

# STATIN THERAPY IN CHRONIC KIDNEY DISEASE

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## REZUMAT

Boala cronică de rinichi (BCR) evoluează spre insuficiență renală cronică terminală și reprezintă în același timp un factor major de risc pentru boala cardiovasculară (BCV). Bolnavii cu BCR dezvoltă dislipidemii cu prevalență crescută. Aceste dislipidemii reprezintă nu numai un factor de risc pentru BCV, dar și pentru accelerarea evoluției BCR, prin mecanisme multiple. Intervențiile cu terapie hipolipemiantă corectează dislipidemia și par să reducă rata evoluției BCR. Tratatamentul cu statine, pe lângă rolul cardioprotector, pare să dezvolte și un efect nefroprotector la bolnavii cu BCR în predializă, precum și la bolnavii cu transplant renal. În baza datelor existente, cardioprotecția oferită de statine are în schimb rezultate discutabile la bolnavii hemodializați cu diabet zaharat. Articolul trece în revistă și efectele pleiotropice ale statinelor.

**Cuvinte cheie:** boală cronică de rinichi, dislipidemie, statine, nefroprotecție, cardioprotecție

## ABSTRACT

Chronic kidney disease (CKD as defined by K/DOQI) has a potential evolution to end stage renal failure (ESRF) and in the same time represents a major risk factor for cardiovascular disease. The prevalence of dyslipidemia in CKD is higher as compared to the general population and the presence of dyslipidemia represents not only a risk factor for CVD, but for the progression of CKD to end stage renal failure also. Lipid lowering interventions tend to correct dyslipidemia and to reduce the progression rate of CKD. Statin therapy, beside a proven cardioprotective effect, seems to develop a nephroprotective effect also in pre-dialysis CKD and in kidney transplant patients. According to the existing data, the cardioprotective effect of statins in dialysis CKD is debatable. The article reviews some of the pleiotropic effects of statins also.

**Key Words:** chronic kidney disease, dyslipidemia, statins, nephroprotection, cardioprotection

## INTRODUCTION

Chronic kidney disease (CKD) was defined by The Kidney Disease Outcome Quality Initiative (K/DOQI) work group in 2002 as a persistent (more than 3 months) kidney damage and/or decreased GFR ( $< 60\text{ml}/\text{min}/1.73\text{m}^2$ ). Kidney damage is defined by pathologic abnormalities or the presence of damage markers (albuminuria, proteinuria, pathologic urine sediment or imaging studies).<sup>1</sup> It seems that CKD is one of the world's major public health problems and

according to The Third National Health and Nutrition Examination Survey (NHANES III) in the United States alone, 20 million people, or one in nine adults, have CKD and 20 million more are at increased risk for its development.<sup>2</sup>

CKD has a potential evolution to end stage renal failure (ESRF) and in the same time represents a major risk factor for cardiovascular disease (CVD). The Seventh Report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) has included in the major risk factors for CVD albuminuria, proteinuria, and decreased GFR ( $< 60\text{ml}/\text{min}/1.73\text{m}^2$ ), the defining elements of CKD.<sup>3</sup> In fact, in CKD patients, the probability to die due to major cardiovascular events is significantly higher than the probability to develop ESRF.<sup>1</sup> Concerning renal risk markers, the most important seem to be albuminuria and hypertension.<sup>1,4</sup>

Early detection of CKD and early intervention targeting blood pressure control and reduction of

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albuminuria using ACE inhibitors and ARB proved to be effective tools in improving CVD survival and in reducing the progression of the renal disease.<sup>4-8</sup> The “lessons from RENAAL” revealed the fact that, at least in type two diabetes mellitus (DM) patients, the residual albuminuria after rennin-angiotensin-aldosteron system (RAAS) intervention is a marker of renal outcome with a strength similar to that of baseline albuminuria.<sup>4</sup> So, the reduction of residual albuminuria to the lowest achievable level should be viewed as a goal for future reno-protective treatments.<sup>4</sup> In the recent years some data have been published supporting the albuminuria lowering effect of HMG CoA reductase inhibitors (statins).

