

Lipid lowering in chronic kidney disease: What did we learn from the 4D study?

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ABSTRACT

Currently strategies are developed to combat cardiovascular disease and clinical studies test a number of hypotheses. In this setting the results of the 4D study, comparing atorvastatin with placebo on cardiovascular outcomes in 1255 type 2 diabetic patients on maintenance hemodialysis, came as a great and unexpected surprise among all statin studies that showed potential benefits in high risk patients. After a median follow-up of 4 years, atorvastatin (20 mg/

day) achieved a non significant decrease in relative risk by 8 % (95 percent confidence interval, 0.77 to 1.10; P=0.37) despite a high number of cardiovascular events. This indicates that the risk to type 2 diabetic patients on hemodialysis originates from factors other than an atherogenic lipoprotein phenotype alone. Renal dysfunction profoundly alters the pathogenesis of cardiovascular disease, conferring a very high risk to the patients (48% mortality during 4 years of follow-up). Due to non significant effects of atorvastatin on the primary endpoint and the different quality of such endpoints in dialysis patients as well as an unexplained higher rate of fatal strokes in atorvastatin treated patients, we do not recommend initiating statin treatment in patients with type 2 diabetes mellitus undergoing hemodialysis therapy at the present time. Statin therapy

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should be implemented earlier during the course of progressive vascular damage.

Key words: Haemodialysis, type 2 diabetes mellitus, dyslipidemia, cardiovascular disease, atorvastatin.

INTRODUCTION

Observational studies have so far failed to demonstrate a positive relationship between total cholesterol and mortality in hemodialysis patients as the relationship between serum lipids and accelerated cardiovascular disease (CVD) is confounded by underlying comorbid diseases. In fact, a reverse relationship exists whereby low cholesterol is associated with higher mortality rates¹. This does not necessarily preclude that lipid lowering might not be effective in patients on maintenance hemodialysis treatment. Equally so, renal disease patients may be a group especially prone to be exposed to statin therapy because they have an atherogenic lipoprotein phenotype that cannot be detected by measuring and correlating serum cholesterol alone. Patients typically have raised serum triglyceride levels, low HDL-cholesterol levels and elevated LDL-cholesterol concentrations which are considered to be highly atherogenic. Individuals in the general population with this profile have been described as exhibiting an 'atherogenic lipoprotein phenotype'. Growing evidence indicates that all components of this type of dyslipidemia are independently atherogenic, each conferring an atherogenic risk additional to that of LDL-cholesterol alone.

In addition, prominent oxidative stress and inflammation (C-reactive protein levels are 10-fold higher than in the general population), and multiple comorbidities may result in higher ben-

efits from statin treatment, a type of therapy with antioxidative and anti-inflammatory capacities. Nevertheless, most major statin trials excluded patients with end-stage renal disease (ESRD) so there are little data on efficacy and safety in patients with type 2 diabetes mellitus on chronic hemodialysis treatment who represent the highest risk group for cardiovascular disease.

THE 4D STUDY - ATORVASTATIN IN PATIENTS WITH TYPE 2 DIABETES MELLITUS UNDERGOING HEMODIALYSIS TREATMENT

The trial included patients with type 2 diabetes mellitus, aged 18-80 years, who had been receiving maintenance haemodialysis therapy for no more than 24 months and lipid parameters included LDL cholesterol between 80 and 190 mg/dL, triglycerides < 1000 mg/dL, with no CVD events 3 months prior to screening. The design included a run-in phase of 4 weeks, after which patients were randomized to 20 mg atorvastatin (n = 619) or placebo (n = 636). Baseline characteristics were well matched between both groups and included a duration of diabetes of approximately 18 years, a relatively low BMI of 26, a well controlled HbA1c of 6.8 %, a low albumin of 36 g/L and a high phosphate of 6.8 mmol/L.

Within a period of 4 weeks, atorvastatin lowered LDL cholesterol to 72 mg/dL (-41%); triglycerides decreased (-20%), and HDL increased (+4.5%). Over the 4-year study period, the LDL-cholesterol stabilized at 70 mg/dL in the atorvastatin group, with a 17% reduction observed in the placebo group as well. This might be attributed to the cholesterol-lowering effect of inflammation and malnutrition as well as a minor percentage of drop-ins to statin therapy.

An 8% relative risk reduction in the primary composite endpoint (cardiac death, nonfatal MI,

and stroke) was observed in the atorvastatin group compared with the placebo after a median follow-up of 4 years, which was not statistically significant². Of note, there was a higher incidence of fatal stroke in the atorvastatin group compared with the placebo (27 versus 13; relative risk 2.03; $P = 0.04$).

This could not be explained and might well be a chance finding, but contributed to the small (non-significant) difference in risk reduction observed between atorvastatin and placebo for the primary endpoint. The overall rate of stroke was not different from that observed in epidemiological studies in this population.

