Atherosclerosis newsletter

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Atherosclerosis 60th ANNIVERSARY

"BEST PAPER AWARD 2020"

Atherosclerosis was founded in 1960, hence, in 2020 the journal will turn 60.
The Editors and Publisher take this opportunity to announce a contest for "Best Paper Award 2020".

Eligible manuscripts are original research articles of young scientists (< 40 years) as first or corresponding authors, submitted between **July 1, 2019 and October 31, 2019,** either as first or revised version.

The Editor-in Chief and CoEditors will select the winner among the top rated papers accepted for publication before April 1, 2020. The winner will be invited to present the work in a lecture and will receive a certificate and an award of 1000 € during the **88th EAS (European Atherosclerosis Society) Congress** held May 31-June 03, 2020 in Geneva, Switzerland. Moreover, her/his Congress registration fees and travel/accommodations costs will be covered by EAS. The winning article will be published with promotional open access, free of charge for the authors.

First or corresponding authors younger than 40 years shall state in the covering letter that she/he applies for the "Best Paper Award 2020".

We look forward to the submission of your important and breakthrough research.

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Biomarkers are important tools of risk assessment, diagnosis of disease, stratification for different therapeutic options, and monitoring of safety and efficacy of treatment. This issue of *Atherosclerosis* contains several articles on studies aimed at validation of established biomarkers, as part of novel models or towards novel disease endpoints, or at validation of novel biomarker candidates.

A third of nonfasting plasma cholesterol is in remnant lipoproteins: Lipoprotein subclass profiling in 9293 individuals

Lipoproteins contain different concentrations of cholesterol esters, free cholesterol, triglycerides, phospholipids, and various proteins. The atherogenic part of triglyceride-rich lipoproteins is most likely the cholesterol content, also known as remnant cholesterol, while plasma triglycerides are a marker of the amount of remnant cholesterol because of the correlation between these two lipid components of the same particles. Increased concentrations of remnant cholesterol in triglyceride-rich lipoproteins are observationally and genetically, causally associated with increased risk of ischemic heart disease. However, when measured directly, the fraction of plasma cholesterol present in remnant particles is unclear. Balling et al. tested the hypothesis that a major fraction of plasma cholesterol is present in remnant lipoproteins in individuals in the general population.

The authors examined 9293 individuals from the Copenhagen General Population Study (a prospective population-based cohort study initiated in 2003 with ongoing enrolment of individuals of Danish descent aged 20 or above, who underwent a physical examination and had blood samples drawn), using nuclear magnetic resonance spectroscopy measurements of total cholesterol, free- and esterified cholesterol, triglycerides, phospholipids, and particle concentration. Fourteen subclasses of decreasing size and their lipid constituents were analysed: 6 subclasses were very low-density lipoprotein (VLDL), 1 intermediate-density lipoprotein (IDL), 3 low-density lipoprotein (LDL), and 4 high-density lipoprotein (HDL). Remnant lipoproteins were VLDL and IDL combined.

Mean nonfasting cholesterol concentration was 1.84 mmol/L for remnants, 2.01 mmol/L for LDL, and 1.83 mmol/L for HDL, equivalent to remnants containing 32% of plasma total cholesterol. Of 14 lipoprotein subclasses, large LDL and IDL were the ones containing most of plasma cholesterol. The plasma concentration of remnant cholesterol ranged from ∼1.4 mmol/L at age 20 to

~1.9 mmol/L at age 60. Corresponding values for LDL cholesterol ranged from ~1.5 mmol/L to ~2.1 mmol/L.

Direct measurements indicated that a third of plasma cholesterol was present in remnant lipoproteins. Of 14 lipoprotein subclasses, large LDL and IDL contained most cholesterol. Remnant cholesterol was highest in older individuals.

Potential utility of the SAFEHEART risk equation for rationalising the use of PCSK9 monoclonal antibodies in adults with heterozygous familial hypercholesterolemia

Familial hypercholesterolemia (FH) is the most frequent monogenic disorder associated with elevated LDL-cholesterol (LDL-C) levels and premature atherosclerotic cardiovascular disease (ASCVD). Its prevalence may be higher than 0.4% and confers a more than three-fold greater risk of premature ASCVD compared with normolipidemic individuals. Early diagnosis and early initiation of statin therapy significantly reduce ASCVD. Patients with FH may require proprotein convertase subtilisin/kexin-type 9 (PCSK9) mAb as add-on therapy to achieve LDL-cholesterol (LDL-C) goals. However, the current cost of these therapies means that choosing suitable patients is based on consensus or clinical judgement rather than a quantitative risk assessment. Pérez de Isla et al. used the SAFEHEART Risk Equation (SAFEHEART-RE) to estimate the number needed to treat (NNT) at different risk thresholds and baseline LDL-C to identify those FH patients more likely to derive the greatest benefit from PCSK9 mAb. The SAFEHEART Risk Equation (SAFEHEART-RE) is a risk prediction equation that can estimate the risk of incident ASCVD events in FH patients using the following variables: age, gender, history of atherosclerotic cardiovascular disease, presence of hypertension, body mass index (BMI), smoking, and plasma LDL-C and Lp(a) levels. This tool was developed using information provided by the Spanish Familial Hypercholesterolemia-registry (SAFEHEART), a real-world clinical practice multicentre, nationwide, long-term prospective cohort study in Spain, which includes molecularly defined heterozygous FH patients, treated as per local guidelines with lipid lowering therapy, with or without ASCVD at baseline.

