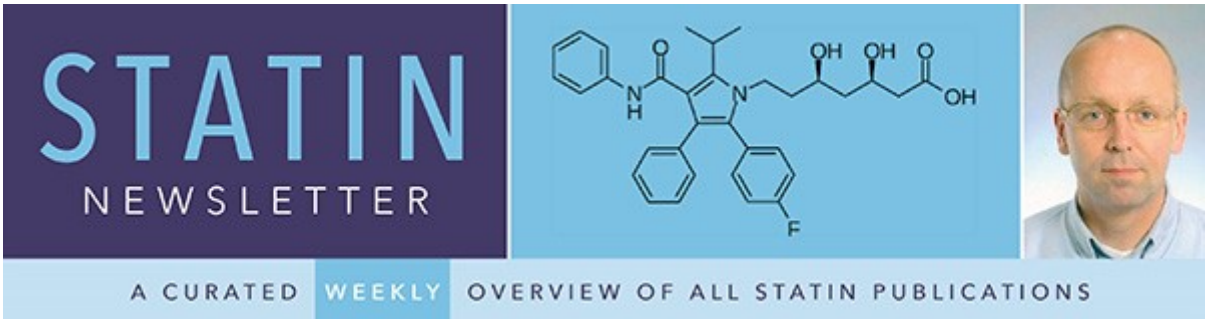

Update week 27 & 28 - 2023

Dr. Peter Lansberg is a Dutch lipidologist, educator and innovator. He has been instrumental in setting up The Dutch National Lipid Clinic Network, the Dutch Lipid Clinic Criteria for Familial Hypercholesterolemia (FH), and the Dutch National FH screening program

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The Statin Newsletter will keep you up-to-date with all recent statin publications. Based on a curated approach to select relevant articles.

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Key Publications

1. **Statin intolerance, what have different guidelines to say**
2. **Primary prevention - statins keep their promise**
3. **The pleiotropic effects of statins in preeclamptic women**
4. **Metformin as add-on treatment for SAMS?**
5. **Dialysis patients and statins - some do benefit!**

Join us in Prague!

Review of current guidelines on managing statins intolerance

"Statin Intolerance: an Overview of US and International Guidance" presents a concise overview of recent international and domestic guidelines, considerations, and treatment methods for statin intolerance and statin-associated muscle symptoms (SAMS). The primary strength of the article lies in its comprehensive review of a critical area of cardiovascular care, where managing statin intolerance and adherence are significant challenges. Moreover, the explicit highlighting of both commonalities and differences between national and international guidance documents contributes to the overall clarity. Limitations of this review included the variation in statin intolerance incidence due to the "nocebo" effect. this is briefly mentioned, but further clarification on this phenomenon, which might impact patient-reported symptoms, would be beneficial. Moreover, the discrepancy between incidence rates in clinical trials versus literature needs better contextualisation. While the authors mention the PCSK9 monoclonal antibodies' efficacy, they provide no detailed discussion on potential implications on statin intolerance management strategies. Lastly, the article addresses the differences in guidance for CK monitoring and statin rechallenge intervals without offering clear insights into why these differences might exist or their potential implications on patient care. In conclusion, the article provides a solid overview of guidance on statin intolerance but lacks deeper exploration on some key aspects, which, if addressed, could significantly enhance the value of this work to the target audience.
Statin Intolerance: an Overview of US and International Guidance. Curr Atheroscler Rep **2023; Cheeley MK, Clegg K, Lockridge C *et al.* http://www.ncbi.nlm.nih.gov/pubmed/?term=37410332**