Secondary endpoints included all-cause mortality, all combined cardiovascular events, all combined cerebrovascular events, and percent change in lipid profile. Atorvastatin reduced the rate of all cardiac events combined (relative risk, 0.82; 95 percent confidence interval, 0.68 to 0.99; $P=0.03$, nominally significant) but not all cerebrovascular events combined (relative risk, 1.12; 95 percent confidence interval, 0.81 to 1.55; $P=0.49$) or total mortality (relative risk, 0.93; 95 percent confidence interval, 0.79 to 1.08; $P=0.33$).

The incidence of adverse events was comparable between groups and consistent with previous studies conducted in similar populations.

EXPLANATIONS FOR THE RESULTS OF THE 4D TRIAL

Clearly, chronic kidney disease patients show an altered pathogenesis of atherosclerosis, a higher incidence of sudden death and a lower proportion of coronary artery versus all-cause mortality as compared with persons from the general population. Vascular disease in dialysis patients, which is in part also dependent on other risk factors in their progression of calcification,

is also called arteriosclerosis. High serum phosphate levels and consequently a high calcium x phosphate product are prominent predictors of cardiovascular complications and are involved in the pathogenesis of the disease.

In comparing causes of death in 4D and the USRDS database with data from randomized controlled trials in persons with normal kidney function from the general population, large differences become evident. Diabetic dialysis patients in 4D show a 9 percent death rate from coronary origin, relatively consistent with patients from the USRDS database (6 percent). In contrast, the rate of death from coronary heart disease in persons with normal kidney function was 42 percent (Meta-analysis from large randomized controlled trials; Cholesterol Treatment Trialist collaboration; personal communication). Other cardiac deaths occurred with a frequency of 7 percent in the general population whereas 35 percent of deaths were from cardiac origin in 4D and 33 percent in USRDS. Therefore the different pattern and expression of the cardiovascular disease appears to reflect structural heart disease in the hemodialysis population rather than sclerotic vascular disease and may explain the lack of a therapeutic effect of atorvastatin in 4D study patients. Comparing the results of 4D with data from large randomized controlled statin trials from the general population, we also should ask to what extent the randomized evidence fits with the observational evidence. Indeed, the results of 4D are largely in line with expectations if allowance is made for the high proportion of non-coronary heart disease cardiac deaths. Certainly 4D had insufficient power to demonstrate a 7% reduction in the primary endpoint but uncertainty remains about the unexpected increase in stroke. Therefore, much larger trials are needed to generate randomized evidence, trials such as AURORA and SHARP. A meta-analysis of all relevant trials should be

done as soon as possible to come to a final conclusion. Nevertheless, we urge all nephrologists to randomize patients into prospective controlled trials whenever possible to verify the efficacy and safety of lipid-lowering agents in CKD patients of all stages.

The lack of a therapeutic effect of atorvastatin treatment also suggests that once the patients are dependent on dialysis they are beyond treatment. Accumulating evidence suggests that arteriosclerosis manifests via alternative pathomechanisms unresponsive to statin therapy. Nontraditional cardiovascular risk factors, such as phosphate and anemia, in a setting of high-grade inflammation and malnutrition are among the potential candidates.

Patients with diabetes mellitus of long duration also represent a very special population not reflecting the normal CVD risk population. Conventional cardiovascular risk factors may not play such a big role. As survivors, these patients may also exhibit protective genes. Therefore, a completely different pathophysiology and set of risk factors may have influenced the endpoints in this study.

Furthermore, the inclusion of stroke in the primary endpoint changed the findings with statins. The higher rate of stroke in the atorvastatin group may be a chance effect. At present several colleagues ignore the additional negative stroke results and continue to advocate statin therapy. The implications in clinical practice are whether we should believe that all cardiovascular endpoints combined are valid and ignore the additional cerebrovascular endpoints, or simply interpret this as a negative finding for statins. It was suggested that perhaps stroke manifests differently in dialysis patients and that statins may not offer appropriate protection against stroke in these patients. It should be pointed out that the majority of strokes were ischemic in nature,

which would normally be reduced with statin therapy. Importantly however, risk factors related to CKD, such as anemia, abnormal calcium and phosphate metabolism, enhanced sympathetic activity, and chronic inflammation are non-traditional mediators of cardiovascular disease.

In summary, half of the deaths in 4D were not cardiovascular related, which is in accordance with USRDS but slightly more than in the general population. Therefore, reduction of any primary endpoint has to occur with a prominent effect to overcome this competing risk, especially in respect to effects on all-cause mortality. The non-significant relative risk reduction seen in this randomized controlled trial highlights the importance of further trials that prove or disprove the conclusions drawn here and drawn from retrospective observational cohort studies or post hoc subgroup analyses in the dialysis population. The lack of a pronounced effect suggests the necessity to start lipid lowering treatment with a statin earlier in stages of the disease where comorbid diseases and the damage of the vasculature are less prominent than in renal failure patients. Results from the CARDS trial also underline this suggestion.

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