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Atherosclerosis newsletter

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"Call for Original Research Papers on Lp(a)"

With the advent of specific Lp(a)-lowering therapies, the Lp(a) field is experiencing a sense of excitement and optimism. Therefore, *Atherosclerosis* as the journal of the European Atherosclerosis Society (EAS) is **calling for the submission of Original Research Papers** on various topics in Lp(a), which contribute **novel findings** to the field. These manuscripts will undergo a regular review process and in case of acceptance will go online within the usual time of processing.

The submitted Original Research Articles will be handled by Marlys L. Koschinsky as Guest Editor and Florian Kronenberg as Co-Editor of *Atherosclerosis*. They will decide on the peer reviewers of the submitted articles. If a manuscript is accepted for publication, these Original Research Articles will appear printed together in a combined issue of the journal containing roughly a dozen in-depth review articles on Lp(a), which aims to provide the most comprehensive, insightful, and current overview of the Lp(a) field. The topics and authors for these review articles have already been decided and secured for this project. The publication is planned for the first quarter of 2022 and is expected to receive a high visibility.

For preparation of the Original Research manuscripts please see the **"Guide for authors"** at https://www.elsevier.com/journals/atherosclerosis/0021-9150/guide-for-authors.

The possibility for submission of the first draft of Original Research Papers for the mentioned issue of *Atherosclerosis* will end on October 31, 2021. This call is only open for Original Research Articles and no review articles are allowed. Please select "Special issue: Lp(a)" as article type at submission.

To submit your paper go to: Editorial Manager®

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At the end of June, Clarivate™ Analytics released the new impact factors. We are proud to report that the 2020 impact factor of *Atherosclerosis* has increased substantially from 3.919 to 5.162. Also on behalf of the co-editors, we thank the readers and authors for their sustained interest and confidence.

The June issues of *Atherosclerosis* contain several articles on the efficacy and safety of statins and PCSK9 inhibitors and first clinical experiences with the treatment of homozygous FH patients with an ANGPTL3 inhibitor.

Utilizing coronary artery calcium to guide statin use

Cardiovascular disease (CVD) is the leading cause of death worldwide. Coronary artery calcium (CAC) screening, a highly distinct marker of coronary atherosclerosis, serves as an important arbitrator of atherosclerotic cardiovascular disease (ASCVD). In asymptomatic individuals in particular, CAC testing offers a model for initiating or prolonging preventative statin therapies and subsequently up- or down-risking of patients.

Though the 2018 ACC/AHA Guidelines on Blood Cholesterol recommend CAC as an arbitrator of statin use, it is not known whether these recommendations have been universally followed. In this review, Golub et al. discuss about CAC as an important determinator of ASCVD risk. They highlight the key points behind coronary artery calcium scoring, as a critical platform for stratifying risk and guiding future preventative treatments.

By summarizing the framework behind recent cholesterol guidelines for ASCVD risk assessment, this review will address the debate of use of CAC for both the clinical setting and preventative therapy applications.

Atherosclerotic cardiovascular disease events among statin eligible individuals with and without long-term healthy arterial aging

Measurement of coronary artery calcium (CAC) is a non-invasive imaging approach that improves atherosclerotic cardiovascular disease (ASCVD) risk stratification beyond traditional risk factors and is recommended when there is uncertainty regarding ASCVD risk. The absence of CAC (CAC = 0) is associated with a low 10-year ASCVD risk and can “de-risk” individuals aged 45–75 years who are classified as moderate-high risk by traditional ASCVD risk factor-based risk scores such as the Pooled Cohort Equations (PCE). A large proportion of statin eligible candidates have a baseline absence

of CAC and low 10-year ASCVD risk, but little is known with regards to how many of these individuals maintain long-term healthy arterial aging and whether their ASCVD event rate remains low beyond 10-year follow-up. Razavi et al. determined the proportion of statin eligible individuals who had long-term healthy arterial aging (persistent CAC = 0) and their 15-year ASCVD outcomes.

They included in the study 561 statin eligible candidates from the Multi-Ethnic Study of Atherosclerosis (MESA,) who were not on statin therapy, with CAC = 0 at Visit 1 and who underwent a subsequent CAC scan at Visit 5. Adjusted Cox proportional hazards regression assessed the association between persistent CAC = 0 and ASCVD events over 15.9 years.