The authors calculated 5-year event rates using SAFEHEART-RE for every patient, overall and across LDL-C strata. A 60% reduction of LDL-C after theoretical treatment with PCSK9 mAb was assumed. Individual absolute risk simulating the effects of PCSK9 inhibition was calculated using the SAFEHEART-RE and, in a similar way, using the Cholesterol Treatment Trialists' (CTT) Collaboration criteria. Absolute risk reduction and NNTs were assessed.

Of the total SAFEHEART population, 2153 were FH cases aged 18 years or older, on maximum tolerated lipid lowering treatment. NNTs were dependent on both baseline predicted risk

and baseline LDL-C level ranging from 44 to 17 for those with 5-year risk of ≥1% to ≥5%. The lowest NNT was observed among those with 5-year risk of ≥5% and LDL-C ≥160 mg/dl. Using the CTT criteria produced similar results.

The results indicate that SAFEHEART-RE may provide a useful quantitative tool for rationalising the selection of FH patients who might derive greater absolute benefits from PCSK9 mAb.

Intra-individual variability in high density lipoprotein cholesterol and risk of end-stage renal disease: A nationwide population-based study

Chronic kidney disease (CKD) and end-stage renal disease (ESRD) are emerging public health issues worldwide with the increasing prevalence of obesity and metabolic disease. There is a growing evidence demonstrating an association between dyslipidemia and progression of chronic kidney disease (CKD). However, the data on the associations of high-density lipoprotein cholesterol (HDL-C) with renal outcomes have been conflicting. In this study, Koh et al. investigated the relationship between HDL-C variability and the risk for progression to end-stage renal disease (ESRD).

The authors analyzed data of 4,283,318 subjects free of ESRD at the time of enrolment, who received more than three medical examinations from 2009 to 2012, and were followed to the end of 2015, based on the Korean National Health Insurance Service database. HDL-C variability was measured using the standard deviation, coefficient of variation, average real variability and variability independent of the mean (VIM).

A total of 2095 new cases of ESRD were observed during a median follow up of 3.38 years. There was a graded association between higher HDL-C variability and incident ESRD. In the multivariable adjusted model, hazard ratio comparing the highest and lowest quartiles of VIM of HDL-C was 1.82. The results were consistent when the variability of HDL-C was modelled using standard deviation, coefficient of variation and average real variability and were independent of other confounding factors, including the presence of CKD.

HDL-C variability independently predicted an increased risk for developing ESRD. These findings suggest that identification of HDL-C variability may help improve risk stratification for the prevention of ESRD.

Eosinophils count in peripheral circulation is associated with coronary artery disease

Allergic asthma can accelerate atherosclerosis and hence the manifestation of coronary artery disease (CAD). Eosinophils are the most important effector cells in allergic asthma. However, the relationship between eosinophil count and CAD remains unclear. Gao et al. aimed to evaluate this relationship and the utility of eosinophils in predicting CAD.

A total of 5287 patients who underwent coronary angiography were recruited. Their biochemical parameters, including eosinophil count, were measured, and their correlation with the severity of coronary artery stenosis, as quantified by the Gensini score system, was evaluated.

The percentages of eosinophils in leukocytes (PELs) were lower in CAD patients, and had a significant negative correlation with Gensini scores. PELs were also significantly lower in acute myocardial infarction patients. After adjusting for baseline differences, low PELs remained strongly associated with severe CAD and acute coronary events. Receiver-operating characteristic curve analysis showed that the addition of PELs improved the predictive performance of models with traditional risk factors only.

PELs, at least in patients undergoing coronary angiography, may be strongly related to the subtype and severity of CAD and, therefore, may be an accurate and independent biomarker to predict risk of recurrent coronary events.

