

# Lipid Abnormalities and Cardiovascular Risk in Renal Disease

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## ABSTRACT

The recent 4D study failed to provide definitive evidence for benefit of statin use in type 2 diabetics on dialysis. This finding stands in stark contrast to a number of other observations in patients with early stages of chronic kidney disease where substantial benefit of statins had been documented. Here we discuss some potential explanations for the unexpected finding of the 4D study and for the negative association between below average total cholesterol and vascular mortality among dialysis patients. Admittedly, in the absence of definite evidence in dialysis patients, we still conclude that the administration of statins is appropriate in patients with manifest coronary disease.

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Unless a nephrotic syndrome is present,<sup>1</sup> lipid abnormalities captured by routine measurements are not impressive in patients with kidney disease; high-density lipoprotein (HDL) cholesterol concentrations tend to be low and triglycerides levels tend to be elevated. More importantly, the lipid parameters conventionally used to assess the indication for statins (total cholesterol and low-density lipoprotein [LDL] cholesterol) tend to be normal or even low.<sup>2</sup>

As shown in Table 1, however, more sophisticated analyses point to profound disturbances in lipid metabolism. Mainly as a result of decreased catabolism<sup>3</sup> of chylomicrons<sup>4</sup> and endogenous lipoprotein particles,<sup>5</sup> remnants of chylomicron and very-low-density lipoprotein<sup>4</sup> as well as LDL<sup>6</sup> accumulate, and in parallel so does small dense LDL.<sup>7,8</sup> Another typical disturbance is post-translational modification of apolipoproteins,<sup>9</sup> particularly apolipoprotein B100 by gly-

cation,<sup>10</sup> oxidation,<sup>11</sup> and carbamylation.<sup>12</sup> Such modifications of lipids<sup>13</sup> interfere with uptake of LDL by the classical LDL receptor, favoring uptake by the scavenger receptor LOX1, which plays an important role in atherogenesis.

Of particular interest are abnormalities of lipoprotein(a) (Lp(a)). Many controversial findings in the literature are explained by the impact of Lp(a) concentrations on cardiovascular endpoints, depending strongly on a gene polymorphism: low molecular weight and high molecular weight phenotypes.<sup>9</sup> In hemodialysis patients, the apo(a) phenotype is an independent and even stronger predictor of coronary events than the absolute Lp(a) concentration,<sup>14</sup> patients with low molecular weight phenotype being at greater risk. In uremia, the catabolism of Lp(a) is diminished.<sup>15</sup> It has also been known for some time that, in acute inflammation, HDL particles incorporate serum amyloid A and act not as protec-

tive, but paradoxically as pro-atherogenic particles.<sup>16</sup> Such transformation of HDL into “inflammatory,” acute phase HDL has also been documented in uremic patients.

## CORRELATIONS BETWEEN DYSLIPIDEMIA AND CARDIOVASCULAR EVENTS

In 1982, Degoulet *et al.* made the somewhat paradoxical observation in hemodialysis patients that low cholesterol is associated with increased mortality.<sup>17</sup> This finding has been confirmed by numerous authors.<sup>18</sup> Many studies have also evaluated the correlation between cardiovascular outcome and differences in other lipid parameters (LDL cholesterol, HDL cholesterol, and triglycerides).<sup>19</sup> None of these routinely measured parameters consistently predicts cardiovascular events, with one notable exception. Nishizawa proposed to measure non-HDL cholesterol,<sup>20</sup> which is mainly a reflection of the accumulation of incompletely catabolized lipid particles. This parameter predicts cardiovas-

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**Table 1.** Dyslipidemia in chronic kidney disease

Lipids	Lipoproteins
Abnormal	VLDL remnants/IDL
low HDL cholesterol	Chylomicron remnants
high triglyceride	Small dense LDL
	Apolipoprotein modifications (glycation, oxidation, carbamylation)
	AGE-ApoB
	high Lp(a)
	acute-phase HDL
Normal	
total cholesterol	
LDL cholesterol	

cular events in Japanese patients with end-stage renal disease.