Participants were on average 61.7 years old, 50% were women, and 43% maintained long-term CAC = 0. Individuals with a low-density lipoprotein cholesterol (LDL-C) ≥190 mg/dL (54%) and those with an ASCVD risk ≥20% (33%) had the highest and lowest proportion of persistent CAC = 0, respectively. There were 57 ASCVD events, and 15-year ASCVD event rates were low for individuals with and without healthy arterial aging, but the 10-year number needed to treat to prevent one ASCVD event differed by more than two fold. In multivariable modeling, persistent CAC = 0 conferred a 51% lower risk of ASCVD compared to those with incident CAC.

More than 40% of statin eligible individuals with baseline CAC = 0 had long-term healthy arterial aging. Statin eligible candidates with persistent CAC = 0 had a very low 15-year ASCVD risk, suggesting that statin therapy may be of limited benefit among this group of individuals.

Fetal toxicity associated with statins: A systematic review and meta-analysis

Statins are the drugs of choice for decreasing elevated low-density lipoprotein cholesterol (LDL-C). Based mostly on animal studies and case reports, they are not recommended to pregnant women and in the preconception period because of their possible teratogenic effects, for which causality has never been proven. Vahedian-Azimi et al. aimed to identify and analyze all the existing studies on such topic, and to perform a meta-analysis to collect scientific evidence that proves that statin therapy is associated with an increased rate of birth defects in women exposed to statins during pregnancy.

PubMed/MEDLINE, Scopus, and Web of Science were searched since the inception until May 16, 2020. The risk of bias for each clinical trial was evaluated using the Cochrane handbook criteria for systematic reviews. The National Institutes of Health (NIH) quality assessment tool was used for the evaluation of cohort and cross-sectional studies. Meta-analysis was performed on the extracted data. Heterogeneity was assessed using I^2 measure and Cochrane's Q statistic. A pooled estimate of odds ratio (OR) and 95% confidence intervals (CI) using a random-effects model were calculated.

Twenty-three studies with 1,276,973 participants were included in the systematic review and 6 of them (n = 1,267,240 participants) were included in the meta-analysis. The results of the review

did not suggest a clear-cut answer to the question whether statin treatment during pregnancy is associated with an increased rate of birth defects or not, while the results of the meta-analysis indicated that statin use does not increase birth defects and other congenital anomalies.

No significant increase of birth defects after statin therapy was observed. Thus, there is still no clear evidence that statin treatment during pregnancy is teratogenic, and this issue needs to be further investigated.

Meta-analysis of randomized clinical trials comparing PCSK9 monoclonal antibody *versus* ezetimibe/placebo in patients at high cardiovascular risk

Elevated low-density lipoprotein cholesterol (LDL-C) levels correlate with an increased risk of atherosclerotic cardiovascular disease (ASCVD) and are the primary target of lipid-lowering therapy. Proprotein convertase subtilisin/kexin type 9 monoclonal antibodies (PCSK9 mAbs) reduce circulating LDL-C by controlling the expression of LDL-receptor on the surface of hepatocytes. In this meta-analysis, Ma et al. aimed at evaluating the efficacy of PCSK9 mAbs on clinical and lipid-lowering outcomes.

PubMed, Embase, and ClinicalTrials.gov were searched from inception until November 2020 for randomized controlled trials (RCTs) that compared PCSK9 mAbs with ezetimibe or placebo in patients at high cardiovascular risk. Twenty-eight RCTs with a total of 89,115 participants were included.

Compared with placebo, PCSK9 mAbs significantly reduced the risk of major adverse cardiac events (MACEs). However, no difference was observed in MACEs between PCSK9 mAbs and ezetimibe. Secondary analyses show that PCSK9 mAbs were not superior to ezetimibe in preventing stroke, myocardial infarction, and cardiovascular death. Compared with placebo, PCSK9 mAbs significantly reduced the incidence of stroke and myocardial infarction, but not the risk of cardiovascular death. As for lipid-lowering efficacy, PCSK9 mAbs markedly reduced percent change of LDL-C from baseline to week 12 and 24 compared to ezetimibe or placebo.

In patients at high cardiovascular risk, PCSK9 mAbs could effectively reduce MACEs, stroke, and myocardial infarction compared with placebo. However, PCSK9 mAbs were not superior to ezetimibe in preventing adverse cardiovascular events.

Regression in carotid plaque lipid content and neovasculature with PCSK9 inhibition: A time course study

Low-density lipoprotein (LDL) cholesterol lowering with statins reduces atherosclerotic cardiovascular disease (ASCVD)-related major events in both primary and secondary prevention. Adding ezetimibe or proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors to statin therapy

has been shown to further reduce ASCVD events in secondary prevention, but the effects of PCSK9 inhibitors on atherosclerotic plaque remain elusive. Using serial magnetic resonance imaging (MRI), Lepor et al. studied changes in carotid plaque lipid content and neovasculature under PCSK9 inhibition with alirocumab.

