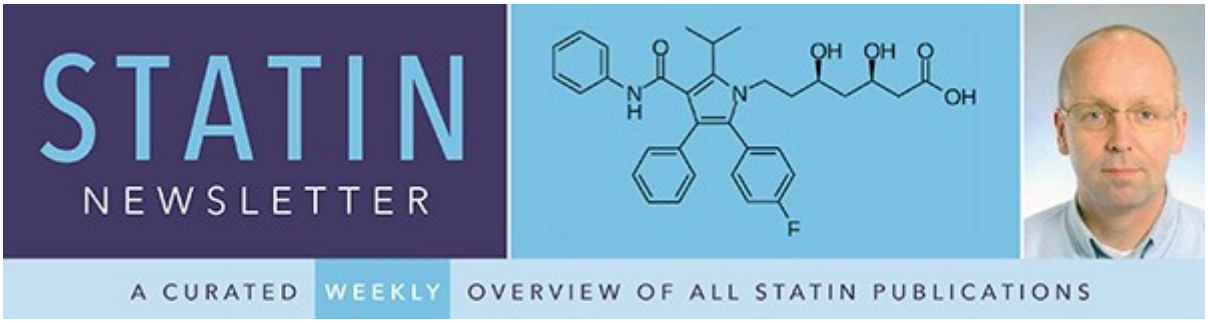

Update week 41 & 42 - 2023

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. **A systematic review on implementing cholesterol management in primary care**
2. **Can statins be used to prevent or treat cancer - Review on potential targets**
3. **Consequences when implementing guidelines dictated statin therapy in diabetics fails**
4. **The LDL paradox in ACS revealed**
5. **The rationale for adding ezetimibe to statins**

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Key publications

Systematic review of cholesterol management for Primary Care

This systematic review of systematic reviews on lipid-lowering therapies for cardiovascular disease prevention and management in primary care is a valuable contribution to the field. Cardiovascular diseases remain a significant global health concern, and understanding the efficacy and safety of various lipid-lowering agents is crucial for guiding clinical practice. The study's inclusion of a wide range of lipid-lowering agents, including statins, ezetimibe, PCSK9 inhibitors, fibrates, BAS, niacin, and omega-3 supplements, provides a comprehensive overview of available options. This comprehensive approach allows for a more nuanced understanding of the benefits and harms associated with these interventions. The findings highlight the importance of statins as the most consistent lipid-lowering drugs, demonstrating a significant reduction in major adverse cardiovascular events (MACE) and all-cause mortality. Statins' efficacy in both primary and secondary cardiovascular prevention underscores their importance in clinical practice. The review also sheds light on the limited evidence for primary cardiovascular prevention, with most data originating from secondary prevention trials. This emphasizes the need for further research in primary prevention settings to better understand the potential benefits of lipid-lowering therapies in individuals without a history of cardiovascular disease. The inclusion of omega-3 supplements and eicosapentaenoic acid ethyl ester as potential options for reducing cardiovascular mortality adds to the discussion, although their effects on other outcomes are less pronounced. The study's focus on patient-oriented outcomes and exclusion of studies relying solely on surrogate markers ensures that the results have practical implications for shared decision-making in clinical settings. However, the review has its limitations, such as the reliance on industry-funded trials and the exclusion of some newer drugs like inclisiran. Additionally, the study acknowledges the challenges in extrapolating results to a more typical primary care population.In conclusion, this systematic review of systematic reviews provides valuable insights into the benefits and limitations of various lipid-lowering therapies for cardiovascular disease prevention and management. It underscores the central role of statins while highlighting the need for more research in primary prevention contexts. These findings will undoubtedly inform updated guidelines and contribute to evidence-based decision-making in cardiovascular care.

Lipid-lowering therapies for cardiovascular disease prevention and management in primary care: PEER umbrella systematic review of systematic reviews. Canadian family physician Medecin de famille canadien **2023; 69:701-711Dugré N, Lindblad AJ, Perry D *et al.***

