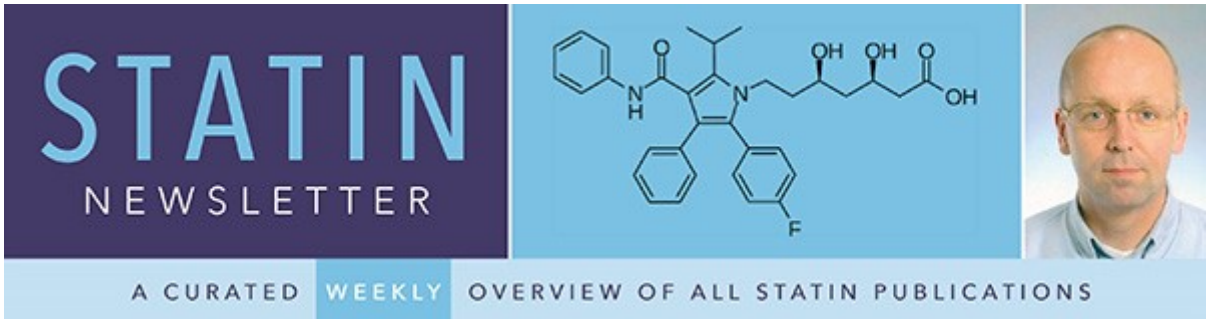

Update week 25 & 26 - 2023

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. **Review on LDL-c focused novel treatment**
2. **Atorvastatin vs Rosuvastatin post STEMI**
3. **Bempedoic acid in statin intolerant primary prevention patients**
4. **Statin use associated with hepato protective effects**
5. **Lower LDL-c improves outcomes in post stroke patients**

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Managing LDL-c by different pathways - review

This article explores the progress in hypercholesterolemia treatment, focusing on LDL receptor (LDLR)-dependent and independent pathways. The review is comprehensive, discussing a variety of treatment modalities, including statins, PCSK9 inhibitors, IDOL, angiopoietin-like 3 (ANGPTL3), and apolipoprotein-based therapies. The authors elucidate these different pathways and therapies and their roles in managing familial hypercholesterolemia (HoFH and HeFH). They also spotlight the potential of CRISPR-Cas9 genome/base editing technology to revolutionize the treatment of such conditions.
However, there are areas that the authors could further delve into. While it explains the role of LDLR mutations in hypercholesterolemia, the review does not discuss the heterogeneity of these mutations or their varied effects on the disease course and response to treatment. Additionally, there is a lack of detail on how CRISPR-Cas9 genome/base editing technology can specifically target LDLR and ANGPTL3, which is a significant part of the authors' arguments.
The authors address the limitation of the LDLR-expression enhancement approach that necessitates at least one functional LDLR allele to target. However, they need to suggest potential solutions to this problem or ways to circumnavigate this limitation.
While the paper has good insights on animal models and their potential translational value in humans, the authors have yet to provide much detail on the results from human trials or any potential challenges, which is crucial to understanding these therapies' real-world applicability and potential limitations.
In conclusion, the paper provides a useful summary of the development in treatments for hypercholesterolemia. However, it could have given more depth in several key areas, such as mutation heterogeneity, details on how CRISPR technology can be utilized, potential solutions to identified limitations, and results from human trials.A Review of Progress on Targeting LDL Receptor-Dependent and -Independent Pathways for the Treatment of Hypercholesterolemia, a Major Risk Factor of ASCVD. Cells 2023; 12Srivastava RAK. http://www.ncbi.nlm.nih.gov/pubmed/?term=37371118

