β-, γ- and δ-tocopherol and α-, β-, δ- and γ-tocotrienols. Of these compounds, α-tocopherol has been found to be the most abundant and active antioxidant of LDL.[81] Gamma-tocopherol is the predominant form of vitamin E in human diets, α-tocopherol is the primary form of vitamin E supplements.

Alpha-tocopherol acts by scavenging reactive oxygen species and singlet oxygen that otherwise would attack biomolecules such as lipids, proteins, sugars and nucleic acids.[82] In the process of lipid peroxidation, lipids react by propagation of a lipid peroxyl radical so that a lipid radical and lipid hydroperoxide are formed. Alpha-tocopherol scavenges the lipid peroxyl radical before it attacks its substrate (lipids). In this reaction, the lipid peroxyl radical is neutralised to lipid hydroperoxide and (the neutral) α-tocopherol is formed into a stable α-tocopherol radical which does not propagate radical chains and lipid peroxides. Moreover, vitamin C can donate an electron to the α-tocopherol radical so that α-tocopherol can be regenerated. In this way, the weak antioxidant vitamin C can enhance the antioxidative effects of vitamin E.
Alpha-tocopherol scavenges the peroxyl radical about ten times faster than the lipid reacts with the radical. Therefore, α-tocopherol prevents lipids from being modified by peroxyl radicals.

It is generally accepted that patients with CRF and ESRD suffer from increased oxidative stress resulting in increased lipid peroxidation. This is one of the contributing factors to the accelerated atherosclerosis in this population.

Himmelfarb *et al*. studied the α- and γ-tocopherol metabolism in patients with ESRD.[83] They found that serum α-tocopherol levels were similar between haemodialysis patients and controls. However, the levels of serum γ-tocopherol were higher in haemodialysis patients. This finding suggests that renal failure influences the γ-tocopherol metabolism. The metabolites of both α- and γ-tocopherol, α- and γ-carboxyhydroxychromans (CEHC) were tenfold and sixfold higher in haemodialysis patients compared with healthy subjects, respectively. These results confirm the role of urinary excretion of the water-soluble metabolites of tocopherol in subjects with normal renal function.

The observation that increased oxidative stress may contribute to progressive atherosclerosis has stimulated searches for antioxidant therapies.
It has been hypothesised that treatment with vitamin E can prevent the oxidative modification of LDL and in this way attenuate the development of atherosclerosis and cardiovascular disease. However, the results of studies on this subject are conflicting.
A meta-analysis by Vivekananthan *et al*. included 15 randomised controlled trials, seven evaluating the effects

of vitamin E and eight evaluating β-carotene.[84] The studies with vitamin E contained 81,788 patients from different populations, most with normal renal function. Both primary and secondary prevention trials were pooled. No beneficial effects of vitamin E were found. A similar conclusion was reached in an earlier meta-analysis by Asplund.[85] Moreover, data published by Miller *et al.* suggested that high-dosage vitamin E supplementation might unexpectedly increase all-cause mortality.[86]

What is known about the treatment with vitamin E in patients with chronic renal failure and ESRD?

Many studies on surrogate endpoints with vitamin E have been performed on ESRD.[87-92] These studies range from treatment with oral supplementation of vitamin E to treatment with vitamin E coated artificial kidneys. A problem in comparing and interpreting these studies is that the results are conflicting, probably as the result of the lack of uniform methods to assess oxidative stress.

In a post-hoc analysis of the Heart Outcome Prevention Evaluation study (HOPE), 993 patients with mild-to-moderate renal failure were analysed.[93] Primary endpoints were defined as the composite of myocardial infarction, stroke or cardiovascular death. Secondary endpoints included revascularisation, total mortality and clinical proteinuria. Treatment with 400 IU vitamin E once daily did not result in reduction of primary or secondary endpoints after an average follow-up of 4.5 years.

Thus far, the only RCT with vitamin E on hard clinical endpoints has been performed by Boaz *et al.*[94] The Secondary Prevention with Antioxidants of Cardiovascular disease in End stage renal disease (SPACE) showed that in 196 haemodialysis patients with known cardiovascular disease, supplementation with 800 IE/day of vitamin E reduced the risk on composite cardiovascular endpoints and myocardial infarction. This study suggests that vitamin E may be effective in patients with ESRD, and the differences with other studies could be explained by the higher grades of oxidative stress in ESRD. Although the results seem convincing, there are some caveats. Overall mortality was not influenced. Furthermore, the population in the study is somewhat different from the normal ESRD population as reflected by a rather low sudden death rate. Apparently, the authors have included a population at low risk for nonatherosclerotic death. Notably, although many patients had experienced a previous myocardial infarction or cerebrovascular accident, less than 50% of the patients were treated with aspirin. Since the results of SPACE were mainly driven by the difference in myocardial infarctions, it needs to be proven that similar benefits would have been obtained if all patients had received aspirin. Therefore, although the results of the SPACE study are very appealing they should be confirmed in a new study with noncomposite cardiovascular endpoints.

CONCLUSIONS

Cardiovascular risk is increased in patients with CRF, and is particularly high in patients with ESRD. However, in patients with ESRD cardiovascular mortality is not primarily the consequence of classical coronary heart disease but more often caused by sudden cardiac death. The latter is likely related to rhythm disturbances due to cardiac fibrosis and hypertrophy. In patients with CRF both traditional cardiovascular risk factors such as hypertension, diabetes mellitus, smoking, hypercholesterolaemia and nontraditional risk factors such as increased oxidative stress, malnutrition, disturbed calcium-phosphate balance and hyperparathyroidism contribute to the increased risk

Although cholesterol-lowering treatment is generally effective in patients with increased CVD risk, the evidence is lacking in patients with ESRD. The absence of proof should not lead to therapeutic nihilism. Interpretation of the data is hampered by reverse epidemiology in patients with ESRD, the high mortality rate due to nonatherosclerotic disease and malnutrition and inflammation. We would argue that cholesterol lowering should be considered in patients with known CVD and patients with ESRD without evidence of malnutrition and inflammation and a life expectancy of more than five years. Obviously, apart from cholesterol, treatment in patients with ESRD should be directed at optimising all other risk factors such as hypertension, calcium-phosphate balance, vitamin D and hyperparathyroidism. The role of influencing altered lipids in ESRD is unclear.

Randomised controlled trials that are underway will hopefully assist in further defining the population at risk who will benefit from interventions directed at cholesterol. In the meanwhile, treatment of patients with ESRD should be multitargeted. Also in this population cholesterol should not be an overlooked target.

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