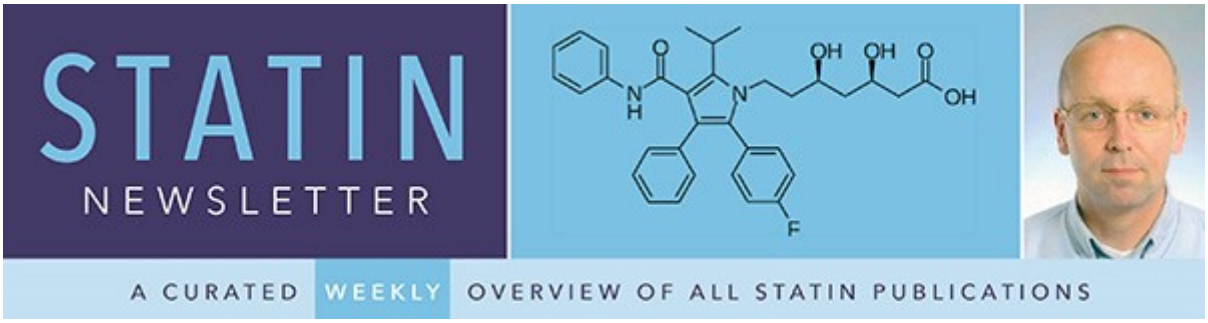

Update week 51 & 52 - 2023

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. **Rethinking Statin Intolerance: Separating Fact from Perception in Cardiovascular Care**
2. **Enhancing Blood Pressure Control: A Fresh Look at Atorvastatin in a Pioneering Study**
3. **Decoding the Intricate Dance of Immune Responses and Metabolism in Atherosclerosis**
4. **The Unexpected Impact of Statins on Alzheimer's Cognitive Trajectory**
5. **How Statins May Offer a Dosage-Specific Shield Against Dementia in Diabetic Patients**

Key publications

Atorvastatin Amplifies Antihypertensive Effects: Insights from a Novel Pilot Study

This small randomized controlled trial assessed the antihypertensive effects of atorvastatin, a commonly used statin, in patients newly diagnosed with hypertension. The primary objective was to observe whether atorvastatin, could also serve as an effective antihypertensive agent. The study enrolled 120 participants over 35 years, divided into two groups: one received amlodipine (a calcium channel blocker) only, while the other group received a combination of amlodipine and atorvastatin. Blood pressure was recorded before and 14 days post-treatment initiation. The key finding was that the combination group showed a more significant reduction in both systolic and diastolic blood pressures compared to the amlodipine-only group, suggesting a synergistic effect of atorvastatin with antihypertensive medication. The discussion section compares these results with similar studies, noting that while some have shown statins' antihypertensive effects in patients with dyslipidemia, this study extends the potential benefits to those with normal lipid profiles. However, it acknowledges the need for larger, population-based studies to confirm the magnitude of this effect and understand the long-term implications. The study's strengths include its randomized controlled design and focus on a novel use of atorvastatin. However, it is limited by its small sample size and short follow-up period, which may not fully capture long-term effects or dose relationships. Additionally, the exclusive focus on newly diagnosed hypertensive patients without prior antihypertensive medication could limit the generalizability of the findings. This pilot study provides preliminary evidence suggesting that atorvastatin, in conjunction with antihypertensive drugs, might enhance blood pressure control. This could have significant implications for patients with concurrent hypertension and dyslipidemia, but further research is necessary to validate these findings and establish clinical guidelines.