comparing Rosuvastatin vs atorvastatin on microcirculation in STEMI patients

The article titled "Effects of atorvastatin and rosuvastatin on dysfunctional coronary circulation in patients with ST-segment elevation myocardial infarction" investigates the impact of atorvastatin and rosuvastatin on dysfunctional coronary circulation in patients with ST-segment elevation myocardial infarction (STEMI) who underwent primary percutaneous coronary intervention (pPCI). The authors aimed to compare the effects of these two statins on coronary microcirculation and clinical outcomes in STEMI patients.
The study, which was retrospective in nature, included 597 consecutive patients with STEMI who underwent pPCI in three centers. Dysfunctional coronary circulation was assessed using the thrombolysis in myocardial infarction (TIMI) grade and the TIMI myocardial perfusion grade (TMPG). Logistic regression analysis was employed to evaluate the impact of atorvastatin and rosuvastatin on dysfunctional coronary circulation.
The findings of the study revealed that the incidence of TMPG no/slow reflow was significantly lower in the atorvastatin group compared to the rosuvastatin group. Furthermore, multivariate adjustment demonstrated that rosuvastatin was associated with a higher odds ratio for after pretreatment TMPG no/slow reflow and after stenting TMPG no/slow reflow. However, there were no significant differences between the two groups regarding clinical outcomes during hospitalization.
The discussion section of the article elaborates on the pathophysiology of dysfunctional coronary circulation and the pleiotropic effects of statins, such as endothelial protection, plaque stabilization, and anti-inflammatory properties. The authors suggest that the different molecular structures and mechanisms of action of atorvastatin and rosuvastatin may explain their discordant effects on coronary microcirculation. Additionally, the study highlights the benefits of atorvastatin in improving coronary microvascular function in STEMI patients undergoing pPCI, although its impact on clinical outcomes requires further

investigation.
While the study provides valuable insights into the differential effects of atorvastatin and rosuvastatin on dysfunctional coronary circulation in STEMI patients, there are several limitations to consider. These include the retrospective design, potential selection bias and confounders, limited sample size, moderate statin dose levels, and the need for more precise indicators and imaging evaluation methods to assess coronary microcirculation.
In conclusion, the study suggests that atorvastatin is associated with better coronary microcirculation and reduced dysfunctional coronary circulation compared to rosuvastatin in STEMI patients undergoing pPCI. However, further research is needed to determine the impact of different statin types on clinical outcomes in this patient population.
Effects of atorvastatin and rosuvastatin on dysfunctional coronary circulation in patients with ST-segment elevation myocardial infarction. J Int Med Res 2023; 51:300060523118254 7Zhou L, Hu X, Zhang H *et al.* http://www.ncbi.nlm.nih.gov/pubmed/?term=37377087

Bempedoic acid reduced MACE in statin intolerant primary prevention patients

In this secondary analysis of a larger randomized trial bempedoic acid use was associated with a significant reduction on cardiovascular outcomes in statin-intolerant patients without prior cardiovascular events. The study enrolled a substantial number of participants from multiple centres in various countries, providing a diverse sample. The results indicate that bempedoic acid treatment was associated with reduced major cardiovascular events, including a significant risk reduction for the primary composite endpoint and key secondary endpoints. The study also highlights the potential value of lipid-modulating therapy in high-risk primary prevention patients.
However, there are certain limitations to consider. Firstly, this is a secondary analysis of a subpopulation within a larger trial, which increases the risk of false-positive findings and the play of chance. While the consistency of event reduction across multiple endpoints strengthens the reliability of the results, the smaller number of events and wider confidence intervals due to the subset analysis should be considered. Moreover, the study focused on patients who reported statin intolerance, resulting in a high mean baseline LDL-C level. The effects of cholesterol lowering on cardiovascular events in populations with lower pre-treatment LDL-C levels remain uncertain.
Additionally, the article suggests that lipid-modulating therapies are underutilized in high-risk primary prevention patients, particularly women and those from racial and ethnic minority populations. While this is an important point, the study does not explore the underlying reasons for underutilization or propose strategies to address this issue.
In conclusion, the study provides valuable insights into the effects of bempedoic acid on cardiovascular outcomes in statin-intolerant primary prevention patients. The results indicate significant risk reductions for major cardiovascular events, MI, cardiovascular death, and all-cause mortality. However, the study's limitations and the secondary nature of the analysis should be considered. Further research is needed to explore the applicability of these findings to broader populations and to address the underutilization of lipid-modulating therapies in high-risk primary prevention patients.
Bempedoic Acid for Primary Prevention of Cardiovascular Events in Statin-Intolerant Patients. Jama 2023; Nissen SE, Menon V, Nicholls SJ *et al.* http://www.ncbi.nlm.nih.gov/pubmed/?term=37354546