The original observation by Degoulet *et al.* of an inverse relation between total cholesterol and survival is currently interpreted to be the result of confounding by comorbid conditions, particularly an activated acute-phase response.<sup>21</sup> This interpretation gained credence with the observation of Liu *et al.*,<sup>22</sup> in a large cohort of dialysis patients, and in patients with high C-reactive protein (CRP), that an inverse relationship exists between total cholesterol and mortality, while in patients with low CRP (pointing to the absence of micro-inflammation), the relationship is continuous and positive as it is in the general population. Against this background, it is obvious that classical guidelines, such as the national cholesterol education program adult treatment panel III ([www.nhlbi.nih.gov/guidelines/cholesterol](http://www.nhlbi.nih.gov/guidelines/cholesterol)) cannot be used to establish indications for lipid-lowering therapy, at least in patients with advanced renal disease. It is also argued that chronic kidney disease (CKD) should, on the basis of the high overall risk, be treated as a coronary equivalent similar to diabetes mellitus, thus lowering the decision threshold.<sup>23</sup> A reliable database to support this notion is still lacking.<sup>24</sup>

## STATINS IN PATIENTS WITH EARLY RENAL DISEASE

Although the pattern of dyslipidemia with low HDL and elevated triglycerides would *a priori* seem a classic indication for fibrates, fibrates have not been popular in the renal community. This is

mainly because most fibrates or their active metabolites accumulate in renal failure and occasionally cause rhabdomyolysis. Alternative interventions, such as dietary changes<sup>25</sup> or switching to polyunsaturated fatty acids,<sup>26</sup> carry a considerable risk of malnutrition or are difficult to implement. The nephrologist is thus left with cholesterol-lowering drugs, such as statins or ezetimibe. Potential indications for statins in patients with renal disease might be to assist in the reduction of proteinuria or to reduce the rate of loss of glomerular filtration (progression) apart from the goal to reduce cardiovascular events.

Statins are highly effective in inhibiting progression of renal damage in numerous experimental models,<sup>27</sup> mainly through their pleiotropic effects. In contrast, only some suggestion of efficacy, but no definite information, has been provided by observational<sup>28</sup> and isolated, prospective controlled trials in humans.<sup>29</sup> Nevertheless, meta-analyses of participants with cardiovascular disease in randomized controlled studies with statins who had impaired renal function and/or proteinuria show a modest, though statistically significant reduction in the loss of eGFR with statins (except in patients with diabetic nephropathy or glomerulonephritis) as well as a modest, significant reduction of proteinuria or albuminuria.<sup>30</sup> The data on reduction of proteinuria are currently not sufficient or compelling, however, to justify recommendations to use statins with the rationale of attenuating the rate of loss of renal function.

More convincing are findings con-

cerning the effect of statins on cardiovascular endpoints in patients with the initial stages of CKD (CKD stage 2 or early CKD stage 3). The effect of statins has been analyzed in several subgroups of patients with elevated serum creatinine who participated in prospective intervention trials on the effect of statins in patients with high cardiovascular risk. *Post hoc* analyses in these subgroups with impaired GFR suggest that the benefit is at least as high, if not higher, in patients with CKD compared with patients without CKD.<sup>31</sup> A similar effect was observed in the subgroup of patients with diabetic kidney disease.<sup>32</sup> Significant benefit with respect to lowering cardiovascular events is seen in patients with CKD (stage 2 and stage 3) based on serum creatinine concentration and eGFR. In the Cholesterol and Recurrent Events (CARE) study, this was restricted to patients with GFR <40 ml/min with or without proteinuria.<sup>32</sup>

In the Assessment of Lescol in Renal Transplantation (ALERT) study, Holdaas *et al.*<sup>33</sup> demonstrated a trend for, and in a recent long-term follow-up, significant benefit<sup>34</sup> with respect to cardiovascular outcome from statins in kidney graft recipients. One has to consider, however, that in transplant patients numerous potential confounders are operating. More compelling for the indication to use statins are analyses of subgroups of patients with elevated serum creatinine in trials such as the Anglo-Scandinavian Cardiac Outcomes Trial,<sup>35</sup> Medical Research Council/British Heart Foundation Heart Protection Study,<sup>36</sup> and the meta-analyses on the effect of simvastatin on all-cause mortality and coronary events in the patient with mild CKD in the 4D study (Die Deutsche Diabetes Dialyse Studie).<sup>37</sup>

These controlled trials also suggested benefit with respect to loss of renal function and reduction of proteinuria. In meta-analyses of intervention trials with statins in patients with coronary heart disease treated with Pravasin, a modest although significant lower rate of loss of GFR was found,<sup>32</sup> with some modest reduction in proteinuria as well. It is remarkable that in the Physicians Health Study high cholesterol was predictive of a

late rise in serum creatinine.<sup>38</sup> Nevertheless, there is consensus that these effects on GFR loss in and by themselves also do not justify the use of statins.<sup>39</sup>

