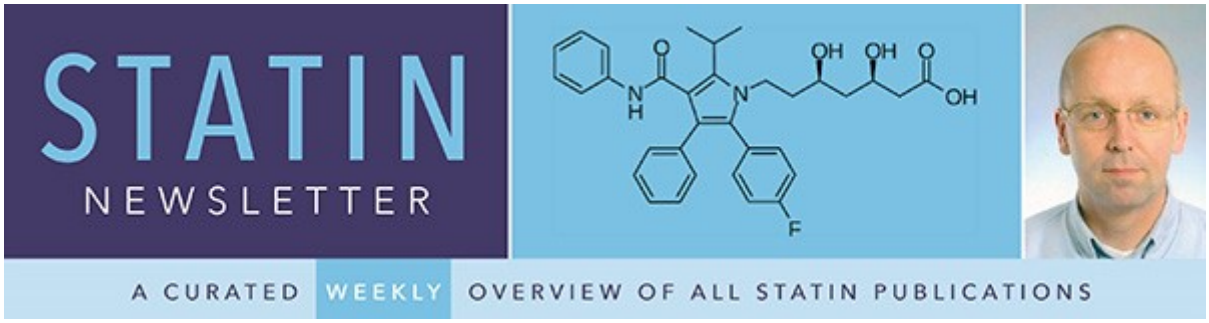

Update week 11 & 12 - 2022

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. **60--years of FH care; LDL-c management**
2. **Twin study on genetics vs environment risk for non-calcified plaques**
3. **Statin side effects - meta-analysis based on >4 million patients**
4. **New practive advisory on sICAS management**
5. **statins associated with reduced cognitive decline in post-stroke patients**

LDL-c in Czech FH patients – 60 years of experience!

Effective lipid management in FH – lessons from the first European Lipid Clinic in Prague The management of FH patients has improved significantly over the last decade. In this retrospective analysis to evaluate the lipid values of FH patients, data collected in the first European Lipid Clinic located in the General University Hospital Prague (established in the 1960s) was used. Included were 1236 FH patients, 841 women and 395 men; the mean age was 44.8 (±16.7) years. Clinical diagnosis was based on the Dutch Lipid Clinic Network Criteria. Genetic analysis was performed using PCR-RFLP to detect familial defective apo B (FDB) and apolipoprotein E (APOE) polymorphism. Baseline LDL-c and total C levels were 6.49 ± 1.92 mmol/L and 8.95 ± 1.95 mmol/L, respectively. Treatment improved both parameters significantly, with an LDL-c of 3.26 ± 1.57 mmol/L and a TC of 5.43 ± 1.69 mmol/L. Noteworthy are the differences between baseline LDL-c and TC levels of the FDB patients, 5.57 ± 1.46 mmol/L and 7.88 ± 1.58 mmol/L at baseline and decreasing to 3.45 ± 0.24 mmol/L and 5.58 ± 1.37 mmol/L, respectively. Despite the lower baseline lipid values, FDB patients showed a less effective response resulting in slightly higher LDL-c and TC during follow-up. Apo E2E2 carriers showed significantly lower LDL-c levels on treatment compared to Apo E3/E3 and E/4E4. In a follow-up study the clinical outcome data in this historic cohort will be reporte.. Todorovova V, Altschmiedova T, Vrablik M, Ceska R. Familial

Hypercholesterolemia: Real-World Data of 1236 Patients Attending a Czech Lipid Clinic. A Retrospective Analysis of Experience in More than 50 years. Part I: Genetics and Biochemical Parameters. Frontiers in genetics 2022; 13:849008. http://www.ncbi.nlm.nih.gov/pubmed/?term=35295947

