Atherosclerosis newsletter

Simona Negrini and Arnold von Eckardstein

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".

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Volume 285, Issue June 2019

It is now widely accepted that lowering of plasma cholesterol is a mainstay in the management of cardiovascular risk. However, the lower-the-better concept is not perfectly translated into clinical practice. Reasons and consequences of this gap are addressed by several articles in this issue of *Atherosclerosis*: incomplete adherence, very high risk or cholesterol levels at baseline, difficult differential diagnosis of rare dyslipidemia, finding the right time-point to initiate treatment, monitoring treatment success in the vasculature, or unknown reasons of hypercholesterolemia.

Management of dyslipidaemia in patients with coronary heart disease: Results from the ESC-EORP EUROASPIRE V survey in 27 countries

Since 1994, the European Society of Cardiology has set up a comprehensive program of cardiovascular disease (CVD) prevention by developing and updating guidelines and implementation strategies. All this is regularly evaluated through the European Society of Cardiology – Eurobservational Research Programme (ESC-EORP) EUROASPIRE (European Action on Secondary and Primary Prevention by Intervention to Reduce Events) surveys. The EUROASPIRE IV survey incorporated the EuroHeart Survey on Diabetes to create the first European Survey of CVD prevention and diabetes. The aim of the prevention guidelines and the results from the EUROASPIRE I-IV surveys have been extensively communicated. The most recent survey (EUROASPIRE V) in coronary patients was conducted in 2016–17 in 27 countries. One of the objectives of the EUROASPIRE V survey was to determine how well European guidelines on the management of dyslipidaemias are implemented in coronary patients.

Standardized methods were used by trained technicians to collect information on 7824 patients from 130 centers in 27 countries, from the medical records, and at a visit at least 6 months after hospitalization for a coronary event. All lipid measurements were performed in one central laboratory. Patients were divided into three groups: on high-intensity LDL-C-lowering-drug therapy (LLT), on low or moderate-intensity LLT, and on no LLT.

At the time of the visit, almost half of the patients were on a high-intensity LLT. Between hospital discharge and the visit, LLT had been reduced in intensity or interrupted in 20.8% of the patients and had been started or increased in intensity in 11.7%. In those who had interrupted LLT or had reduced the intensity, intolerance to LLT and the advice of their physician were reported as the reason for the interruption in 15.8 and 36.8% of the cases, respectively. LDL-C control was better in those on high-intensity LLT compared to those on low or moderate intensity LLT. LDL-C control was better in men than women, and in patients with self-reported diabetes.

These results show that most coronary patients have a less than optimal management of LDL-C. The striking variability between countries and centers with several examples of well managed patients illustrates that more professional strategies are needed, aiming at lifestyle changes and LLT adapted to the individual patients' needs.

Achievement of low density lipoprotein (LDL) cholesterol targets in primary and secondary prevention: Analysis of a large real practice database in Italy

Dyslipidaemia is one of the most common modifiable risk factors for cardiovascular (CV) disease in Western countries, including Italy. A large number of randomized clinical trials and meta-analyses demonstrated that lipid-lowering therapies, mostly based on statins, are able to reduce the incidence of major CV events in both primary and secondary prevention, as well as in both genders and all age groups. Target and intensity of low-density lipoprotein cholesterol (LDL-C) lowering therapy should be tailored according to the individual global cardiovascular (CV) risk. Despite recommendations from international guidelines and recent evidence in favour of the beneficial effects derived from even intensive LDL-C reductions in very high risk patients, several observational studies and clinical surveys reported poor control rates of LDL-C in different clinical settings. Presta et al. aimed at retrospectively evaluating real-life LDL-C goal attainment and predictive factors for predefined LDL-C therapeutic goals both in primary and secondary prevention.