## **DYSLIPIDEMIA IN CHRONIC KIDNEY DISEASE**

The prevalence of dyslipidemia in CKD patients is higher when we compare it with the general population.<sup>9,10</sup>

In nephrotic syndrome patients total and LDL cholesterol levels are elevated, related to an increased production and a decreased catabolism of LDL cholesterol, HDL cholesterol levels are normal to low and hypertriglyceridemia is also frequently detected due to altered catabolism. Total and LDL cholesterol levels are negatively correlated with serum albumin levels.<sup>11</sup>

In many non nephrotic CKD patients a secondary form of dyslipidemia was described, similar to the atherogenic dyslipidemia of insulin-resistant patients. This form of lipid abnormality is characterized by an increase in serum triglycerides with elevated VLDL, small dense LDL particles, and low HDL cholesterol. These particles are triglyceride-rich apolipoprotein B containing complex lipoproteins.<sup>12</sup> The hypertriglyceridemia and the abnormal composition of triglycerides are primarily due to the downregulation of lipoprotein lipase, hepatic lipase, and of the very-low-density lipoprotein receptor, as well as, to the upregulation of hepatic acyl-CoA cholesterol acyltransferase (ACAT). Impaired maturation of HDL seems to be related to the downregulation of lecithin-cholesterol acyltransferase (LCAT) and, to a lesser extent, to the increased plasma cholesteryl ester transfer protein (CETP).<sup>13</sup> At least in part, the accelerated atherosclerosis of CKD patients and the high CVD risk was attributed to these alterations.<sup>1</sup>

Of a particular interest is considered the group of patients with CKD and DM, since DM is the first cause of ESRF in the USA and in many Western European

countries. The retrospective analysis performed in the Pravastatin Pooling Project (pooled analysis of WOSCOPS, CARE and LIPID studies) evidenced the fact that patients with DM and CKD present an almost three fold increase of all-cause mortality rate, as compared to patients with no DM and no CKD and an almost double all-cause mortality rate compared to patients with DM or with CKD.<sup>14</sup> There are few data about lipid metabolism disorders in patients with DM and CKD still; the same Tonelli analysis offered some answers.<sup>14</sup> (Table 1)

**Table 1.** Lipid metabolism profile in the Pravastatin Pooling Project.<sup>14</sup>

	<b>DM (-)</b>	<b>DM (-)</b>	<b>DM (+)</b>	<b>DM (+)</b>
	<b>CKD (-)</b>	<b>CKD (+)</b>	<b>CKD (-)</b>	<b>CKD (+)</b>
<b>N</b>	14,194	4099	873	571
<b>Average (mg/dl)</b>				
LDL cholesterol	166.1	152.6	143.6	140.2
HDL cholesterol	40.5	38.4	36.4	36.3
Trygliceride	158.0	160.9	175.7	181.1
<b>Outcome events (rate)</b>				
Major CV events	16.7	21.2	25.2	31.7
All-cause mortality	6.4	10.3	11.6	18.5

Beside cardiovascular effects there are data supporting the idea that dyslipidemia is a risk factor for the progression of CKD. In animal models with experimental renal disease, consumption of a high-fat diet exacerbates the severity of glomerulosclerosis and tubulointerstitial fibrosis.<sup>13</sup> Samuelson showed in a study of only 44 patients, followed up for two and a half years, that there is a correlation between some of the intact or partially metabolized triglyceride-rich apo-B containing lipoprotein particles and the progression of renal insufficiency.<sup>15</sup> The Physicians Health Study (PHS) evidenced a significant increase in the risk of deterioration of renal function in persons with elevated baseline serum creatinine who had high serum cholesterol and/or reduced HDL cholesterol concentrations.<sup>16</sup> Similar data have been demonstrated earlier in the MDRD study.<sup>17</sup> A post hoc analysis of RENAAL evidenced that high levels of total and LDL cholesterol were associated with increased risk of developing ESRF.<sup>18</sup> In a recent paper of Boes, Fliser and Ritz it was suggested that Apo A IV levels are associated with the progression of CKD. In fact the authors identified eight studies dealing with dyslipidemia and progression of CKD and in five of them, different forms of dyslipidemia proved to be associated with the risk of CKD progression.<sup>19</sup>