Atorvastatin as an Antihypertensive Agent: A Pilot Study. Cureus 2023; 15:e49532Ali N, Faheem M, Ullah H *et al.* http://www.ncbi.nlm.nih.gov/pubmed/?term=38156151

Unravelling the Statin Paradox: A Critical Look at Intolerance and the Power of Perception"

Statins, often face discontinuation due to perceived intolerance, primarily myalgia. The study investigates whether individuals previously intolerant can resume statin therapy under blinded conditions, a pertinent question given the nocebo effect, where the expectation of symptoms might exacerbate or mimic true adverse effects. The review meticulously scrutinizes eight randomized controlled trials involving 1941 studies, focusing on the success of blinded statin rechallenge versus matched placebo. It revealed that while intolerance was indeed more common in statin users compared to placebo (36% vs. 26%), the difference in myalgia or global symptom scores was statistically insignificant. This suggests that a significant proportion of symptoms attributed to statins might be exaggerated by patient expectation rather than the drug itself. Moreover, only one-third of the previously intolerant participants were unable to tolerate statins upon blinded rechallenge, indicating that many could potentially continue with statin therapy. Critically, the study's robustness is underscored by its low risk of bias, consistency across subgroup and sensitivity analyses, and the diverse range of statins and demographic settings. However, limitations like the potential for carryover effects in crossover trials, a small number of trials, and the possibility of attrition bias invite caution. The study also emphasizes the need for alternative strategies to reintroduce statins before resorting to second-line agents, given their crucial role in managing cardiovascular risk. In summary, Kraut et al.'s analysis sheds light on the complex interplay between actual drug intolerance and the psychological anticipation of adverse effects. It underscores the necessity for clinicians to critically reassess statin discontinuation due to alleged intolerance and consider strategies to mitigate the nocebo effect. As always, a personalized approach, balancing the benefits and potential adverse effects, is paramount in clinical decision-making.

Intolerance upon statin rechallenge: A systematic review and meta-analysis of randomized controlled trials. PLoS One 2023; 18:e0295857Kraut R, Wierenga F, Molstad E *et al.* http://www.ncbi.nlm.nih.gov/pubmed/?term=38128013

The Complex Interplay of Immunity and Metabolism in Atherosclerosis

The authors shed light on the complex interplay between metabolic changes, immune responses, and the development of atherosclerosis, particularly focusing on the role of statins. The process of atherosclerosis involves the activation of endothelial cells, infiltration of immune cells, and other changes causing arterial sclerosis and potentially leading to thrombosis. The review highlights the potential of immune regulation as a treatment strategy for atherosclerosis, evidenced by clinical trials like CANTOS and LoDoCo2. It underscores the intricate relationship between metabolic regulation and immune responses, suggesting that controlling the metabolic environment could significantly impact disease progression. Detailed discussions on the metabolic reprogramming of various immune cells, such as macrophages, T cells, dendritic cells, and B cells, are presented. Macrophages exhibit a shift to "Warburg metabolism" under inflammatory conditions, increasing glycolysis and ATP production for enhanced inflammatory response. T cells, undergo significant metabolic changes upon activation, with different subsets showing varied metabolic dependencies which can influence their role in atherosclerosis. The article also discusses the metabolic behaviour of dendritic and B cells in the context of atherosclerosis, indicating their role in promoting immune-mediated damage to the vascular wall. lipid metabolism plays in integral part in these metabolic changes particularly focusing on the role of apolipoprotein A1 (ApoA1) in modulating T cell responses and its potential therapeutic implications. The authors provide insights into how metabolic changes in endothelial cells (ECs) and vascular smooth muscle cells (VSMCs) contribute to the progression of atherosclerosis. It discusses the role of glycolysis and other metabolic pathways in ECs and VSMCs, suggesting that targeting these metabolic pathways could offer new therapeutic strategies. Atherosclerosis is not just a lipid disorder but a complex interplay of metabolic, immune, and cellular processes. The potential of targeting these metabolic pathways for therapeutic benefit is clear, yet it also underscores the need for a nuanced and comprehensive approach, considering the multifaceted nature of the disease. Understanding these complex interactions is crucial for developing more effective therapies and for a deeper understanding of cardiovascular health and disease.
Metabolic changes with the occurrence of atherosclerotic plaques and the effects of statins. Frontiers in immunology 2023; 14:1301051Zhao L, Ma D, Wang L *et al.* http://www.ncbi.nlm.nih.gov/pubmed/?term=38143759