The novel adipokine CTRP1 is significantly associated with the incidence of major adverse cardiovascular events

Adipose tissue acts as a highly active endocrine organ by releasing into the circulation numerous polypeptide hormones and cytokines, collectively termed adipokines. One of the most intensely studied adipokines is the hormone adiponectin, which has well documented anti-diabetic, anti-atherogenic, and anti-inflammatory properties and is down-regulated in obesity and diabetes. The recently identified adiponectin paralogue C1q and tumor necrosis factor-related protein 1 (CTRP1) has been associated with coronary atherosclerosis and has been recognized to play a major role in glucose and energy homeostasis. However, the impact of circulating CTRP1 on the incidence of future cardiovascular events is unclear. Muendlein et al. aimed at investigating the association between CTRP1 and future cardiovascular risk.

CTRP1 serum levels were assessed in 539 patients undergoing coronary angiography for the evaluation of established or suspected stable coronary artery disease (CAD). Major adverse cardiovascular events (MACE) were prospectively defined as the incidence of cardiovascular death, non-fatal myocardial infarction and non-fatal stroke over an 8-year follow-up period.

Obesity, metabolic syndrome, type 2 diabetes, and non-alcoholic fatty liver disease were significantly associated with increased CTRP1 at baseline. MACE rates were lowest in the first quartile and increased over the second to the third and fourth quartile.

These results suggest that high serum levels of CTRP1 are significantly associated with future MACE. Further studies are needed to clarify the causal role of CTRP1 in these findings.

Effects of dietary intervention and n-3 PUFA supplementation on markers of gut-related inflammation and their association with cardiovascular events in a high-risk population

Dysbiosis, defined as unfavourable changes in the bacterial composition of the gut microbiome, is associated with increased levels of circulating lipopolysaccharide (LPS), known potent activators of innate immunity leading to subsequent activation of systemic inflammation. Diet is an important modulator of the gut microbiome. In this study, Awyemi et al. investigated whether circulating markers of gut-related inflammation, LPS binding protein (LBP) and soluble CD14 (sCD14) can be modulated by n-3 polyunsaturated fatty acids (PUFAs) supplementation and/or diet counselling, and whether these markers are related to cardiovascular (CV) outcome.

Four hundred eighty-four men aged 65–75 years, at high CV-risk, were included in the analysis and randomized in a 2×2 factorial design to 36-month intervention with dietary counselling, n-3 PUFA supplementation, or both. N-3 PUFA supplementation was placebo-controlled. ELISAs were used for biomarkers determination, measured at baseline and study end. A composite endpoint was defined as new CV events and CV mortality after 36 months.

There were no significant differences in changes of either LBP or sCD14 in the intervention groups compared to their respective controls. The group with LBP levels above median had about 2-fold unadjusted risk of suffering an endpoint compared to the group below. A similar trend was observed for sCD14. After adjusting for covariates, LBP remained significantly associated with a two-fold CV-risk, whereas sCD14 gained statistical significance, however, lost when high sensitive C-reactive protein (hsCRP) was added to the model.

In the studied population, markers of gut-related inflammation are associated with 36-month CV outcome and this is not affected by diet intervention.

Identification of circular RNA *Hsa_circ_0001879* and *Hsa_circ_0004104* as novel biomarkers for coronary artery disease

Circular RNAs (circRNAs) are a class of endogenous RNA composed of transcripts from exons, introns, or both to form a closed continuous loop. They regulate gene expression through multiple mechanisms. Recent studies have shown that circRNAs are implicated in a variety of pathological conditions, including myocardial infarction, heart failure, and colorectal cancer. Due to their stability and sequence conservation characteristics, circRNAs have been reported to become a novel class of biomarkers for human diseases. Currently, expression profiles and biological functions of circRNAs in CAD remain elusive. In this paper, Wang et al. aimed at profiling circRNAs expression in CAD patients and assess their relevance as diagnostics biomarkers for CAD.

circRNA profiles of 24 CAD patients and 7 controls were assessed by microarray. The expression levels of candidate circRNAs were further verified by qRT-PCR in large cohorts. Logistic regression and receiver operating characteristic analyses were conducted to assess the diagnostic value. Gain-of-function approach was used to determine the functional significance of validated circRNA in THP-1-derived macrophages.

The authors found that a total of 624 circRNAs and 171 circRNAs were significantly upregulated and downregulated, respectively, in CAD patients relative to controls. Hsa_circ_0001879 and hsa_circ_0004104 were validated to be significantly upregulated in large cohorts. The combination of hsa_circ_0001879 and hsa_circ_0004104, together with CAD risk factors, had the better performance to discriminate CAD patients from healthy controls. Overexpression of hsa_circ_0004104 resulted in dysregulation of atherosclerosis-related genes in THP-1-derived macrophages.

The study gives a transcriptome-wide overview of aberrantly expressed circRNAs in CAD patients, identifying two novel circRNA biomarkers to diagnose CAD. Hsa_circ_0004104 might contribute to the pathogenesis of atherosclerosis and CAD by regulating atherosclerosis related genes expression.