Observed benefits of statin in hypertensive primary prevention patients

The results of this study hammers another solid nail in the coffin of the statin sceptics and cholesterol critics. The benefits of statin of statins on mortality and cardiovascular disease in primary care hypertensive patients without cardiovascular disease or diabetes is a critical contribution to the field. This study underlines the potential role of statins in primary prevention. Robustly designed using data from the Swedish primary healthcare register QregPV, reveals that statins can significantly reduce all-cause and cardiovascular mortality in hypertensive individuals without CVD or diabetes. This potentially has transformative implications for primary care practices. Despite the limitations to this study, the reported results are in line with what was observed in RCT's. Limitations of this retrospective analysis and suggested by the authors included the inability to incorporate high-density lipoprotein cholesterol or family history of CVD in the propensity score matching introduces potential bias in risk profiles between statin and control groups. The issue of overlapping individuals serving as their own controls in different timelines might introduce potential inaccuracies in the interpretation of statin effects. The non-adjudicated nature of the study outcomes, being dependent on the clinical decision of the doctor filing the death certificate, might lead to some errors in attribution of cause of death. Another critical observation is the lack of significant effect of statins on the incidence of myocardial infarction, barring the noticeable difference in the female subgroup. This gender-specific effect invites further exploration. This study provides essential insights into the role of statins in primary prevention among hypertensive patients, it invites more comprehensive, multicentric research, particularly including additional critical factors like family history of CVD in propensity score matching, and a more accurate mechanism for outcome ascertainment.
The effect of statins on mortality and cardiovascular disease in primary care hypertensive patients without other cardiovascular disease or diabetes. Eur J Prev Cardiol **2023; Andersson T, Natman J, Mourtzinis G *et al.* http://www.ncbi.nlm.nih.gov/pubmed/?term=37368941**
Real-world data shows effect of statin in primary prevention. Eur J Prev Cardiol **2023; Mariampillai JE, Kjeldsen SE. http://www.ncbi.nlm.nih.gov/pubmed/?term=37439146**

Statins not only lower LDL! Pravastatin in women at risk of

preeclampsia

The authors of this article delve into the potential use of pravastatin in managing preeclampsia (PE), specifically addressing its impact on plasma levels of extracellular vesicles (EVs). The authors frame their research within the larger context of how PE is a risk factor for future cardiovascular diseases and how the subclinical vascular dysfunction that persists postpartum could contribute to cardiovascular disease development. The study is particularly relevant because it highlights the need for early detection and prevention of potential gestational complications. The authors demonstrate how women at high risk of term PE have significantly elevated markers of oxidative stress, inflammation, and endothelial dysfunction. They argue that statins, like pravastatin, which have primarily been used to reduce plasma cholesterol levels, might be useful in reducing these markers due to their pleiotropic effects.

The authors show that pravastatin-treated women at high risk of term PE exhibited fewer LEVs compared to those receiving a placebo. Additionally, they report that platelet-derived LEVs were abundant in the circulation of pregnant women at high risk of PE, reinforcing previous findings linking elevated levels of such EVs with various cardiovascular diseases. A strength of the study lies in its comprehensive examination of various LEVs' effects and how pravastatin can modulate these. However, the authors could provide more clarity on the relationship between changes in the levels of angiogenic factors and the sFlt-1/PlGF ratio. Also, the study could benefit from a larger and more diverse sample size to increase the generalizability of the results. In conclusion, the study contributes valuable insights into the potential role of pravastatin in managing risk factors associated with PE and, by extension, future cardiovascular diseases. Future research should continue to explore these connections and determine whether pravastatin or other statins can help prevent PE in high-risk pregnancies.

Pravastatin reduces plasma levels of extracellular vesicles in pregnancies at high risk of term preeclampsia. Frontiers in pharmacology **2023; 14:1166123Santoyo JM, Noguera JA, Avilés F *et al.* http://www.ncbi.nlm.nih.gov/pubmed/?term=37426825**

