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Editorial
Statins in patients with chronic kidney disease – an attempt at recommendations

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Chronic kidney disease (CKD) is associated with cardiovascular disease (CVD) even in the early stages of the disease and a large number of patients die from CVD before developing advanced CKD[1–3]. Beyond established risk factors (e.g. hypertension, dyslipidaemia, obesity, smoking and diabetes) these patients might also have additional predictors of CVD such as proteinuria, electrolyte imbalances, inflammation, oxidative stress and endothelial dysfunction that amplify vascular risk[2–5]. Dyslipidaemia is an independent risk factor for the progression of CKD[4,6]. CKD with significant proteinuria is commonly associated with substantial alteration of serum lipid levels. The most common changes being lowered high density lipoprotein cholesterol (HDL-C) levels and elevated level of triglycerides (TG)[3]; hypercholesterolemia *per se* might be present in around 50% of patients on dialysis[7].

Among lipid lowering drugs, statins are the most effective in improving the lipid profile and cardiovascular (CV) outcomes in patients with CKD[5–10]. However, despite several studies and meta-analyses there are still questions regarding their role in CKD. For example, the role of statins in primary prevention of CVD risk in CKD patients still remains to be clarified, as no large randomized clinical trial has provided evidence that they reduce CVD in these patients[10–12]. We still do not know at what stage of renal insufficiency statin therapy might be the most effective (stage 1–3, and possibly 1–4?; what is the glomerular filtration rate [GFR] cut-off value for their efficiency?) and at what stage is statin administration not effective or even harmful (dialysis patients?). Should we use statins in patients on dialysis? If yes – which statin, what dose and is duration of treatment important[10–14]?

The available data suggest that statins are effective and appear safe for secondary prevention of cardiovascular (CV) events in individuals with mild chronic renal insufficiency and not in end-stage renal disease (ESRD)[10,14]. According to the update of the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) Clinical Practice Guideline for Diabetes and Chronic Kidney Disease withholding statin treatment initiation in dialysis patients is suggested[15]. The effect of statins in CKD patients is due to their lipid-lowering properties, but also (or even mainly?) attributable to their protective role on the endothelium, anti-inflammatory and anti-oxidant effects, as well as enhancement of renal perfusion and reduction of abnormal permeability to plasma proteins[5,8,11,16]. Their role in the inhibition of renal damage progression has still to be confirmed in large interventional trials in humans[17].

As mentioned above, studies in ESRD patients on dialysis gave conflicting, mostly negative results, and no significant effects were found in the 4D (Die Deutsche Diabetes Dialyse) (except for the fatal stroke and cardiac events) and AURORA (A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events)

studies[18,19]. Even in the SHARP (Study of Heart and Renal Protection) study despite significant reduction in major atherosclerotic (by 17%; $p = 0.0022$) and vascular (by 15.3%, $p = 0.0012$) events, there was only an insignificant trend toward reducing CV events in dialysis patients; this trial also had several design limitations[18–23].

Taking into account the existing doubts we performed three meta-analyses to evaluate the impact of statin therapy on: (1) lipid parameters, (2) CV events and death from all causes, and (3) renal outcomes. These meta-analyses were conducted by the Lipid and Blood Pressure Meta-analysis Collaboration (LBPMC) group[6,11,24].

In the first meta-analysis we evaluated the hypolipidaemic properties of statins in CKD patients requiring and not requiring dialysis, treated with short (<3 months) or long-term (≥3 months) statin therapy[6]. We included 16 trials with 3594 individuals with CKD, of whom 1938 were treated with statins as monotherapy[6]. Statin therapy was highly effective in patients with CKD not on dialysis therapy (with longer treatment showing a more effective trend: 56.3 vs. 66.8, 22.5 vs. 24.1, and 53 vs. 56.1 mg/dL, for total cholesterol [TC], TG, and low density lipoprotein cholesterol [LDL-C], respectively). In patients requiring dialysis TC and LDL-C improved only with short-term (<3 months) treatment. Comparing statin therapy in patients on dialysis for ≤3 and >3 months a reduction in TC and LDL-C levels was observed (26.3 vs. 25.9, and 42.2 vs. 29.8 mg/dL, respectively), with an increase in TG (4.5 vs. 13.4 mg/dL) and a fall in HDL-C levels (mean 2.4 mg/dL for long-term therapy)[6]. We concluded that statin therapy in dialysis patients is not effective, and might even be harmful (TG increase and HDL-C decrease)[6].