http://www.ncbi.nlm.nih.gov/pubmed/?term=37833094

Review on statins potential for cancer prevention and treatment

The relationship between statin use and cancer is confusing and intriguing. Contradictory outcomes and the lack of RCT's provide ingredients for a heated debates This concise review provides and up-to-date and a comprehensive exploration of the multifaceted effects of statins, particularly their emerging role in cancer prevention and treatment. Statins, initially developed for lipid management, have evolved beyond their primary purpose. This article underscores the expanding interest in harnessing the pleiotropic effects of statins to combat cancer, a topic of increasing significance in both clinical and research settings. The article effectively begins by tracing the historical development of statins, highlighting their pivotal role in managing hypercholesterolemia and cardiovascular diseases. It then delves into the intriguing aspect of repurposing statins for cancer therapy, a subject that has gained substantial attention in recent years. The primary strength of this article lies in its thorough exploration of the molecular mechanisms underlying the potential anticancer effects of statins. The authors provide insights into how statins influence key cancer pathways, such as inhibiting proliferation, angiogenesis, metastasis, and cancer stemness. Additionally, the discussion of statin-induced oxidative stress, cell cycle arrest, autophagy, and apoptosis in cancer cells enhances our understanding of their diverse mechanisms of action. Furthermore, the inclusion of clinical studies demonstrating a reduced risk of cancer

development, lower-grade tumors at diagnosis, decreased local recurrence, and improved survival in statin users underscores the clinical significance of these findings. These results not only highlight the potential of statins as a valuable tool in cancer prevention and treatment but also open avenues for further research in this domain. The article also addresses the affordability and widespread availability of statins, making them an attractive option for repurposing in cancer treatment, particularly in a healthcare landscape marked by rising drug development costs. In conclusion, this review provides a comprehensive overview of the evolving role of statins in cancer therapy. It successfully combines historical context, molecular insights, and clinical evidence to emphasize the potential of statins as a cost-effective and readily available option in the fight against cancer. However, the article appropriately acknowledges the need for further in vitro studies and clinical trials to fully elucidate the mechanisms and optimize their application in cancer prevention and treatment.

Unraveling the Anticancer Potential of Statins: Mechanisms and Clinical Significance. Cancers 2023; 15Zaky MY, Fan C, Zhang H, Sun XF. http://www.ncbi.nlm.nih.gov/pubmed/?term=37835481

Consequences of not implementing guideline dictated statin therapy in diabetic patients

The study conducted by Pokharel et al. aimed to assess the use of guideline-directed statin intensity (GDSI) and its impact on atherosclerotic cardiovascular disease (ASCVD) outcomes in patients with diabetes within a contemporary healthcare system. The findings of this research shed light on critical issues in diabetes management. The study included a substantial cohort of over 282,000 patients, with approximately 10.2% having diabetes. Notably, the study revealed a significant gap in GDSI use among high-risk patients with diabetes. Only two-thirds of intermediate- and high-risk patients with diabetes were receiving GDSI therapy at the 5-year follow-up. This finding is concerning as statin therapy is a proven means of reducing the elevated risk of ASCVD in diabetic patients. Furthermore, the study demonstrated that patients with diabetes who were not taking statins had a significantly higher risk of stroke and mortality, particularly in the intermediate- and high-risk groups. This underscores the importance of proper guideline-directed statin therapy in primary prevention, as it can substantially improve outcomes in diabetic patients. The study also highlighted the issue of suboptimal implementation of societal prevention guidelines. Despite the clear recommendations for statin use in diabetic patients with elevated ASCVD risk, a substantial proportion of individuals remained without GDSI. This suggests the need for improved healthcare delivery and guideline implementation strategies. The limitations of the study include the use of electronic health record data, limited racial and ethnic diversity, and the inability to assess treatment received outside of the healthcare system. Additionally, socioeconomic data and insurance status were not considered, which could have influenced statin nonadherence. In conclusion, this study underscores the critical importance of guideline-directed statin therapy in primary prevention for diabetic patients at intermediate to high ASCVD risk. The findings emphasize the need for improved strategies to address the gaps in statin utilization and reduce cardiovascular morbidity and mortality in this high-risk population. Healthcare providers and policymakers should take note of these results to enhance the management of diabetes and its associated cardiovascular risks.

Impact of Guideline-Directed Statin Intervention for Primary Prevention in Patients With Diabetes. Diabetes Care 2023; Muluk P, Zhu J, Thoma F *et al.* http://www.ncbi.nlm.nih.gov/pubmed/?term=37851356

The cholesterol paradox in ACS patients; more than meets the eye.