Hepato protective effects of statins

The authors of this study examined the correlation between regular statin use and reduction in liver disease, hepatocellular carcinoma (HCC), and liver-related deaths. Data was obtained from UK Biobank, TriNetX, and Penn Medicine Biobank and used propensity score matching for fair comparisons. The authors found an association between regular statin use and reduced risk of liver disease, HCC, and liver-related deaths.
The authors convincingly made use of a substantial dataset from three different cohorts. The cohort selection provides broad demographic coverage, enhancing the study's generalizability. The application of propensity score matching enhances the robustness of the findings. However, the observational nature of the study cannot definitively prove

causality.
One methodological concern is the reliance on self-reported statin usage in the UK Biobank. This can introduce recall bias, potentially affecting the accuracy of the findings. The authors also acknowledge that early stages of liver disease might have gone undetected, which may impact the result interpretation.
In terms of statistical analysis, it would have been beneficial if the authors had used a correction method for multiple comparisons. The high number of comparisons raises the possibility of Type I errors.
The study raises compelling suggestions about the hepatoprotective role of statins. Still, it acknowledges the necessity of conducting randomized clinical trials before implementing statins as a liver disease preventive strategy. This careful approach is commendable given the observational nature of the current study and the potential risks associated with statin use.
In conclusion, while the study has methodological limitations, its findings contribute to the growing literature on the potential hepatoprotective role of statins and paves the way for more rigorous interventional studies to confirm these findings.
Association of Statin Use With Risk of Liver Disease, Hepatocellular Carcinoma, and Liver-Related Mortality. JAMA network open 2023; 6:e2320222Vell MS, Loomba R, Krishnan A *et al.* http://www.ncbi.nlm.nih.gov/pubmed/?term=37358849

Lower LDL-c targets in post-stroke patient

This sub-analysis of the Treat Stroke to New Targets (TST) study discusses the effectiveness of different strategies in reducing LDL cholesterol levels after a stroke. The study conducted in France and South Korea involved patients with recent ischemic stroke or transient ischemic attack, who were randomly assigned to two target LDL cholesterol groups: <70 mg/dL or 100±10 mg/dL. The primary outcome measured was the occurrence of ischemic stroke, myocardial infarction, urgent coronary or carotid revascularization, and vascular death.
This post hoc analysis of the TST trial found that among patients assigned to the <70 mg/dL target group, those who achieved >50% reduction in LDL cholesterol from baseline had a significant reduction in the primary outcome compared to those with <50% reduction. This suggests that the magnitude of LDL cholesterol reduction is as important as the target level itself. However, it is important to note that this analysis was limited by the lack of randomization of LDL reduction percentages from baseline.
The study also compared Korean and French patients and found that the uncertain benefit observed in Korean patients may be due to a lesser magnitude of LDL cholesterol reduction from baseline compared to French patients. Furthermore, the authors suggest that future trials should explore even lower target levels, such as <55 or <40 mg/dL, as recommended by the European Society of Cardiology guidelines.
While the findings of this analysis are hypothesis-generating and should be tested in a randomized controlled trial, they highlight the importance of achieving both a target LDL cholesterol level and a significant reduction in LDL cholesterol from baseline. The study adds to the existing evidence supporting intensive statin therapy and LDL cholesterol reduction in patients with atherosclerotic cardiovascular disease.
Overall, this article provides valuable insights into the relationship between LDL cholesterol reduction and clinical outcomes in stroke patients. Further research is warranted to confirm these findings and explore optimal LDL cholesterol targets and reduction strategies in this population.
More Than 50 Percent Reduction in LDL Cholesterol in Patients With Target LDL <70 mg/dL After a Stroke. Stroke 2023; Amarenco P, Lavallée PC, Kim JS *et al.* http://www.ncbi.nlm.nih.gov/pubmed/?term=37376989

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Basic Science

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