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Editorial Comment

EDITORIAL COMMENT

Lifelong statins for long life in dialysis patients?

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ABSTRACT

Dyslipidemia in chronic kidney disease (CKD) contributes to the increasing cardiovascular risk during progression of the disease. Statins reduces the risk of ischemic cardiovascular events in CKD patients not treated with dialysis and treatment is generally recommended in patients above 50 years old. In CKD patients on maintenance dialysis treatment, it is not recommended to initiate statins based on evidence from randomized clinical trials. In an article by Marx *et al*. in this issue of *CKJ*, a *post hoc* analysis of cardiovascular events in the 4D study of dialysis patients with diabetes mellitus shows different time trends for events in statin-treated patients compared with those in the placebo group. Although the numbers of cardiovascular events were not different, the risk increased over time in the placebo group whereas it stabilized after 1.5 years and remained constant in the atorvastatin group. In this Editorial we discuss this analysis in the context of current guidelines and clinical practice in dialysis patients.

Keywords: cardiovascular, chronic kidney disease, dialysis, dyslipidemia, statins

LIFELONG STATINS FOR LONG LIFE IN DIALYSIS PATIENTS?

Dyslipidemia in chronic kidney disease (CKD) is characterized by a low level of high-density lipoprotein and hypertriglyceridemia. Lipoprotein composition is altered, plasma levels of apolipoprotein B and lipoprotein (a) are typically increased, while apolipoprotein A levels are low [1, 2]. This proatherogenic pattern starts early and progresses in late stages of CKD. In dialysis patients, additional factors such as hyperparathyroidism, high phosphate levels, uremic toxins and inflammation contribute to the accelerated arteriosclerotic processes in both the intima and media layers of the vessel wall. In non-dialysis CKD patients, cholesterol-lowering treatment with statins (or statin/ezetimibe combination) is recommended based mainly on the Study of Heart and Renal Protection (SHARP) study [3] and *post hoc* subgroup analysis of large, randomized studies comparing statin treatment versus placebo [4]. In dialysis patients, data from the 4D trial in hemodialysis patients with type 2 diabetes mellitus [5], A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events (AURORA) [6] and the subgroup of dialysis patients in the SHARP study show no significant effects regarding cardiovascular outcomes or mortality [7]. These counter-intuitive data are supported by association studies in patients on hemodialysis linking higher cholesterol levels to reduced mortality [8]. Accordingly, the KDIGO guideline for lipid management in CKD from 2013 does not recommend initiating treatment with a statin in dialysis patients, while it is suggested to continue treatment in patients receiving statins at the time of dialysis initiation (evidence level 2C) [9].

The *post hoc* analysis of cardiovascular events in the 4D study by Marx *et al*. [10] in this issue of *CKJ* provides some additional data of clinical interest for nephrologists and cardiologists. Overall, the number of major adverse cardiovascular events (MACE) and mortality were not different between the statin-treated groups and the placebo group. However, when analyzing recurrent events, the risk of MACE over a median follow-up of

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4 years increased in the placebo group, whereas it stabilized and remained constant in the atorvastatin group approximately 1.5 years after study start. Although this time trend is of interest, this finding should be interpreted with caution because of the limitations of the study. The suggested effect of statin on cardiovascular events comes late in the disease progression of patients with advanced kidney disease. In analogy, there was no effect on total mortality in the Assessment of LEscol in Renal Transplantation (ALERT) Study of kidney transplant patients, a positive effect on MACE was established only after a 2-year extension of the original study [11]. Competing risks of mortality due to infections and sudden death in the dialysis patients affect the analysis of the 4D study. A review by Wanner and co-workers describes the concept of a change in cardiovascular risk during the course of CKD and summarizes the therapeutic potential of statins in patients with advanced CKD [12]. Thus, statin treatment might reduce atherosclerotic, but not non-atherosclerotic, cardiovascular diseases in CKD. As non-atherosclerotic cardiovascular events (e.g. arrhythmias) markedly increase with decreasing renal function, potential protective effects of statins, therefore, might not translate into an improved survival, especially in dialysis patients. Consequently, cost-effectiveness of statin treatment in this patient group will remain low if a subgroup cannot be defined with precision to provide more clear benefits. Dialysis patients with long life expectancy and expected to undergo kidney transplantation may be a subgroup who are candidates for early statin treatment.

Several questions remain regarding statin treatment in dialysis patients. Secondary prevention after a coronary event has not been evaluated in randomized trials. Observational data from Taiwan [13] and South Korea [14] suggest a positive effect of statins after myocardial infarction and/or coronary interventions. The 4D, AURORA and SHARP studies have all used fixed low–moderate doses of statins; targets for low-density lipoprotein cholesterol were not defined. Treatment to low target levels of low-density lipoprotein have not been tested in dialysis patients, partly because of the fear of side-effects. Optimal cardiovascular protection in dialysis patients remains to be defined. Total mortality has declined during the last 20 years but is still exceedingly high [15]. In short, the paper by Marx *et al*. may be hypothesis-generating for future studies, but guidelines for statin treatment in dialysis patients remain unchanged.

CONFLICT OF INTEREST STATEMENT

P.B. is member of the *CKJ* editorial board.

(See related article by Marx et al. Recurrent cardiovascular events in patients with type 2 diabetes and haemodialysis: analysis from the 4D Study. *Clin Kidney J* (2023) 16: 1612–1621.)

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