In this study the authors explores the intriguing phenomenon known as the "cholesterol paradox" in the context of acute coronary syndrome (ACS) and its long-term implications. The study, conducted on 410 statin-naïve ACS patients, aimed to investigate whether the LDL-C levels at admission influence long-term prognosis. Patients were divided into low- and high-LDL-C groups based on a cut-off of 122 mg/dL. The primary composite endpoint included all-cause death, myocardial infarction, and ischemic stroke occurrences over a median follow-up of 6.1 years. The findings revealed a significant association between low

LDL-C levels at admission and a worse long-term prognosis. Patients in the low LDL-C group had a 2.3-fold higher risk of experiencing the primary endpoint compared to those in the high LDL-C group. This challenges the conventional wisdom that lower LDL-C levels are universally beneficial. Furthermore, the study identified factors associated with poor prognosis in patients with low LDL-C levels, including frailty, chronic inflammation, and endothelial dysfunction. These factors seem to exacerbate the already compromised cardiovascular health in this subgroup.The study's clinical implications are noteworthy. It underscores the importance of considering individual patient characteristics and pathophysiological factors in the management of ACS. Specifically, the findings highlight the potential benefits of anti-inflammatory therapies and cardiac rehabilitation in patients with low LDL-C levels. However, it's important to acknowledge the limitations of this research, such as its retrospective nature, sample size, and the need for further investigation into the role of atherogenic lipoproteins and lipid-lowering drugs beyond statins. In conclusion, this study challenges the conventional understanding of LDL-C levels in ACS patients by revealing the "cholesterol paradox." It emphasizes the need for a more nuanced approach to patient care, taking into account factors like frailty and inflammation. Future studies should explore therapeutic interventions to improve outcomes in patients with low LDL-C levels at ACS admission. This research contributes valuable insights to the complex landscape of cardiovascular medicine and warrants further exploration in larger, prospective studies.

Impact of Low-Density Lipoprotein Cholesterol Levels at Acute Coronary Syndrome Admission on Long-Term Clinical Outcomes. J Atheroscler Thromb **2023; Sato R, Matsuzawa Y, Yoshii T *et al.* http://www.ncbi.nlm.nih.gov/pubmed/?term=37821363**

Review on the roloe of ezetimibe as add-on after maximising statin therapy

This comprehensive review assesses the role of ezetimibe as a non-statin therapy in managing dyslipidemia). The paper highlights key clinical trials such as IMPROVE-IT and RACING, which have demonstrated that adding ezetimibe to statin therapy can lead to further reductions in low-density lipoprotein cholesterol (LDL-C) levels and significant decreases in major adverse cardiovascular events (MACEs), especially in high-risk ASCVD patients. One of the crucial takeaways from this review is the emphasis on the "lower is better" approach in managing dyslipidemia. It underscores the importance of achieving target LDL-C levels, as supported by epidemiological studies and clinical trials. Statins have long been the cornerstone of lipid-lowering therapy, but it's recognized that some patients fail to reach their LDL-C goals with statin monotherapy. Ezetimibe, a cholesterol absorption inhibitor, emerges as a valuable adjunct therapy. The article provides insights into the safety and tolerability of ezetimibe, noting that it does not exhibit the muscle-related adverse effects associated with statins. This distinction makes ezetimibe an attractive option, especially for patients who experience statin intolerance. The review acknowledges the recommendations of various global clinical guidelines, which uniformly prioritize statin therapy as the first-line treatment for reducing LDL-C levels. However, when statins alone are insufficient in achieving target goals, the addition of ezetimibe is considered an effective second-line option. The differentiation in guidelines, such as those by the American College of Cardiology and American Heart Association (ACC/AHA) and the European Society of Cardiology/European Atherosclerosis Society (ESC/EAS), is addressed, with a focus on the specific LDL-C targets recommended for different risk groups. The paper also touches upon the potential pleiotropic effects of ezetimibe, which go beyond LDL-C reduction. These effects include protection against atherosclerosis, inflammation reduction, modulation of lipoprotein oxidation, and potential benefits related to glucose metabolism, insulin resistance, and non-alcoholic fatty liver disease (NAFLD). However, it acknowledges that more research is needed to fully understand the long-term pleiotropic effects of ezetimibe. In conclusion, this article offers a comprehensive analysis of the clinical implications of ezetimibe in the management of dyslipidemia. It highlights the value of ezetimibe as a non-statin therapy, particularly in high-risk ASCVD patients who struggle to achieve target LDL-C levels with statin monotherapy. While the pleiotropic effects of ezetimibe hold promise, further research is essential to elucidate its long-term benefits. Overall, this review provides valuable insights for clinicians and researchers in the field of cardiovascular medicine.

Expanding the therapeutic landscape: ezetimibe as non-statin therapy for dyslipidemia. The Korean journal of internal medicine 2023; Lee J, Lee SH. http://www.ncbi.nlm.nih.gov/pubmed/?term=37866817

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