Metformin reduces risk for SAMS

The authors of this study address an important concern in clinical practice, as dyslipidemia and diabetes often coexist and pose significant cardiovascular risks. The study investigates the potential influence of metformin, a commonly prescribed glucose-lowering agent, on the incidence of myopathy in dyslipidemia patients treated with statins. The authors start by providing a comprehensive overview of dyslipidemia's prevalence and its association with diabetes. They emphasize the significance of statins in lipid management and their wide usage globally. However, the main focus of the study lies in the adverse effects of statins, specifically statin-associated myopathy, which can lead to non-adherence and increased cardiovascular risks. Several prior studies have reported varying incidences of statin-associated myopathy, ranging from mild symptoms to severe rhabdomyolysis. The article discusses the potential interaction between statins and antidiabetic medications, such as SGLT-2 inhibitors and DPP-4 inhibitors, which have been associated with myotoxicity risks. However, the safety and efficacy of metformin when combined with statins in dyslipidemia patients have not been extensively studied, warranting further investigation.This is a retrospective cohort design, utilizing national health insurance claims data to examine the risk of myopathy in dyslipidemia patients receiving statins with or without metformin. The results suggest that the addition of metformin to statin therapy decreases the risk of myopathy in dyslipidemia patients. However, the study does not identify any specific statin with elevated myopathy risk in combination with metformin.

The authors hypothesize that metformin's pleiotropic effects, including AMPK activation and improvement of mitochondrial function, may contribute to its potential protective role against statin-induced muscle toxicities. Moreover, metformin's glucose-lowering properties may also benefit statin-receiving patients at increased risk for incident diabetes mellitus. While the study provides valuable insights into the potential benefits of combining metformin with statins in dyslipidemia patients, several limitations should be acknowledged. The retrospective nature of the study may introduce biases and limit the ability to fully account for confounding variables. Additionally, the lack of complete information on lipid panels and glycemic control levels hinders a comprehensive analysis.

Overall, this study is a valuable contribution to the understanding of the interplay between statins, metformin, and their impact on myopathy risks. It suggests that metformin is a safe and potentially beneficial addition to statin therapy in dyslipidemia patients with metabolic disorders. Nevertheless, further research is needed to validate these findings, consider the potential effects of different statin, and investigate long-term outcomes in a larger patient population. Clinicians can consider these findings when making treatment decisions for patients with both dyslipidemia and diabetes, with a potential to improve medication compliance and reduce cardiovascular complications.

Impact of metformin on statin-associated myopathy risks in dyslipidemia patients. Pharmacol Res Perspect 2023; 11:e01114Bak K, Moon S, Ko M *et al.* http://www.ncbi.nlm.nih.gov/pubmed/?term=37417539

Should dialysis patients with ASCVD take statins?

In this large-scale observational study the focus was on the influence of statin therapy on long-term mortality in patients on dialysis with atherosclerotic cardiovascular disease (ASCVD). The study utilized data from the Korean National Health Insurance Service database, which lends it a robust character due to the large sample size.The study makes a substantial contribution to the current discourse on statin therapy in patients on dialysis, a topic that has remained largely uncertain due to inadequate evidence and a lack of clear guideline recommendations. The study suggests that over 55% of the patients on dialysis were prescribed statins post their first ASCVD event. The use of statins was found to be associated with a lower risk of all-cause mortality. This is an important finding, especially considering the high prevalence of ASCVD and its related mortality among dialysis patients. However, the study has some limitations, including potential residual biases due to uncontrolled variables, the lack of laboratory data such as lipid profiles, and no information regarding the duration of dialysis. The retrospective design and reliance on observational data also limit the causal interpretations of the findings.

The study concludes with a crucial suggestion that statin therapy might be effective in reducing long-term all-cause mortality in patients on dialysis after ASCVD. However, it calls for large-scale, well-designed trials for definitive conclusions, which is a responsible and scientifically rigorous approach. Overall, this study adds valuable insights to the existing knowledge base about the role of statin therapy in dialysis patients with ASCVD, but further research is needed for firm conclusions and guideline development.

Association between statin therapy and mortality in patients on dialysis after atherosclerotic cardiovascular diseases. Scientific reports 2023; 13:10940Lee M, Choi WJ, Lee Y *et al.* http://www.ncbi.nlm.nih.gov/pubmed/?term=37414847

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