

Effectiveness of statins on haemodialysis patients with concomitant peripheral arterial disease – a narrative review

Celso Nunes , Juliana Sousa, Vânia Oliveira, Eduardo Silva , Leonor Baldaia , Miguel Silva , Luis Orelhas , Manuel Fonseca

Angiology and Vascular Surgery Department, Centro Hospitalar e Universitário de Coimbra, Portuga

Submitted: May 9, 2023; Reviewed: May 23, 2023; Accepted: August 9, 2023

ABSTRACT

INTRODUCTION: The use of statins in hemodialysis patients is a topic of ongoing research and debate. Patients with chronic kidney disease on hemodialysis constitute a large proportion of patients treated in the vascular surgery field. Clinical data of the protective statin effect on this group is scarce and conflicting results exist regarding cardiovascular, cerebrovascular and limb outcomes.

METHODS: We performed a thorough electronic search of the literature using PubMed and Embase databases to understand the relationship between statin effect and cardiovascular, limb outcomes and cerebrovascular outcomes. A narrative review was constructed, based on the obtained literature.

RESULTS: Although the use of statins in hemodialysis patients may provide cardiovascular benefits, the optimal dosage and safety profile of these medications in this population remain uncertain. A carefully evaluation of the risks and benefits of statins should be made based on each patient's specific requirements and circumstances.

CONCLUSION: The role of statins for patients with peripheral arterial disease who are on hemodialysis remains unclear. Further analyses should focus on this subgroup of dialysis patients, who are becoming more prevalent on the vascular surgery departments, allowing for an optimized treatment with better patient outcomes.

Keywords: Statin; Hemodialysis; peripheral arterial disease; patient outcomes;

INTRODUCTION

The use of statins in hemodialysis patients is a topic of ongoing research and debate. Statins are medications that are commonly used to lower cholesterol levels in patients with or at risk for cardiovascular disease. However, hemodialysis patients often have unique metabolic profiles and comorbidities that may affect the efficacy and safety of statins. Patients with chronic kidney disease on hemodialysis constitute a large proportion of patients treated in the vascular surgery field, either for occlusive arterial disease of the lower limbs or for cerebrovascular disease. Clinical data of the protective statin effect on this group is scarce

and conflicting results exist regarding cardiovascular, cerebrovascular and limb outcomes.

METHODS

We performed a thorough electronic search of the literature using PubMed and Embase databases to understand the relationship between statin effect and cardiovascular, limb and cerebrovascular outcomes. We used the following combination of keywords in our search strategy ((statin effect) OR (LDL lowering effect) AND (hemodialysis) AND (vascular events) OR (limb revascularization) OR (cereberovascular)).



Only articles in English published in the last 10 years were included. Titles and abstracts were screened and served to select full text for further assessment. Cross-referencing was performed.

RESULTS

After removal of duplicates, titles and abstracts screening and full text analysis, we included 11 articles in our review (Table).

Table 1. Summary of articles included in this review

Article	Year	Type of study	Endpoints	Main conclusion
Barylski et al ^[1]	2013	Meta-analysis	Impact of statin therapy on cardiovascular events and death from all causes in CKD patients	Non-significant effect on death from all causes and stroke. Positive effect of reducing death from cardiac causes and cardiovascular events.
Palmer et al ^[2]	2013	Systematic Review	Assess the benefits and harms of statin use in adults who require dialysis	No beneficial effects on mortality or cardiovascular events and uncertain adverse effects.
Nikolic et al ^[3]	2013	Meta-analysis	Effects of statins on lipid profile of CKD Patients	Less beneficial effect in patients on dialysis with the trend to be less effective with longer duration of therapy.
Wang et al ^[4]	2014	Meta-analysis	Overall incidence of stroke, fatal stroke and hemorrhagic stroke	A significant reduction in the incidence of overall stroke; No significant reduction in the incidence of fatal or hemorrhagic stroke.
Sun et al ^[5]	2015	Meta-analysis	Effect of statins on all cardiac events, cardiovascular deaths and all-cause mortality. (Dialysis Patients)	No significant difference in reducing all-cause mortality and cardiovascular deaths. Reduced major cardiovascular events.
Wang et al ^[6]	2015	Meta-analysis	Stroke, fatal stroke and hemorrhagic stroke incidences with high dose statin;	Subgroup Dialysis/Renal transplant: no statistically significant reduction in all stroke incidences;
Herrington et al ^[7]	2016	Meta-analysis	Cardiovascular events, stroke, and cause-specific mortality	No evidence of benefit for any outcome in CKD5;
Krane et al ^[8]	2016	Post-trial follow-up of the 4D Study	11-year cardiovascular outcomes, cause-specific mortality, and myopathy on hemodialysis patients with type 2 Diabetes	Non-significant reduction in cardiovascular events and significant reductions in cardiac deaths and in all cardiac events combined.
Messow et al ^[9]	2017	Meta-analysis	Cardiovascular events, death and all-cause mortality in CKD patients	No evidence of benefit for any outcome in CKD5.
Ghayda et al ^[10]	2021	Umbrella Review of meta-analysis	Statin effect on all-cause and cardiovascular mortality	No benefit on dialysis patients.
Lo et al ^[11]	2022	Retrospective study	All-cause death and the composite of endovascular therapy (EVT) and amputation	Associated with reductions in the risk of all-cause death, CV death, and the composite adverse limb outcome of endovascular treatment and amputation.

