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Title: Statins for haemodialysis patients with diabetes? Long-term follow-up endorses the original conclusions of the 4D study.

Authors: David C Wheeler[1] and Bertram L Kasiske[2]

Relevant to: KI-08-15-1332.R1. Effects on 11-year mortality of 4 years of randomized treatment with atorvastatin in patients with type 2 diabetes mellitus on haemodialysis, the 4D Post-Trial-Follow-Up. Krane V, Schmidt K-R, Gutjahr-Lengsfeld L, Mann J, März, W, Swoboda F, Wanner C for the 4D Study Investigators (The German Diabetes Dialysis Study Investigators).

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Address for correspondence: David Wheeler, Centre for Nephrology, University College London, Rowland Hill Street, London, NW3 2PF, UK

[1]Centre for Nephrology, University College London, UK.
[2]Department of Medicine, Hennepin County Medical Center, Minneapolis, MN, USA

Lipid-lowering trials involving haemodialysis patients

The German Diabetes and Dialysis (or “4D”) Study, addressed whether lowering low density lipoprotein (LDL) cholesterol with statin therapy would reduce cardiovascular events in haemodialysis patients with type II diabetes. Between March 1998 and October 2002, the 4D investigators randomly allocated 1,255 patients at 178 dialysis centres throughout Germany to either atorvastatin 20 mg or placebo. The primary endpoint was a composite of death due to cardiac causes, non-fatal myocardial infarction and stroke. The study was terminated in March 2004 after the pre-specified 424 endpoints had been recorded during a median follow-up of 4 years. Despite a 42% reduction in LDL cholesterol concentration (compared to 1.5% with placebo), atorvastatin had no statistically significant effect on the composite primary endpoint, which was recorded in 226 patients randomized to atorvastatin as compared to 243 patients assigned to placebo (relative risk 0.92, 95% confidence interval 0.77 to 1.10, p=0.37) [1].

Taken in the context of accumulating evidence that statins reduced cardiovascular events in populations without stage 5 CKD [2], the results of 4D were controversial. However, they were supported by data from A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events (AURORA), published just 4 years later. The AURORA investigators randomly allocated 2776 haemodialysis patients, approximately 25% of whom had diabetes, to rosuvastatin 10 mg or placebo. They reported a non-significant 6% reduction in a composite endpoint very similar to that used in 4D (but including death due to vascular as well as cardiac causes) among patients randomized to rosuvastatin (hazard ratio 0.96; 95% confidence interval 0.84 to 1.11; P=0.59) [3].

At a time when many nephrologists were starting to abandon statin treatment in haemodialysis patients, the Study of Heart and Renal Protection (SHARP) reported a 17% reduction in cardiovascular events specifically attributable to atherosclerotic disease among 9270 patients with chronic kidney disease,

including 2527 haemodialysis patients randomly allocated to simvastatin 20 mg plus ezetimibe 10 mg as compared to placebo (rate ratio 0·83, 95% CI 0·74-0·94; log-rank p=0·0021) [4]. In contrast to 4D and AURORA, the primary endpoint in the SHARP study, a composite of non-fatal myocardial infarction or death due to coronary artery disease, non-haemorrhagic stroke, or any revascularization procedure, was selected to reflect events likely to result from underlying atherosclerotic arterial disease. The SHARP study was not powered to separately assess the impact of LDL cholesterol lowering in the haemodialysis population, but clinicians remaining loyal to the 4D and AURORA results noted that the impact of LDL-lowering was less marked among the 3023 SHARP participants who were receiving dialysis at the time of randomization (including 496 on peritoneal dialysis). However, this trend was not statistically significant and may be largely explained by the poorer compliance with study medication in the dialysis subgroup.

The LDL-weighted proportional effects of statin or statin-based therapy on specific atherosclerosis-related vascular outcomes are statistically comparable in 4D, AURORA and SHARP [4]. In other words, the impact of LDL-lowering on complications of atherosclerosis was similar in all three studies. The absence of significant reductions in cardiovascular events observed in 4D and AURORA may simply reflect a smaller patient population and the fact that the primary outcomes included fewer events attributable to atherosclerosis and therefore amenable to lipid lowering intervention.

Faced with the available data, which had been subject to meta-analysis [5], (figure 1) the workgroup assigned to write the Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guideline for Lipid Management in Chronic Kidney Disease recommended that a statin or statin-based lipid-lowering regimen should not be commenced in patients receiving dialysis, but that if patients were already on these therapies, they should be continued [6].