Data from a large cohort of outpatients aged 40–65 years, followed by general practitioners, cardiologists and diabetologists in Italy, were collected and centrally analysed for global CV risk assessment and rates of control of major CV risk factors, including LDL-C. Study population was stratified according to the presence or absence of previous CV events, including coronary artery disease (CAD), peripheral artery disease (PAD) or stroke/TIA. CV risk profile characterization was based on the European SCORE. Predefined therapeutic goals were set according to the European guidelines on dyslipidaemia: LDL-C levels <70 mg/dl for very high CV risk patients in primary prevention and for those in secondary prevention, and <100 mg/dl LDL-C levels for high CV risk patients in primary prevention. Logistic regression analysis with clinical covariates was used to identify predictive factors for achieving these goals; lipid lowering therapy entered in the analysis as continuous (model 1) or categorical variable (model 2).

4142 outpatients (43,7% female) were included: 2964 (71.6%) in primary and 1178 (28.4%) in secondary prevention. In primary prevention, none of the patients at very high CV risk had LDL-C <70 mg/dl and 8.9% of patients at high CV risk showed LDL-C <100 mg/dl. Only 5.8% of patients in secondary prevention had LDL-C levels <70 mg/dl, specifically 6.5% of patients with CAD, 2.6% of patients with PAD and 4.7% of patients with CVD. Beyond diabetes and lipid lowering therapy, high

risk SCORE estimation was a strong and independent predictor for the lack of achieving all predefined therapeutic targets, including LDL-C <100 mg/dl, and LDL-C <70 mg/dl in primary prevention.

Despite a high or very high SCORE risk and use of lipid lowering therapies, a poor achievement of LDL-C targets was observed in this large cohort of outpatients followed in a setting of real practice in Italy.

Evaluation of two approaches to lysosomal acid lipase deficiency patient identification: An observational retrospective study

Lysosomal acid lipase deficiency (LALD) leads to the accumulation of cholesteryl esters and/or triglycerides (TG) in lysosomes due to the lack of the enzyme codified by the *LIPA* gene. The most common symptoms are dyslipidaemia and hypertransaminasemia. Signs and symptoms of LALD may sometimes be confused with those of other lysosomal storage disorders (LSDs) causing visceral involvement, such as Gaucher disease, Niemann-Pick disease types A/B/C. In addition, plasma LSD biomarkers such as chitotriosidase (ChT) or chemokine (CC motif) ligand 18/pulmonary and activation-regulated chemokine (CCL18/PARC) are elevated in LSDs and atherosclerosis. To date, alteration of the lipid-liver profile (LLP) has been widely applied as a criterion for LALD screening. However, ChT and CCL18/PARC have not been explored in retrospective LALD programs. Cebolla et al. aimed to explore the utility of plasma ChT activity and CCL18/PARC concentration in addition to LLP to identify LALD patients in an observational retrospective study of two different sample collections.

Collection 1 (primary hypercholesterolemia suspected) included unrelated individuals with hyperlipidaemia and without *LDLR*, *APOB* and *PCSK9* gene mutations (Set 1), and Collection 2 (LSD suspected) included individuals without definitive LSD diagnosis (Set 2). Plasma LLP (total cholesterol and its fractions, TG concentration and transaminases activities), as well as plasma ChT and CCL18/PARC, were assessed. All subjects with anomalous LLP and/or biomarker levels were *LIPA* sequenced.

Twenty-four subjects showed altered LLP and/or biomarkers. Two LALD patients (one homozygous and one compound heterozygous) and one carrier of a novel *LIPA* variant were identified.

Combination of LSD biomarkers and lipid-liver profile (LLP) enhances the power to identify LALD patients in natural history cohorts.

Coronary computed tomography angiography and echocardiography in children with homozygous familial hypercholesterolemia

Homozygous familial hypercholesterolemia (hoFH) is a rare genetic disease, hallmarked by a lifelong exposure to very high levels of low-density lipoprotein cholesterol (LDL-C). Untreated, patients can experience a cardiovascular event in the first decade of life. Early detection and monitoring of subclinical atherosclerosis in these patients is therefore extremely important. Luirink et al. assessed the diagnostic yield of low-dose coronary computed tomography angiography (cCTA) compared to echocardiography in detecting subclinical atherosclerosis.