The second meta-analysis evaluated the effect of statin therapy on CV outcomes, stroke and all-cause mortality[11]. We included 21,295 CKD **non-dialysis and dialysis-dependent** patients from 11 randomized trials. The use of statins resulted in a 34% reduction in death from all causes ($p < 0.0001$), 31% reduction in death from cardiac causes ($p = 0.0012$), 45% reduction in CV events ($p = 0.0001$) and 34% reduction in stroke ($p = 0.004$) in CKD patients not on dialysis[11]. Clinical studies in ESRD patients on dialysis did not confirm these results – we showed no effect on death from all causes (relative risk [RR] 0.99, 95% CI: 0.88–1.11; $p = 0.85$) and stroke (RR 1.31; 95% CI: 0.9–1.89; $p > 0.05$), but noted the effect of reducing death from cardiac causes (by 21%) and CV events (by 19%; $p < 0.05$ for both). However, these results should be treated with caution since they are based only on one available study. We emphasized that we still lack studies in dialysis patients in order to definitively evaluate the effect of statins[11]. We concluded that the use of statins should be indicated in CV prevention especially in patients with **non-dialysis-dependent** CKD, but we suggested caution in expecting a reduction in CV events after starting statin therapy in patients on haemodialysis[11].

In the last meta-analysis (unpublished data) we evaluated whether statins modulate renal function in CKD patients, and whether this effect might depend on the duration of therapy[25]. We included 12 trials with 6452 subjects with CKD treated with either statins or placebo. Statins exerted renoprotective effects especially in patients not on dialysis therapy, influencing urinary protein with an effect both for short-term (≤1 year) and long-term therapy (3 years), and serum creatinine but only for long-term therapy (3 years). Statins modestly preserved GFR, with a significant increase for between 1–3 years (this interesting observation requires further investigation)[25]. These results support those from the first meta-analysis, showing a trend for greater effectiveness with longer statin therapy in patients with CKD not requiring dialysis[6]. On the basis of these findings and due to the lack of well designed studies (as emphasized in the meta-analysis on CV endpoints[11]) that include dialysis patients we cannot answer the question regarding role of statins on renal outcomes in these patients, and we cannot recommend using statins in CKD patients requiring dialysis[25].

In the current European Society of Cardiology (ESC)/European Society of Atherosclerosis (EAS) 2011 guidelines, it is clearly stated that CKD patients should be automatically treated as subjects at very high or high total cardiovascular risk who need active management of all risk factors[26]. CKD is acknowledged as a coronary artery disease equivalent. Also, for these patients additional analyses of such biomarkers as non-HDL-C and apolipoprotein B (IIa/C level of recommendation/evidence) should be considered for screening for CVD risk[26]. According to these guidelines statin therapy should be considered to slow the rate of kidney function loss, and protect against the development of ESRD requiring dialysis (IIa/C level of recommendation/evidence)[26]. Statin should be also considered in CKD patients at stages 2–4, and in moderate to severe CKD statins in monotherapy or in combination with other drugs should be considered to achieve LDL-C <70 mg/dL (1.8 mmol/L) (IIa/C level of recommendation/evidence)[26]. In the recent 2012 update of the Canadian Cardiovascular Society guidelines for the diagnosis and treatment of dyslipidaemia for the prevention of cardiovascular disease in the adult it is also recommended that all individuals with CKD should be treated as high risk patients, for whom statin therapy should be considered[27]. Finally, in the just published *International Atherosclerosis Society* (IAS) *Position Paper: Global Recommendations for the Management of Dyslipidemia*, the authors confirm the suggestion of considering CKD patients as subjects from the moderately high-risk group of patients, for whom the optimal range of LDL-C should be <100 mg/dL (2.6 mmol/L)[28]. The results of the meta-analyses support the above recommendations concerning treating of CKD

patients as high risk subjects and the efficacy of statin therapy in this group of patients. However, our meta-analyses also add new data on the lack of effect of statin therapy in dialysis patients, on the role of duration of the therapy, and on the influence of statins on renal outcomes (and not only proteinuria)[6,11,25,29–32].