## STATINS IN PATIENTS WITH ADVANCED RENAL DISEASE

Currently, there is a complete lack of controlled information on the effects of statin treatment on outcome in patients with advanced CKD (stage 4). In the past, information on use of statins in dialysis patients had also not been uniform. In an observational study, based on U.S. Renal Data System data, Seliger *et al.* found better survival in a small subgroup of statin users ( $n = 362$ ) compared with nonstatin users ( $n = 3354$ ).<sup>40</sup> More recently, in an open prospective randomized study of a small group of patients ( $n = 143$ ) followed over 20 mo, Holmberg *et al.*<sup>41</sup> found that Atorvastatin had no significant effect on primary cardiac endpoint in patients on dialysis whereas an effect was seen in individuals with pre-end-stage renal disease, potentially suggesting that one may be too late when starting statin treatment if the patient is ready for dialysis.

More definite evidence has meanwhile been provided, at least for diabetic patients, by the randomized prospective controlled 4D study.<sup>42</sup> In this study, a total of 1255 dialysis patients with type 2 diabetes were randomized to receive Atorvastatin (20 mg/d) or placebo. The LDL cholesterol concentration was lowered from a median of 121 mg/dl to 72 mg/dl in the Atorvastatin group; in the placebo group, LDL cholesterol values remained significantly higher throughout the study, although there was a tendency for LDL cholesterol to decrease in the course of the study, presumably because of progressive malnutrition. Patients with fasting LDL cholesterol >190 mg/dl had been excluded, so the study results cannot necessarily be extrapolated to diabetic dialysis patients with cholesterol values above this level.

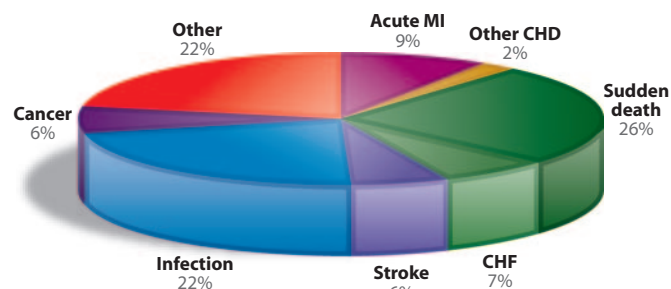
The cumulative incidence of primary composite cardiovascular endpoints comprising death from cardiac causes,

fatal stroke, nonfatal myocardial infarction, or nonfatal stroke was not significantly lower over an average observation period of 4 yr (relative risk reduction 8%, 0.77 to 1.10, not significant). There was a positive result, however, for the secondary endpoint of all combined cardiovascular events (205 *versus* 246 cases in Atorvastatin *versus* placebo-treated patients, relative risk = 0.82,  $P = 0.03$ ). It remains unclear whether these data in diabetic patients can be generalized or extrapolated to nondiabetic patients. This will be clarified by two ongoing trials (a study to evaluate the use of Rosuvastatin in subjects on regular dialysis: an assessment of survival and cardiovascular events [AURORA] and Study of Heart and Renal Protection [SHARP]).

The negative outcome of the 4D study came as a surprise, but several explanations have been advanced. Experimental studies suggest that, as originally postulated by Lindner *et al.*,<sup>43</sup> atherogenesis is accelerated by even minor reductions in renal function.<sup>44</sup> It is likely that in patients on dialysis the mechanisms of progression of coronary heart disease differ from those operating in the general population. A clinical pointer in this direction may be the observation of Fathi *et al.*<sup>45</sup>; in a small prospective study, they assessed the effect of aggressively lowering of LDL cholesterol with Atorvastatin, comparing patients with primary coronary artery disease without renal dysfunction against patients with advanced renal failure. In nonrenal patients with coronary artery disease, the maximum intima/media thickness of the carotid artery (as an index of vascular damage) decreased significantly by this intervention

during a 2-yr observation period; it remained unchanged, however, in patients with CKD. This observation is compatible with the assumption that the beneficial effect of statins is counteracted or abrogated by uremic-specific mechanisms. Anatomical studies of the coronary arteries point in the same direction. When we compared the coronaries of patients with coronary heart disease who either had no kidney disease or advanced CKD, the coronaries of CKD patients had a dramatically 5-fold higher prevalence of coronary calcification.<sup>46</sup> More recently, we also found in uremic patients significantly more intense pro-inflammatory changes (increased deposition of CRP, C5b9, or macrophage infiltration), higher expression of TGF- $\beta$  and endothelin, as well as evidence of more intense postintraplaque hemorrhage, indicated by more frequent and intense deposits of the erythrocyte membrane protein, glycophorin.<sup>47</sup>