Among patients with LDL-C ≥70 mg/dl but ineligible for high-dose statin therapy, those with lipid core on carotid MRI were identified to receive alirocumab 150 mg every 2 weeks. Follow-up MRI was performed at 3, 6, and 12 months after treatment. Pre- and post-contrast MRI was acquired to measure percent lipid core volume (% lipid core). Dynamic contrast-enhanced MRI was acquired to measure the extravasation rate of gadolinium contrast (K^{trans}), a marker of plaque neovasculature.

Twenty-seven out of 31 patients enrolled completed the study. From 9.8% at baseline, % lipid core was progressively reduced to 8.4% at 3 months, 7.5% at 6 months, and 7.2% at 12 months, which was accompanied by a progressive increase in % fibrous tissue but not % calcification. K^{trans} was not reduced until 12 months. Lumen and wall areas did not change significantly during the study period.

Regression in plaque composition and neovasculature was observed under PCSK9 inhibition on carotid MRI, which provides unique insight into the biological process of plaque stabilization with disease-modifying therapies.

Effects of proprotein convertase subtilisin kexin type 9 modulation in human pancreatic beta cells function

Proprotein Convertase Subtilisin Kexin Type 9 (PCSK9) is an endogenous inhibitor of the LDL receptor (LDLR). Mendelian randomization studies suggest that PCSK9 deficiency increases diabetes risk, but the underlying mechanisms remain unknown. Ramin-Mangata et al. investigated whether PCSK9 or its inhibition may modulate beta cell function.

PCSK9 and insulin colocalization in human pancreatic sections were assessed by epifluorescent and confocal microscopy. Moreover, the expression and the function of PCSK9 in the human EndoC−βH1 beta cell line were investigated by ELISA and flow cytometry, respectively. PCSK9 was inhibited with alirocumab or siRNA and LDLR expression and LDL uptake were assessed by flow cytometry.

PCSK9 was expressed by and secreted from human pancreatic beta cells and EndoC−βH1 cells. PCSK9 secretion was enhanced by statin treatment. Recombinant PCSK9 decreased LDLR abundance at the surface of these cells, an effect abrogated by alirocumab. alirocumab and *PCSK9* silencing increased LDLR expression at the surface of EndoC−βH1 cells. Neither exogenous PCSK9, nor alirocumab, nor *PCSK9* silencing significantly altered glucose-stimulated insulin secretion (GSIS) from these cells. High-low density lipoproteins (LDL) concentrations decreased GSIS, but the addition of PCSK9 or its inhibition did not modulate this phenomenon.

While PCSK9 regulates LDLR abundance in beta cells, inhibition of exogenous or endogenous PCSK9 does not appear to significantly impact insulin secretion. Inhibiting circulating PCSK9 appears safe in terms of beta cell function and associated diabetes risk.

Marked plaque regression in homozygous familial hypercholesterolemia

Homozygous familial hypercholesterolemia (HoFH) is a rare inherited condition characterized by extremely elevated low-density lipoprotein (LDL) cholesterol levels. Despite treatment with statins, the majority of HoFH children between 3 and 16 years already show coronary lesions, which typically develop to severe plaques in the second decade of life. Whether intensive lipid lowering strategies result in plaque regression in adolescent patients is unknown. In this study, Reeeskamp et al. report two adolescent HoFH patients with null/null *LDLR* variants, who participated in the R1500-CL-1629 randomized clinical trial (NCT03399786) evaluating the LDL cholesterol lowering effect of evinacumab (a human antibody directed against ANGPTL3; 15 mg/kg intravenously once monthly). Patients underwent coronary computed tomography angiography (CCTA) before randomization and after 6 months of treatment.

Both patient A (aged 12) and B (aged 16) were treated with a statin, ezetimibe and weekly apheresis. Evinacumab decreased mean pre-apheresis LDL cholesterol levels from 5.51 ± 0.75 and 5.07 ± 1.45 mmol/l to 2.48 ± 0.31 and 2.20 ± 0.13 mmol/l, and post-apheresis LDL levels from 1.45 ± 0.26 and 1.37 ± 39 mmol/l to 0.80 ± 0.16 and 0.78 ± 0.13 mmol/l in patient A and B, respectively. Total plaque volumes were reduced by 76% and 85% after 6 months of evinacumab treatment in patient A and B, respectively.

In these two severely affected young HoFH patients, profound plaque reduction was observed with CCTA after intensive lipid lowering therapy with statins, ezetimibe, LDL apheresis, and evinacumab. This shows that atherosclerotic plaques possess the ability to regress at young age, even in HoFH patients.