On the basis of the results from the meta-analyses the following suggestions seem appropriate:

(1) Patients with CKD not requiring dialysis should be treated with statins as appropriate for high CV risk.

(2) Statin therapy in patients not requiring dialysis significantly decrease TC, LDL-C and TG, with a trend for longer duration of treatment to be more effective. Statins also significantly influence all-cause and cardiac mortality, stroke and cardiovascular events, and exert significant renoprotective effects, especially for urinary protein, serum creatinine and GFR (with the similar trend for treatment as for the lipid parameters analysis).

(3) Duration of treatment might be important in order to achieve better effects of statin therapy (on lipid and renal outcomes) in CKD patients not on dialysis (the longer, the better trend). However this requires further investigations.

(4) On the basis of available data we cannot recommend initiating statin treatment in ESRD patients requiring dialysis. On the other hand we do not have enough data to stop treatment in patients who are already on statins. Finally, it should be emphasized that we still need large, well designed, randomized trials in well selected CKD patients on dialysis, in order to finally confirm or refute the limited benefits of statin therapy.

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References

1. Gluba A, Mikhailidis DP, Lip GY, et al. Metabolic syndrome and renal disease. Int J Cardiol 2013;164:141-50
2. Yamagata K, Ishida K, Sairenchi T, et al. Risk factors for chronic kidney disease in a community-based population: a 10-year follow-up study. Kidney Int 2007;71:159-66
3. Franczyk-Skóra B, Gluba A, Banach M, et al. Prevention of sudden cardiac death in patients with chronic kidney disease. BMC Nephrol 2012;13:162
4. Muntner P, He J, Astor BC, et al. Traditional and non-traditional risk factors predict coronary heart disease in chronic kidney disease: results from the atherosclerosis risk in communities study. J Am Soc Nephrol 2005;16:529-38
5. Nannayakkara PWB, van Guldener C, ter Wee PM, et al. Effect of a treatment strategy consisting of pravastatin, vitamin E, and homocysteine lowering on carotid intima–media thickness, endothelial function and renal function in patients with mild to moderate chronic kidney disease: results from the Anti-Oxidant Therapy in Chronic Renal Insufficiency (ATIC) Study. Arch Intern Med 2007;167:1262-70
6. Nikolic D, Nikfar S, Salari P, et al.; Lipid and Blood Pressure Meta-Analysis Collaboration Group. Effects of statins on lipid profile in chronic kidney disease patients: a meta-analysis of randomized controlled trials. Curr Med Res Opin 2013;29:435-51
7. Saltissi D, Morgan C, Rigby RJ, Westhuyzen J. Safety and efficacy of simvastatin in hypercholesterolemic patients undergoing chronic renal dialysis. Am J Kidney Dis 2002;39:283-90
8. Bianchi S, Bigazzi R, Caiazza A, Campese VM. A controlled prospective study of the effects of atorvastatin on proteinuria and progression of kidney disease. Am J Kidney Dis 2003;41:565-70
9. Athyros VG, Hatzitolios AI, Karagiannis A, et al.; IMPERATIVE Collaborative Group. IMproving the imPlemEntation of cuRrent guidelines for the mAnagement of major coronary hearT disease rIsk factors by multifactorial interVEntion. The IMPERATIVE renal analysis. Arch Med Sci 2011;7:984-92
10. Rysz J, Aronow WS, Stolarek RS, et al. Nephroprotective and clinical potential of statins in dialyzed patients. Expert Opin Ther Targets 2009;13:541-50
11. Barylski M, Nikfar S, Mikhailidis DP, et al.; Lipid and Blood Pressure Meta-Analysis Collaboration Group. Statins decrease all-cause mortality only in CKD patients not requiring dialysis therapy – a meta-analysis of 11 randomized controlled trials involving 21,295 participants. Pharmacol Res 2013;72:35-44
12. Schaeffner ES, Kurth T, Curhan GC, et al. Cholesterol and the risk of renal dysfunction in apparently healthy men. J Am Soc Nephrol 2003;14:2084-91
13. Gluba A, Rysz J, Banach M. Statins in patients with chronic kidney disease: why, who and when? Expert Opin Pharmacother 2010;11:2665-74
14. Banach M, Mikhailidis DP, Kjeldsen SE, Rysz J. Time for new indications for statins? Med Sci Monit 2009;15:MS1-5
15. Rocco MV, Berns JS. KDOQI Clinical practice guideline for diabetes and CKD: 2012 update. Am J Kidney Dis 2012;60:850-86
16. Barylski M, Małyszko J, Rysz J, et al. Lipids, blood pressure, kidney – what was new in 2011? Arch Med Sci 2011;7:1055-66
17. Tonelli M. Statins for slowing kidney disease progression: an as yet unproven indication. Am J Kidney Dis 2008;52:391-4
18. Wanner C, Krane V, März W, et al.; German Diabetes and Dialysis Study Investigators. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. N Engl J Med 2005;353:238-48
19. Fellström BC, Jardine AG, Schmieder RE, et al. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. N Engl J Med 2009;360:1395-407
20. Baigent C, Landray MJ, Reith C et al.; SHARP Investigators. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomized placebo-controlled trial. Lancet 2011;377:2181-92
21. Malyszko J, Bachorzewska-Gajewska H, Malyszko J, et al. Markers of kidney function in the elderly in relation to the new CKD-EPI formula for estimation of glomerular filtration rate. Arch Med Sci 2011;7:658-64