New data from extended follow-up of 4D patients

In this issue of Kidney International, the 4D study investigators publish the results of a long-term follow-up of their original patient cohort [7]. This new analysis covers a median of 11.4 years, with subjects being randomly allocated to atorvastatin versus placebo for only the first 4 years. Once the study closed, treatment was left to the discretion of the physicians responsible for the care of the patients. In the post randomization period, approximately 50% of study participants were prescribed statins, this proportion being similar in the two original groups, as were their LDL cholesterol concentrations during the post study period. Collection of follow-up end-point data involved sending questionnaires to healthcare professionals who had current contact with the study participants or to participant's relatives. The investigators also obtained data from hospital records and death certificates. The response rate to the questionnaires was very high (over 95%) with information obtained on all but 20 of the original 1255 participants.

During the extended 11 year follow-up period, when considering the original primary composite endpoint of the 4D study (death due to cardiac causes, non-fatal myocardial infarction and stroke), there was again no significant difference when comparing groups previously allocated to atorvastatin or placebo, with a relative risk almost identical to that observed in the original analysis (0.91, 95% confidence interval 0.78-1.07, p=0.256). Whilst during the randomized phase of the study, atorvastatin did not impact on any of the individual components of composite primary endpoint (except for an increase in fatal stroke in those randomly allocated to atorvastatin), after the extended follow-up there were fewer fatal cardiac events in this group (0.80, 95% CI 0.66-0.97, p=0.02). There was also a reduction in all cardiac events combined (0.83, 95% CI 0.7-0.97, p=0.019), reflecting the nominally significant reduction in this endpoint reported in the original analysis. Reassuringly, during extended follow-up, prior atorvastatin treatment did not modify the risk of stroke overall or fatal stroke. The extended follow-up also provides additional safety data with no differences in cancer risk, non-vascular death, all-cause

mortality and no cases of rhabdomyolysis reported. There was also no difference in cause specific mortality when comparing the two groups.

Strengths and weaknesses of this new analysis

These findings replicate the original trial results with relative risks that are almost identical to those obtained during the randomized phase of the study. The major strength of the new analysis is the duration of follow-up, possibly the longest for any randomized trial involving haemodialysis patients. As the authors remind us, their results reflect those observed during extended follow-up of cohorts recruited into other statin studies, in which differences in risk attributable to LDL lowering persist for several years after the randomized phase has been completed [8].

The 4D investigators recognize the potential limitations of their unblinded post hoc analysis, but point out that the high response rate to the questionnaires, which was equal in the two groups (97.5% return rate for patients previously randomized to Atorvastatin as compared to 96.5% for placebo), would have minimized the likelihood of bias. However, it remains possible that knowledge of prior treatment assignment might have influenced post randomization reporting of endpoints by physicians. The authors conducted an analysis to check for competing risks by other causes of death, but this did not change their results. Further follow-up of the cohort is unlikely to change the conclusions because, in keeping with the high level of risk in this group, only 81 of the original 1255 participants are yet to experience a cardiovascular event.

The new data in the context of our current knowledge

These new data endorse the original conclusions of the 4D study. The decision to start statin therapy in an individual haemodialysis patient should take into consideration the likely contribution of atherosclerotic disease to future cardiovascular events. Atherosclerosis is one of several pathological processes underlying cardiovascular events in the haemodialysis population

[9], and the benefits of LDL-lowering (which include decreased plaque size and increased plaque stability) will be diluted by the progression of other pathological processes which lead to non-atherosclerotic events. Alternative interventions, for example to reduce myocardial fibrosis, are also required to reduce the clinical burden of cardiovascular disease. Many of the cardiovascular events captured in 4D, both during the original study and extended follow-up, had their origins in non-atherosclerotic pathologies. As shown in the SHARP study, selection of endpoints more directly relevant to atherosclerotic narrowing of arteries might have resulted in a different trial outcome, assuming that a sufficient number of relevant events occurred.

Where should we go from here?

It seems unlikely that there will be more trials comparing statin therapy to placebo in the haemodialysis population, although we may learn more from the trials that have been completed. Extended follow-up of SHARP participants is ongoing, and it may be possible to further evaluate the true benefits of statins by meta-analysis of the 4D, AURORA and SHARP studies, including extended follow-up data. Alternatively, the availability of monoclonal antibodies that inhibit proprotein convertase subtilisin–kexin type 9 (PCSK9) allow greater LDL-reductions (when used in combination with statins) and if safe in the haemodialysis population, may help to tease out the benefits of stabilizing atherosclerotic plaque in the context of the other pathological processes that damage the cardiovascular system. Finally, it is possible that reducing the high non-atherosclerotic disease mortality burden of haemodialysis patients in the future could enable more patients to survive longer and thereby enjoy greater benefits from reductions in LDL cholesterol and atherosclerotic disease events.

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