The possible mechanisms involved in the dyslipidemia dependent progression of renal disease could be: tubulointerstitial inflammation, and tissue injury induced by tubular epithelial cells due to the reabsorption of fatty acids, phospholipids, and cholesterol contained in the filtered proteins; glomerular mesangium accumulation of lipoproteins generating matrix production and glomerulosclerosis more or less linked with oxidative stress.<sup>12,13</sup> According to these data, dyslipidemia seems to be a risk factor for both CVD and CKD.

## **EFFECTS OF LIPID LOWERING INTERVENTIONS ON THE KIDNEY**

Since 1982, when Moorhead, El Nahas and their colleagues postulated that lipid nephrotoxicity may contribute to the progression of chronic glomerular and tubulointerstitial disease (“the lipid hypothesis”) several studies have attempted to explore the effects of lipid-lowering therapies on kidney function both in animal models and humans. These studies targeted mainly albuminuria/proteinuria (as risk factors for kidney disease progression), or the evolution of GFR. Most of the therapy studies explored the effects of HMG CoA reductase inhibitors (statins). Very few studies evaluated the effects on the kidney of other lipid lowering agents.

In a small group of CKD patients with dyslipidemia, short term therapy (12 months) with a nicotinic acid derivate proved to reduce proteinuria and the progression of kidney disease.<sup>20</sup>

Most of the studies investigating the effects of fibrates on kidney function are post-hoc analyses of some cases from larger studies. In 399 cases with CKD stage 3, from the VA-HIT (Veterans Administration–High-density lipoprotein Intervention Trial), treated with gemfibrozil (1,200 mg/d) vs. placebo (follow-up period 61 months) Tonelli found no difference in the rate of change of GFR between the two groups.<sup>21,22</sup> In the FIELD (Fenofibrate Intervention and Event Lowering in Diabetes) study, the effects of 200mg/day fenofibrate vs. placebo was investigated. Significantly more patients showed regression or no progression of urinary albumin excretion in the fenofibrate group as compared to placebo.<sup>23</sup>

The lipid lowering effects of statins have been extensively investigated and many trials pointed out their roll in primary and secondary prevention in CVD. There are also data supporting the renoprotective effects of statin therapy by reducing albuminuria and/or the progression of kidney function loss.

The post hoc analysis of some of the lipid lowering studies, in no CKD population, using statins, evidenced the renoprotective effects of the HMG CoA reductase inhibitors. The post hoc analysis of The GREACE (Greek Atorvastatin and Coronary-heart-disease Evaluation) study pointed out the fact that in dyslipidemic patients with coronary heart disease who have normal baseline renal function, there is a decrease of 5.2% in CrCl over time ( $p < 0.0001$ ), which further increases the risk for clinical events related to arteriosclerotic cardiovascular disease. In patients on various statins there is a 4.9% increase in CrCl ( $p = 0.003$ ) whereas long term aggressive atorvastatin treatment increased CrCl with 12% ( $p < 0.0001$ ).<sup>24</sup> Similar results were registered in the in the HPS (Heart Protection Study).<sup>25</sup> The post hoc analysis of more than 10,000 persons receiving rosuvastatin included in diferent lipid lowering studies and followed up for more than 3.5 years evidenced an increase in GFR and decrease in serum creatinin in patients treated with statins, as compared to placebo.<sup>26</sup>

Lipid lowering studies using statins, addressed to CKD patients, have also been performed. The group of Bianchi in Livorno, Italy investigated the effects of atorvastatin in 56 primary glomerulonephritis patients. They evidenced that the treatment with atorvastatin in addition to ACE inhibitors and/or ARB may reduce proteinuria and the rate of progression of kidney disease. The benefits appear to occur in addition to those of treatment with ACE inhibitor and/or ARBs.<sup>27</sup>

Since 2001 some meta-analyses regarding the problem of statin therapy in CKD have been published also and the results were controversial in some of these papers.