Nature vs nurture of coronary plaques in twins

Limited data is available on the genetics of non-calcified atherosclerotic plaques. In this study, the aim was to assess the relative contribution of genetic and environmental factors on non-calcified plaque (NCP), CAC score, and coronary plaque (CP) volumes using coronary CT angiography (CTA) in adult twin pairs without known CAD. The BUDAPEST-GLOBAL (Burden of Atherosclerotic Plaques Study in Twins—Genetic Loci and the Burden of Atherosclerotic Lesions) is a prospective single-center, classical twin study. All twins underwent coronary computed tomography angiography to assess coronary atherosclerotic plaque volumes. Included were 196 twins, 120 monozygotic and 76 same-gender dizygotic pairs. The mean(±SD) age of the cohort was 56±9 years (63.3% female), and dizygotic subjects were older than the monozygotic subjects (58±8 versus 55±10 years, P=0.005). Both total cholesterol (214.8±42.2 mg/dL) and LDL-cholesterol levels (134.7±38.4 mg/dL) were slightly elevated, with no difference between monozygotic and dizygotic groups (P=0.25 and P=0.35, respectively). The 10-year ASCVD risk estimate was 7.9±7.7% for the total cohort, with 83 subjects as low-risk (<5.0%), 34 subjects as borderline risk (5.0%–7.4%), 63 subjects as intermediate risk (7.5%– 19.9%), and 16 high risks (>20.0%) subjects. A significant difference was observed in the HbA1c levels between the monozygotic and dizygotic groups (5.6±1.0% versus 5.3±0.8%, P=0.01). Based on structural equation models, non-calcified plaque volume was predominantly determined by environmental factors; common environment, 63% (56%–67%), unique environment, 37% (33%–44%). Coronary artery calcification score and calcified plaque volumes had a relatively strong genetic heritability; additive genetic, 58% (50%–66%]; unique environmental, 42% (34%–50%] and additive genetic, 78% (73%–80%); unique environmental, 22% (20%–27%), respectively. Non-calcified plaque volume is mainly influenced by shared environmental factors, whereas coronary artery calcification score and calcified plaque volume are more determined by genetics. These findings emphasize the importance of early lifestyle interventions in preventing coronary plaque formation.

Drobni ZD, Kolossvary M, Karady J *et al.* **Heritability of Coronary Artery Disease: Insights From a Classical Twin Study.** Circulation. Cardiovascular imaging 2022; 15:e013348. http://www.ncbi.nlm.nih.gov/pubmed/?term=35290075

Statin intolerance meta-analysis (>4 million patients)

Statin intolerance (SI) is the most significant obstacle in guideline-directed LDL-c management, resulting in an increased risk of preventable cardiovascular events. This met-analysis included published studies on the prevalence of SI up to 31 May 202. The primary endpoint was overall prevalence and prevalence according to a range of diagnostic criteria [National Lipid Association (NLA), International Lipid Expert Panel (ILEP), and European Atherosclerosis Society (EAS)]. The secondary endpoint was to identify possible risk factors for SI. A total of 176 studies [112 randomized controlled trials (RCTs); 64 cohort studies] with 4 143 517 patients were included in the analysis. Overall, 9.1% (8.0–10%) of the participants reported SI. The different criteria used to define SI showed similar SI prevalence. For the NLA, ILEP and EAS criteria, 7.0% (6.0–8.0%), 6.7% (5.0–8.0%), 5.9% (4.0–7.0%), respectively. In RCTs, the prevalence of SI was significantly lower compared with cohort studies, 4.9% (4.0–6.0%) vs. 17% (14–19%). Studies that included both primary and secondary prevention vs. studies that analyzed primary or secondary prevention patients separately reported a higher prevalence of SI, 18% (14–21%), vs. 8.2% (6.0–10%) and 9.1% (6.0–11%), respectively. No differences were noted based on Statin lipid solubility, 4.0% (2.0–5.0%) vs. 5.0% (4.0–6.0%)]. Factors associated with increased SI reports were age, OR: 1.33 (P=0.04); female Gender, OR: 1.47 (P=0.007), Asian and Black race (P,0.05 for both); obesity, OR: 1.30, P=0.02); diabetes mellitus, OR: 1.26, P=0.02); hypothyroidism, OR: 1.37, P=0.01). Chronic liver and renal failure (P,0.05 for both) were significantly associated with SI in the meta-regression model. Antiarrhythmic agents, calcium channel blockers, alcohol use, and increased statin dose were also associated with a higher risk of SI. Based on the present