For this single-center cross-sectional study, all pediatric hoFH patients treated with lipoprotein-apheresis (LA) in Amsterdam UMC were included. cCTA and echocardiography were performed in all patients as part of routine follow-up. Six hoFH patients were included. Median ages at diagnosis, onset of LA and cardiovascular assessment (cCTA and echocardiography) were 2.6, 6.5, 10.8 and 11.1 years, respectively.

Echocardiography revealed no signs of atherosclerosis in any of the six patients. In two patients, mild dilatation of the cardiac chambers was detected and two patients showed signs of mitral or aortic insufficiency. On cCTA, however, non-calcified plaques without stenosis were detected in four patients. In two patients, calcified coronary plaques were found at the ostia of the right coronary artery or the left main coronary artery. Aortic root calcifications were found in two patients.

These findings suggest that in hoFH children, low-dose cCTA is superior to echocardiography for the detection of subclinical coronary and aortic root atherosclerosis and should therefore be considered in the routine cardiovascular monitoring of these high-risk children.

Decrease in LDL-C is associated with decrease in all components of noncalcified plaque on coronary CTA

Low-density lipoprotein cholesterol (LDL-C) lowering with statins is associated with a reduction in major adverse cardiovascular events. Coronary computed tomographic angiography (CTA) allows noninvasive quantification of plaque burden and plaque composition. LDL-C reduction has been associated with a decrease in noncalcified plaque (NCP) by serial quantitative CTA. Otaki et al. evaluated the effect of LDL-C reduction on specific components of noncalcified plaque (NCP).

154 patients, with baseline LDL-C≥70 mg/dl, undergoing serial CTAs were analyzed. Semi-automated software was used to quantify plaque components based on CT attenuation in Hounsfield units (HU): 30-75, low attenuation plaque (LAP); 76–130, medium-low attenuation plaque (MLAP); 131–350, medium attenuation plaque (MAP); >350, calcified plaque (CP). Decrease in LDL-C was

defined as a reduction >10% of baseline LDL-C. Plaque volume changes were compared between patients with and without LDL-C decrease.

There was an interval reduction in total plaque, LAP, MLAP, and MAP volumes in patients with LDL-C decrease *vs*. patients without LDL-C decrease, before and after adjusting for differences between the two groups. An increase in CP volume occurred in both groups.

These data show that a decrease in LDL-C is associated with reduction in all components of NCP measured by quantitative CTA, suggesting that NCP volume change may be optimal to assess statin efficacy.

^{18}F-FDG PET/MR-imaging in a Göttingen Minipig model of atherosclerosis: Correlations with histology and quantitative gene expression

Cardiovascular disease is one of the greatest threats to global health, with atherosclerosis as the main underlying cause. An increased focus on plaque inflammation and stabilization has prompted exploration of biomarkers of inflammation in addition to morphological aspects of the disease, and with the advances in molecular and multimodal imaging, a novel era for disease visualization has emerged, focusing on functional aspects. Using positron emission tomography (PET) combined with either computerized tomography (PET/CT) or magnetic resonance imaging (PET/MRI), tracers targeting different stages of atherosclerosis have been exploited. The radioactively labelled glucose analogue 18F-fluorodeoxyglucose (18F-FDG) has been validated in clinical settings and provides incremental predictive value to cardiovascular disease outcome, in addition to traditional risk markers. In the pre-clinical phase of drug development, it is a challenge to find optimal disease models of atherosclerosis. The pig as a model has several advantages compared to others. Ludvigsen et al. aimed at evaluating plaque inflammation using ^{18}F-fluorodeoxyglucose (^{18}F-FDG)-PET/MRI, and gene expression in a minipig model of atherosclerosis.

Göttingen minipigs were fed a fat/fructose/cholesterol-rich diet (FFC), chow (Control) or FFC-diet changed to chow midway (diet normalization group; DNO) for 60 weeks. In all groups, ^{18}F-FDG-PET/MRI of the abdominal aorta was assessed midway and at study-end. The aorta was analyzed using histology and gene expression.