The Fried meta-analysis evaluated the effects of six antilipidemic agents (simvastatin, pravastatin, lovastatin, fluvastatin, gemfibrozil, and probucol) on renal function, proteinuria, or albuminuria in patients with CKD in 13 prospective, controlled clinical trials. The treatment with antilipidemic agents slowed the rate of decrease in GFR by a mean of 1.9 ml/min/year and tended to reduce proteinuria ( $p = 0.077$ ). The results were statistically heterogeneous in the studies investigating both diabetic and non diabetic nephropaties.<sup>28,29</sup>

The Sandhu meta-analysis in 2005 evaluating 17 randomized, controlled trials evidenced that statins reduced kidney function loss in 14 out of 17 studies (38,699 patients). The overall results proved the fact that statins significantly reduced loss of CrCl by 1.09 mL/min/yr, (95% CI 0.30 to 1.88). Results were

also heterogeneous: better in diabetes mellitus: 3.54 mL/min/yr (0.24 to 7.32),  $I^2 = 0\%$ , (4 studies), as compared to glomerulonephritis or hypertension: 0.12 mL/min/yr (7.37 to 7.14),  $I^2 = 68\%$ , (7 studies) or to cardiovascular disease: 0.93 mL/min/yr (0.10 to 1.76),  $I^2 = 99\%$ , (6 studies). The effect on kidney function was not dependent of participant age, cholesterol or baseline GFR and atorvastatin appeared to be more beneficial than other statins ( $p < 0.001$ ). Statins reduced proteinuria in 3 out of 5 studies (137 patients), but the overall effect was not-significant: 0.24 g/24h (-0.71 to 1.20),  $I^2 = 86\%$ .<sup>30</sup>

The Levi meta-analysis included 27 studies (39,704 patients with a follow-up time of 3-73 months). In 21 trials that reported eGFR, the rate of renal function decline was 76% lower in the statin groups as compared to the control groups (average difference 1.22 ml/min/year; 95% CI, 0.44-2.00 ml/min per year). There was significant difference in eGFR between the statin and control groups in the 38,311 patients with cardiovascular disease (0.93 ml/min per year; 95% CI, 0.10-1.76 ml/min per year), but not in the patients with diabetes mellitus, glomerulonephritis and hypertension. There was no difference in the impact of statins on proteinuria between any of the four disease subgroups but when the 18 studies that reported proteinuria or albuminuria were combined the mean difference in outcome between statin and control groups was meaningful (- 0.58 SD; 95% CI - 0.98 to - 0.17 SD).<sup>31</sup>

The Douglas meta-analysis investigated the effects of statins on proteinuria or albuminuria. In the 15 analyzed trials (most of the patients with diabetes mellitus) statins reduced albuminuria and proteinuria in 13 of them. The reduction in excretion was greater among studies with greater baseline albuminuria or proteinuria: change of 2% for those with excretion less than 30mg/day, 48% for those with excretion of 30 to 300 mg/day, and 47% for those with excretion more than 300 mg/day.<sup>32</sup>

## **POSSIBLE MECHANISMS OF KIDNEY PROTECTION**

The lipid lowering effects of statins in CKD have been well documented (early stages of CKD, dialysis patients as well as kidney transplant patients).<sup>33-35</sup> In CKD patients statin therapy reduces significantly total cholesterol and LDL cholesterol levels without increase in SAE (serious adverse events) rates (hepatotoxicity or rhabdomyolysis). Due to these results statins may reduce the nephrotoxic effects of dyslipidemias and may develop the nephroprotective actions which were described above.