From the 11 articles, most concern effect of statins on Chronic Kidney Disease patients (CKD) of all stages and not only on hemodialysis patients. Only four articles^(2,5,8,11) concerned specifically hemodialysis patients. While statin medication is effective in reducing cardiovascular events, stroke events and cardiovascular death on CKD patients, it becomes less clear when subgroup analyses are made for CKD stage 5 patients. Sun et al. found that statin therapy reduced major cardiovascular events, nevertheless, the relation with all-cause mortality and cardiovascular deaths had no beneficial effect.^[5] Similarly, Wang et al. discovered a significant reduction in the incidence of overall stroke but no significant reduction in the incidence of fatal or hemorrhagic stroke.^[6] Unfortunately, specific studies of the impact of carotid endarterectomy in this patient subgroup comparing outcomes

in relation to statin therapy were not found in this research.

After lower limb revascularization, a retrospective cohort found a protective association of statin therapy regarding the risk of all-cause death, cardiovascular death, and the composite adverse limb outcome of endovascular treatment and amputation^[11].

DISCUSSION

Statins have the potential to lower the risk of cardiovascular disease through multiple mechanisms, such as decreasing LDL-C levels, inhibiting platelet aggregation, improving endothelial function, reducing inflammation, and providing neuroprotection. Although, there have been safety and

effectiveness concerns regarding the use of statins in dialysis patients, such as myalgia, myopathy, rhabdomyolysis, and liver disease.

Several meta-analyses revealed that statins have no effect on cardiovascular outcomes, even when LDL is effectively lowered, since cardiovascular risk in the dialysis population, is owned to nonatherosclerotic cardiac events.^[12] But even myocardial infarction and stroke are not significantly reduced, probably due to the different inherent cholesterol metabolism in these patients and its resistance to statins. Also, the statin procalcifying effect, through vitamin K metabolism which is known to inhibit vascular calcification and, is usually depleted in dialysis patients, can also play a role in accelerating the vascular calcifications.^[13]

Regarding the impact of statins on hemodialysis access, animal studies have consistently shown a protective effect. However, the translation of these findings to human trials has been more challenging. Some clinical studies have demonstrated benefits of statin therapy, indicating a reduction in stenosis and improved patency of vascular hemodialysis access.^[15,16]

Currently, while the American Heart Association does not have specific recommendations for statin therapy on dialysis patients, the Kidney Disease Improving Global Outcomes (KDIGO) organization recommends avoiding its initiation but not to stop therapy if the patient is already receiving it.

There is no clear consensus in the medical literature regarding the superiority of hydrophilic or lipophilic statins in hemodialysis patients. However, some studies have suggested that hydrophilic statins, such as pravastatin, may be preferred in patients with impaired kidney function because they are less dependent on renal excretion, reducing the risk of drug accumulation and potential side effects in patients with compromised kidney function.^[17,18]

A careful evaluation of the risks and benefits of statins should be made based on each patient's specific requirements and circumstances. It is also still unknown whether statins may be advantageous for specific subgroups of dialysis patients with elevated LDL cholesterol and concomitant history of peripheral arterial occlusive disease. The long-term follow-up of the SHARP study will determine whether the reduction in major atherosclerotic events persists during the long-term follow-up.^[14]

CONCLUSION

Although the use of statins in hemodialysis patients may provide cardiovascular benefits, the optimal dosage and safety profile of these medications in this population remain uncertain. Further analyses should focus on this subgroup of dialysis patients, who are becoming more prevalent on the vascular surgery departments, allowing for an optimized treatment with better patient outcomes.