At study-end, FFC had significantly higher FDG-uptake compared to Control and DNO showed significantly decreased uptake compared to FFC. No difference was observed between DNO and Control. FFC displayed increased atherosclerosis and gene expression of inflammatory markers, including vascular cell adhesion molecule 1 (*VCAM-1*), cluster of differentiation 68 (*CD68*), matrix metalloproteinase 9 (*MMP9*), cathepsin K (*CTSK*) and secreted phosphoprotein 1 (*SPP1*) compared to

Control and DNO. FDG-uptake correlated with gene expression of inflammatory markers, including *CD68*, *MMP9*, *SPP1*, and *CTSK*.

In the minipig model of atherosclerosis, ^{18}F-FDG-PET/MRI technology allows for detection of inflammation in atherosclerotic plaques, consistent with increased inflammatory gene expression. These findings corroborate clinical data and are important in pre-clinical drug development targeting plaque inflammation.

FcγRIIb on CD11c^{+} cells modulates serum cholesterol and triglyceride levels and differentially affects atherosclerosis in male and female *Ldlr* $^{-/-}$ mice

Atherosclerosis is a chronic inflammatory disease of the vessel wall that underlies the vast majority of CVD disorders. Cholesterol and oxidized lipoproteins (oxLDL) are well established mediators of atherosclerotic plaque formation. Circulating levels of oxLDL correlate with myocardial infarction risk and atherosclerosis severity. Interestingly, up to 90% of circulating oxLDL can complex with specific antibodies to form oxLDL immune complexes (oxLDL-ICs). Marlin et al. previously demonstrated that oxLDL-ICs can signal through Fc gamma receptors (FcγRs) on bone marrow-derived dendritic cells (BMDCs) and enhance their activation and inflammatory cytokine secretion. FcγRs can be either activating or inhibitory, containing an immunoreceptor tyrosine-based activation motif or an inhibitory motif, respectively. While global *FcγR*$^{-/-}$ studies have shown that activating FcγRs are proatherogenic, the impact of the inhibitory FcγRIIb on atherogenesis is unclear. The authors sought to determine the role of dendritic cells (DC)-specific FcγRIIb in atherosclerosis.

Bone marrow chimeras were generated by rescuing lethally irradiated *Ldlr*$^{-/-}$ mice with hematopoietic cells from littermate *CD11c-Cre*$^{+}$ or *CD11c-Cre*$^{-}$ *Fcgr2b*$^{fl/fl}$ donors. Four weeks following transplantation, recipients were placed on a Western diet for eight weeks. Various tissues and organs were analyzed for differences in inflammation.

Quantitation of atherosclerosis in the proximal aorta demonstrated that female *CD11c-Cre*$^{+}$ *Fcgr2b*$^{fl/fl}$ recipients have larger plaques than control mice, while male recipients have smaller plaques than control mice. Hepatic cholesterol and triglycerides (TGs) were increased in female *CD11c-Cre*$^{+}$ *Fcgr2b*$^{fl/fl}$ recipients. This was associated with an increase in CD36 and major histocompatibility complex (MHC) Class II expression on hepatic CD11c^{+}CD11b^{+} DCs in female livers. In contrast, male *CD11c-Cre*$^{+}$ *Fcgr2b*$^{fl/fl}$ recipients had decreased hepatic lipids, with a corresponding decrease in CD36 and MHC Class II expression on CD11c^{+} cells. Interestingly, both sexes of *CD11c-Cre*$^{+}$ *Fcgr2b*$^{fl/fl}$ recipients had significant decreases in serum cholesterol and TGs, with corresponding decreases in liver fatty acid synthase (*Fasn)* transcripts.

The lack of FcγRIIb expression on $CD11c^+$ cells results in sex-dependent alteration in liver inflammation, influencing atherogenesis and sex-independent modulation of serum cholesterol and TGs.