An alternative or complementary possibility must also be considered. According to the U.S. Renal Data System registry (www.usrds.org) and confirmed by the 4D study (Figure 1), coronary heart disease accounted for only a small proportion of adjudicated cardiovascular deaths, approximately 9%. A greater proportion of patients, approximately 33%, died of sudden death or congestive heart failure. This is drastically different from the percentages observed in the background population without CKD. It is therefore likely that a statistically significant change in the primary endpoint was missed because the power of the study to find a significant overall difference of the primary composite endpoint was insufficient, particularly in view of



**Figure 1.** Causes of death in the 4D (Die Deutsche Diabetes Dialyse) study. MI, myocardial infarction; CHF, congestive heart failure; CHD, coronary heart disease.

the relatively low frequency of death from coronary heart disease. It is of note that in the past, as well as in the planning stage of the 4D study, it had been assumed that sudden death in dialysis patients was a consequence of ischemic heart disease, which is indeed found in the majority of individuals without renal disease who succumb to sudden death.<sup>48</sup> This negative finding in the 4D study is remarkably reminiscent of “The dog that did not bark” by Sherlock Holmes, see Conan Doyle. It is perhaps a pointer to prompt investigators to study the pathophysiologic mechanisms underlying sudden death and to determine in controlled trials, whether alternative interventions such as reduction of sympathetic overactivity by  $\beta$ -blockers are effective against this outcome.

The side-effect profile of statin therapy in 4D dialysis patients who were diabetic was extremely favorable: 3- to 5-fold elevation of CPK (11 cases on Atorvastatin versus 3 cases on placebo); >5 to 10 times elevation (1 patient in each treatment arm). No cases of rhabdomyolysis were observed. One point deserves attention, however. Although the absolute figures were small, an excess number of fatal strokes were observed in the Atorvastatin arm (27 versus 13 cases), while the number of nonfatal strokes was similar (33 in the Atorvastatin versus 32 in the placebo arm). This problem had not been noted in other statin trials where, to the contrary, even a reduction in stroke rate was found in patients without CKD.<sup>49,50</sup> A statistical fluke cannot be excluded. Definite information will certainly be provided by the combined results of the 4D and the ongoing AURORA<sup>51</sup> and SHARP<sup>52</sup> trials.

## USE OF STATINS IN RENAL PATIENTS

Even in early stages of CKD, the cardiovascular risk is dramatically increased.<sup>53,54</sup> In our opinion, the data from *post hoc* analyses of past statin trials on subcohorts of patients in the early stages of CKD (CKD stage 2 or early CKD stage 3) are sufficiently suggestive

to justify administration of statins. It is our opinion that statins are indicated in these patients based on these above *post hoc* analyses. It has even been argued that CKD should be considered a coronary heart disease equivalent,<sup>23</sup> although the magnitude of excess cardiovascular risk in early CKD undoubtedly needs further assessment.<sup>24</sup>

Certainly, the 4D study does not provide a rationale to start statin treatment in dialyzed diabetic patients, and by extrapolation, presumably also in nondiabetic dialysis patients or patients with CKD stage 4. One presumably comes in too late when starting statins with the aim of primary prevention in the absence of signs and symptoms of coronary heart disease once the patient has advanced to CKD stage 4 or 5. In agreement with current recommendations, however, it is our opinion that patients who are already on statins when entering a dialysis program should be left on statins.

The 4D study, which in retrospect was probably underpowered, showed suggestive benefit (although not statistically significant) in hemodialysis diabetic patients for adjudicated cardiovascular death, nonfatal myocardial infarction, coronary bypass, or percutaneous coronary angiography. The magnitude of reduction (approximately 19% per 1 mmol lowering of LDL cholesterol) was exactly identical to what had been observed previously in patients without CKD.<sup>55</sup> Consequently, in our opinion, it is acceptable, although currently not proven by controlled, prospective evidence, to administer statins to diabetic patients on dialysis who have established coronary heart disease. This argument can presumably be extrapolated to nondiabetic patients as well. Because patients with LDL cholesterol >190 mg/dl had been excluded from the 4D study, administration of statins may also be justified in such rare patients, admittedly in the absence of definite information.

In the future, the results of the ongoing trials, AURORA<sup>51</sup> and SHARP,<sup>52</sup> will hopefully put an end to current uncertainties and place recommendations on statin use on more solid footing, for renal patients with CKD in general and hemo-

dialysis patients more specific. If samples sizes in these trials are still too small to show the evidence, the meta-analyses from all patients combined ( $n = 7100$ ; including 4D) will prove or disprove the benefit of statin treatment in hemodialysis patients by the year 2012.

## DISCLOSURES

None.

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