In the late years more and more data support other effects of statins, not related to cholesterol lowering, defined as pleiotropic effects. These effects tend to enlarge the area of treatment indications for this group of drugs. It seems that statins play an anti-inflammatory role by lowering the CRP and MCP-1 synthesis, inhibiting growth and proliferation of macrophages, amplifying apoptosis, reducing monocyte infiltration and VCAM 1 expression, modifying collagen gene expression and collagen synthesis. Statin therapy induces immunomodulatory effects also by reducing T cell proliferation and activation, by reducing TNF  $\alpha$ , interleukin 1 $\beta$ , IL 8, IL 6 and PPAR  $\alpha$  and  $\gamma$  synthesis, as well as by reducing isoprenylation of Ras and Rho genes. Medium and long term therapy with statins improves endothelial dysfunction by improving NO bioavailability and reducing LDL oxidation and as a consequence develops antioxidant effects. There are experimental data supporting a plaque stabilizing effect, a reduction in the activity of the extrinsic coagulation, as well as decrease of platelet adhesion and aggregation by statin therapy. It seems that statins reduce Angiotensin II synthesis and AT1 receptor and endothelin receptor expression.<sup>36,37</sup> A time course was suggested for these pleiotropic effects varying from days to years, LDL cholesterol lowering being the first answer to therapy followed by endothelial function improvement, reduction of inflammation, reduction of ischemic episodes, plaque stabilization and finally cardiac events reduction.<sup>36</sup> Due to their anti inflammatory and immunomodulatory effects currently statins are tested for treatment in arthritis, sepsis and so on.<sup>38</sup>

Of a particular interest for the nephrologists is statin induced proteinuria. In vitro studies evidenced that the more potent HMG-CoA reductase inhibitors reduce receptor mediated endocytosis of albumin in the proximal tubular cells, both in animals and men, in a dose dependent way.<sup>39,40</sup> The effect seems to be induced by impairment of prenylation of GTP-binding proteins and reversed by the addition of mevalonate and by the addition of the isoprenoid, geranyl-geranyl pyrophosphate and is independent of cholesterol levels.<sup>41</sup> Thus, the proteinuria induced by statins is of a tubular type and contains, beside albumin,  $\alpha_1$ -microglobulin,  $\beta_2$ -microglobulin retinal binding proteins and so on, all reabsorbed in the proximal tubule by receptor mediated endocytosis.<sup>41</sup> So how could be statins renoprotective, as suggested by clinical and biological data? It is probable that, in spite of the increase in protein excretion, HMG CoA reductase inhibitors reduce protein trafficking

across the proximal tubular cells and by this effect diminish inflammation, endothelial dysfunction and tubulointerstitial fibrosis.<sup>41</sup>

Robinson et al, in 2005, in a meta-regression analysis, tried to determine the role of pleiotropic effects of statins in risk reduction of coronary heart disease. Data from five diet, three bile acid sequestrant, one surgery, and 10 statin trials (81,859 participants) were included in the analysis. The results were disappointing for the pleiotropic effect supporters. The pleiotropic effects of statins do not seem to contribute to an additional cardiovascular risk reduction beyond that expected from the degree of LDL-C lowering. It is debatable whether this conclusion should be applied to CKD and other chronic diseases also.<sup>42</sup>

### **SHOULD BE CKD PATIENTS TREATED WITH STATINS ?**

Based on extensive evidence, statins are recommended for primary and secondary prevention of cardiovascular disease in the general population with elevated LDL cholesterol. There are data supporting the benefit of this treatment in lowering LDL cholesterol and providing renoprotective effects in CKD patients also (as stated above). Is there hard evidence supporting the idea that statins prolong survival of CKD patients?