Slowing the Tide: Statins' Surprising Role in Alzheimer's Cognitive Decline

The authors of this article aimed to explore the relationship between the use of statins, and the progression of cognitive decline in patients with Alzheimer's disease (AD) and mixed dementia. The study is based on the understanding that disturbances in brain cholesterol homeostasis may be involved in the pathogenesis of Alzheimer’s disease and that statins, due to their cholesterol-lowering effects and other mechanisms, could potentially influence neurodegenerative processes in AD. The study was a longitudinal cohort investigation using the Swedish Registry for Cognitive/Dementia Disorders, linked with other national registries. The primary outcome was cognitive decline assessed through the Mini-Mental State Examination (MMSE) over time. The researchers compared cognitive trajectories between statin users and non-users and within groups of different statin types. They incorporated various factors such as patient demographics, comorbidities, medication use, and other covariates into their analyses. The cohort consisted of 15,586 patients, predominantly women with an average age of 79.5 years at diagnosis. The study found a dose-response effect where taking an average defined daily dose of statins was associated with a slower rate of cognitive decline compared to non-users. Specifically, statin users had 0.63 more MMSE points after three years than non-users. Among different statins, simvastatin users showed a more significant slowing of cognitive decline compared to atorvastatin and rosuvastatin users. However, no differences were observed concerning

statin lipophilicity. The results of the sensitivity analysis, particularly among incident statin users, were inconsistent, indicating the need for further research to clarify these findings. The study acknowledges the complex interaction of factors influencing the cognitive effects of statins, including patient characteristics, statin properties, and the timing of treatment. Despite the promising results, the researchers caution that the findings, particularly those from sensitivity analyses, need further investigation to fully understand the role of statins in managing cognitive decline in AD and mixed dementia patients.

Statins and cognitive decline in patients with Alzheimer's and mixed dementia: a longitudinal registry-based cohort study. Alzheimer's research & therapy 2023; 15:220Petek B, Häbel H, Xu H *et al.* http://www.ncbi.nlm.nih.gov/pubmed/?term=38115091

Statins and the Brain: Dose-Dependent Key to Dementia Reduction in Diabetics

the study on statin use and dementia risk in older adults with Type 2 Diabetes Mellitus (T2DM) is a exciting piece of research that warrants critical attention. The study explores the connection between statin use, its intensity, and cumulative doses, and the subsequent impact on dementia risk. The authors used the inverse probability of treatment weighting (IPTW) Cox hazards model, exploring a robust dataset from Taiwan's National Health Insurance Research Database. This approach was chosen to address the previous inconsistencies in observational studies and randomized controlled trials, aiming to provide a clearer understanding of statin's role in dementia mitigation. A significant finding of the study is the substantial reduction in dementia risk among statin users, with an adjusted hazard ratio (aHR) of 0.47. Notably, this effect varies with statin types and dosage, indicating a dose-dependent protective effect. The optimal daily statin use was identified as 0.88 defined daily doses (DDDs), associated with the lowest dementia risk. The study's sensitivity analyses demonstrate consistent reductions in dementia risk across various demographic and clinical factors. These analyses affirm the potential of statin use as a significant tool in managing dementia risk in the older T2DM population. However, it's crucial to note the U-shaped pattern in the relationship between statin dose and dementia risk, indicating that both insufficient and excessive doses might not provide the desired protective effects against dementia. This study doesn't just add to the existing literature; it provides a methodological blueprint and substantive evidence for the potential role of statins in dementia prevention. It acknowledges the complexities and nuances involved in understanding drug efficacy, especially in a population vulnerable to both cardiovascular and neurodegenerative conditions. The results not only inform clinical decisions but also hint at broader implications for healthcare policies and patient management strategies.

Protective Effects Against Dementia Undergo Different Statin Type, Intensity, and Cumulative Dose in Older Adult Type 2 Diabetes Mellitus Patients. Journal of the American Medical Directors Association 2023; Sun M, Chen WM, Wu SY, Zhang J. http://www.ncbi.nlm.nih.gov/pubmed/?term=38128583

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