Acknowledgements: None

Conflicts of interest: None

Funding: None

REFERENCES

1. Barylski M, Nikfar S, Mikhailidis DP, Toth PP, Salari P, Ray KK, 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.
2. Nikolic D, Nikfar S, Salari P, Rizzo M, Ray KK, Pencina MJ, 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.
3. Palmer SC, Navaneethan SD, Craig JC, Johnson DW, Perkovic V, Nigwekar SU. HMG CoA reductase inhibitors (statins) for dialysis patients. *Cochrane Database Syst Rev.* 2013;(9):CD004289
4. Wang W, Zhang B. Statins for the prevention of stroke: a meta-analysis of randomized controlled trials. *PLoS One.* 2014;9:e92388.
5. Sun L, Zou L, Chen M, Liu B. Meta-analysis of statin therapy in maintenance dialysis patients. *Ren Fail.* 2015;37:1149-56.
6. Wang J, Chen D, Li DB, Yu X, Shi GB. Comparison of the efficacy and safety of intensive-dose and standard-dose statin treatment for stroke prevention: A meta-analysis. *Medicine (Baltimore).* 2016;95:e4950.
7. Cholesterol Treatment Trialists' (CTT) Collaboration; Herrington WG, Emberson J, Mihaylova B, Blackwell L, Reith C, Solbu MD, et al. Impact of renal function on the effects of LDL cholesterol lowering with statin-based regimens: a meta-analysis of individual participant data from 28 randomised trials. *Lancet Diabetes Endocrinol.* 2016;4:829-39.
8. Krane V, Schmidt KR, Gutjahr-Lengsfeld LJ, Mann JF, März W, Swoboda F, et al. 4D Study Investigators (the German Diabetes and Dialysis Study Investigators). Long-term effects following 4 years of randomized treatment with atorvastatin in patients with type 2 diabetes mellitus on hemodialysis. *Kidney Int.* 2016;89:1380-7
9. Messow CM, Isles C. Meta-analysis of statins in chronic kidney disease: who benefits? *QJM.* 2017;110:493-500
10. Ghayda RA, Lee JY, Yang JW, Han CH, Jeong GH, Yoon S, et al. The effect of statins on all-cause and cardiovascular mortality in patients with non-dialysis chronic kidney disease, patients on dialysis, and kidney transplanted recipients: an umbrella review of meta-analyses. *Eur Rev Med Pharmacol Sci.* 2021;25:2696-710
11. Lo HY, Lin YS, Lin DS, Lee JK, Chen WJ. Association of Statin Therapy With Major Adverse Cardiovascular and Limb Outcomes in Patients With End-stage Kidney Disease and Peripheral Artery Disease Receiving Maintenance Dialysis. *JAMA Netw Open.* 2022;5:e2229706.
12. Wheeler DC, London GM, Parfrey PS, Block GA, Correa-Rotter R, Dehmel B, et al. Evaluation Of Cinacalcet HCl Therapy to Lower CardioVascular Events (EVOLVE) Trial Investigators: Effects of cinacalcet on atherosclerotic and nonatherosclerotic cardiovascular events in patients receiving hemodialysis: The Evaluation Of Cinacalcet HCl Therapy to Lower CardioVascular Events (EVOLVE) trial. *J Am Heart Assoc.* 2015;4:e000570.
13. Caluwé R, Pyfferoen L, De Boeck K, De Vriese AS: The effects of vitamin K supplementation and vitamin K antagonists on progression of vascular calcification: Ongoing randomized controlled trials. *Clin Kidney J.* 2016;9:273-9
14. Sukkar L, Talbot B, Jun M, Dempsey E, Walker R, Hooi L, et al. Protocol for the Study of Heart and Renal Protection-Extended Review: Additional 5-Year Follow-up of the Australian, New Zealand, and Malaysian SHARP Cohort. *Can J Kidney Health Dis.* 2019;6:2054358119879896.
15. Suh D, Amendola MF, Reeves M, Wolfe L, Posner M, Davis R. Statins Protect against Thrombosis of Cannulated Radiocephalic Fistulas in Diabetic Patients. *Ann Vasc Surg.* 2021;75:280-6
16. Chang HH, Chang YK, Lu CW, Huang CT, Chien CT, Hung KY. Statins Improve Long Term Patency of Arteriovenous Fistula for Hemodialysis. *Sci Rep.* 2016;6:22197.
17. Kang MH, Kim W, Kim JS, Jeong KH, Jeong MH, Hwang JY, et al. Hydrophilic Versus Lipophilic Statin Treatments in Patients With Renal Impairment After Acute Myocardial Infarction. *J Am Heart Assoc.* 2022;11:e024649.
18. Climent E, Benaiges D, Pedro-Botet J. Hydrophilic or Lipophilic Statins? *Front Cardiovasc Med.* 2021;8:687585.