In pre-dialysis CKD patients data are offered by the analysis of Tonelli et al on a subgroup of subjects of the CARE trial (Cholesterol And Recurrent Events).<sup>43,44</sup> More than 1700 patients, aged 21-75 years with prior acute myocardial infarction, with total cholesterol < 240 mg/dl, LDL cholesterol 115-174 mg/dl, triglycerides ≤ 350 mg/dl and Cr.Cl <75ml/min have been treated with pravastatin vs. placebo and followed up for 5 years. The authors concluded that pravastatin therapy reduced significantly the incidence of major cardiovascular events [RR 0.72, (0.59–0.88), CI 95%, p = 0.001] and the incidence of cardiovascular mortality [RR 0.72, (0.55–0.95), CI 95%, p = 0.02] but had no impact on all-cause mortality.<sup>44</sup> One year later, patients from WOSCOPS (West of Scotland coronary prevention study) and LIPID (Long-term intervention with pravastatin in ischemic disease) trials have been added to those from CARE, in the Pravastatin Pooling Project analyses. This time results indicated a significant reduction of all-cause mortality in CKD patients treated with pravastatin (RR 0.81; 0.73–0.89, 95% CI; p = 0.03).<sup>45</sup>

Information about statin therapy in kidney transplant patients is offered by the ALERT trial

(Assessment of Lescol in Renal Transplantation). In the ALERT trial 2102 renal or combined renal and pancreas transplant patients with stable graft function (mean age 50 years) have been included and 1050 were treated with fluvastatin. The total mean serum cholesterol in these patients was 4.40mmol/l, (4.0-7.0mmol/l) and they were in evidence with myocardial infarction for more than six months before. The follow-up time was 5.4 years. The fluvastatin treatment decreased coronary events and cardiovascular mortality rates by an extent similar to that observed in patients without CKD [RR 0.65, (0.48–0.88), CI 95%, p = 0.005 and RR 0.62, (0.40–0.96), CI 95%, p = 0.03 respectively]. All-cause mortality was not significantly modified. The renal composite endpoint of graft loss or doubling of serum creatinine was similar in the two groups (fluvastatin and placebo).<sup>46</sup>

Results of statin treatment in dialysis patients are controversial. In two observational studies, i.e. US Renal Data System Dialysis Morbidity and Mortality Wave 2 study (3716 patients) and Dialysis Outcomes and Practice Patterns Study - DOPPS I (7365 patients) the relative risk reduction for all-cause mortality and cardiovascular mortality was significant in patients treated with statins. It has to be mentioned that only a small amount of patients in both studies were treated with HMG-CoA reductase inhibitors (<15%).

In 2005 Wanner published the results of the 4D (Die Deutsche Diabetes Dialyse) study. It was a large randomized, controlled trial that included 1255 type 2 diabetes patients on hemodialysis treatment for less than 2 years, 619 being treated with atorvastatin. The mean age of the patients was 65.7 years, and the biological data showed LDL cholesterol levels of 80–190 mg/dl (2.1–4.9 mmol/l), triglyceride < 1000 mg/dl (11.3mmol/l). The follow-up time was 4 years. The 4D study results were negative: though patients presented a significant relative risk reduction concerning cardiovascular events (stroke excluded) [0.82, (0.68–0.99), p = 0.03], cardiovascular mortality and all-cause mortality did not differ between the statin treated and the placebo treated groups. The combined prevalence of fatal and non fatal stroke did not differ between the two groups.<sup>49</sup> The 4D results have been extensively discussed. One of the possible explanation of these data could be the fact that plasma cholesterol concentration is elevated mainly in nephrotic syndrome and mild to moderate renal insufficiency and only occasionally in end stage renal disease. On the contrary, in dialysis patients low cholesterol levels (denoting intense inflammation), as well as high cholesterol levels are associated with higher mortality rates.<sup>50,51</sup>

It seems that CKD patients in early phases of the disease, as well as kidney transplant patients should benefit from statin therapy. Larger studies are needed to evaluate the use of statins in dialysis patients with and without diabetes mellitus.

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