analysis of >4 million patients, the prevalence of SI is low; when diagnosed according to international definitions even lower. These results support the concept that the prevalence of complete SI might often be overestimated and highlight the need for carefully assessing patients with potential SI symptoms. Clinicians should use these results to encourage adherence to statin therapy in the patients they treat.
Bytyci I, Penson PE, Mikhailidis DP *et al.* **Prevalence of statin intolerance: a meta-analysis**. Eur Heart J 2022. http://www.ncbi.nlm.nih.gov/pubmed/?term=35169843
Cannon CP. **Statin intolerance: how common is it and how do we work with patients to overcome it?** Eur Heart J 2022. http://www.ncbi.nlm.nih.gov/pubmed/?term=35325103

Update practice advisory for sICAS

This updated practice advisory followed the process outlined in the American Academy of Neurology Clinical Practice Guideline Process Manual, 2011 Edition, as amended. For the systematic review, studies were included through November 2020. Recommendations were based on evidence, related evidence, principles of care, and inferences. Currently, treatments consist of aspirin 325 mg/d for long-term prevention of stroke and death. Clopidogrel 75 mg/d can be combined with aspirin for up to 90 days in patients with very high risk (70%–99%) for symptomatic intracranial atherosclerotic arterial stenosis (sICAS). High-intensity statin therapy aims to achieve an LDL-c goal of <70 mg/dL. Additionally, long-term blood pressure targets of <140/90 mmHg should also be part of patient management. Moderate physical activity and treatment of other modifiable vascular risk factors are highly recommended. Percutaneous transluminal angioplasty and stenting are not recommended to prevent strokes in patients with moderate (50%–69%) sICAS risk or as initial treatment in patients with severe sICAS. Patients need to be counseled on the risks of percutaneous transluminal angioplasty and stenting, as well as alternative treatments when percutaneous transluminal angioplasty and stenting are contemplated..
Turan TN, Zaidat OO, Gronseth GS *et al.* **Stroke Prevention in Symptomatic Large Artery Intracranial Atherosclerosis Practice Advisory: Report of the AAN Guideline Subcommittee**. Neurology 2022; 98:486-498. http://www.ncbi.nlm.nih.gov/pubmed/?term=35314513

Post-stroke dementia less frequent observed in statin users

Patients who suffer an ischemic stroke have an increased risk for dementia. This retrospective analysis of the UK Clinical Practice Research Datalink evaluated the association between cognitive function and statin use. For this analysis, patients who suffered an ischemic stroke and were not diagnosed with prior dementia, and did not use statins in the preceding year were followed for 10-years. To estimate observational analogues of intention-to-treat (ITT, statin initiation vs. no initiation) and per-protocol (PP, sustained statin use vs. no use) effects on the risk of dementia in 18,577 statin initiators and 14,613 non-initiators for a mean follow-up period of 4.2 years. Observed was an adjusted hazard ratio (aHR) for dementia was 0.70 (0.64–0.75) in ITT analysis and 0.55 (0.50–0.62) in PP analysis. The observed association of statin use with reduced dementia risk, with a potentially even more significant benefit in patients that persisted with statin use over time. The observed benefits of preventing post-stroke dementia were not influenced by age or the presence of cardiovascular risk factors, underlining the importance to increase the use of statins, particularly in older patients and in those without prior cardiovascular risk factors, and for these reasons, less likely to be on statin treatment
Yang Z, Toh S, Li X *et al.* **Statin use is associated with lower risk of dementia in stroke patients: a community-based cohort study with inverse probability weighted marginal structural model analysis.** European journal of epidemiology 2022. http://www.ncbi.nlm.nih.gov/pubmed/?term=35305172

Correction of statin literature update week 9 & 10

The key article summary "**Clear benefits of statins in very elderly patients after PCI"**, the final conclusions: "*Protective effects were increased in patients who suffered a stroke, peripheral artery disease, and smokers*" Should read: "*Protective effects were decreased as well in patients who suffered a stroke, peripheral artery disease, and smokers"*

Relevant Publications

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Basic Science

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