22. Banach M, Hering D, Narkiewicz K, et al. Lipids, blood pressure, kidney – what was new in 2012? Int J Pharmacol 2012;8:659-78
23. Palmer SC, Craig JC, Navaneethan SD, et al. Benefits and harms of statin therapy for persons with chronic kidney disease: a systematic review and meta-analysis. Ann Intern Med 2012;157:263-75
24. Banach M, Nikfar S, Rahimi R, et al.; Lipid and Blood Pressure Meta-Analysis Collaboration Group. The effects of statins on blood pressure in normotensive or hypertensive subjects – a meta-analysis of randomized controlled trials. Int J Cardiol 2013;doi:10.1016/j.ijcard.2013.03.068. [Epub ahead of print]
25. Banach M, Nikolic D, Nikfar S, et al. Renal outcomes of use of statins in chronic kidney disease patients: A meta-analysis of randomized controlled trials. 81st European Atherosclerosis Society Congress, 2–5 June 2013, Lyon, France. Moderated Poster Session C, Poster No. 1410
26. Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS), Catapano AL, Reiner Z, De Backer G, et al.; ESC Committee for Practice Guidelines 2008–2010 and 2010–2012 Committees. ESC/EAS Guidelines for the management of dyslipidaemias: the Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). Atherosclerosis 2011; 217(Suppl 1):S1-44
27. Anderson TJ, Grégoire J, Hegele RA, et al. 2012 update of the Canadian Cardiovascular Society guidelines for the diagnosis and treatment of dyslipidemia for the prevention of cardiovascular disease in the adult. Can J Cardiol 2013;29:151-67
28. An International Atherosclerosis Society (IAS) Position Paper: Global Recommendations for the Management of Dyslipidemia. Updated 25 July 2013. Available at: http://www.athero.org/IASPositionPaper.asp [last accessed on 2 Aug 2013]
29. Bao YS, Na SP, Jia XB, et al. Prevalence and risk factors for chronic kidney disease in patients with coronary artery disease. Curr Med Res Opin 2012;28:379-84
30. Couser WG, Riella MC. World Kidney Day 2011 – protect your kidneys, save your heart. Arch Med Sci 2011;7:1-4
31. Athyros VG, Karagiannis A, Ganotakis ES, et al.; Assessing The Treatment Effect in Metabolic syndrome without Perceptible diabeTes (ATTEMPT) Collaborative Group. Association between the changes in renal function and serum uric acid levels during multifactorial intervention and clinical outcome in patients with metabolic syndrome. A post hoc analysis of the ATTEMPT study. Curr Med Res Opin 2011;27:1659-68
32. Olechnowicz-Tietz S, Gluba A, Paradowska A, et al. The risk of atherosclerosis in patients with chronic kidney disease. Int Urol Nephrol 2013; doi: 0.1007/s11255-013-0407-1. [Epub ahead of print]

