Atherosclerosis newsletter

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This issue of *Atherosclerosis* contains several articles reporting on preclinical and clinical studies on the progression and regression of atherosclerosis. The clinical studies investigated the effect of controlling dyslipidemia or hyperglycemia on the course of atherosclerotic cardiovascular disease (ASCVD) to assess the clinical utility of either the intervention *per se* or various diagnostic tools to monitor the benefit. Preclinical animal studies investigated novel interventions and searched for novel biomarkers that reflect the course of disease.

Effect of lipid-lowering treatment in cardiovascular disease prevalence in familial hypercholesterolemia

Familial hypercholesterolemia (FH) is one of the most common genetic diseases. The advent of potent lipid-lowering drugs, especially 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors or statins, has been a landmark for people suffering from FH. Since the late 1980s, this pharmacological therapy, sometimes in association with ezetimibe, has substantially reduced or even normalized LDL cholesterol concentrations in heterozygous familial hypercholesterolemia (HeFH), and the natural history of the disease has been importantly modified. However, the impact on HeFH health led by high-intensity lipid-lowering therapy (HILLT) is unknown, and the question remains if there is still an unacceptably high residual risk to justify treatment with new lipid-lowering drugs. Thus, Perez-Calahorra et al. designed this observational, retrospective, multicenter, national study in Spain, with data obtained from a national dyslipidemia registry, to establish the current prevalence of cardiovascular disease (CVD) in HeFH and to define the impact of HILLT on CVD in this population. Odds were estimated using several logistic regression models with progressive adjustment.

1958 HeFH were included in the analysis. Subjects with statin treatment had more than ten times lower odds for CVD than subjects naïve to treatment. 10% of HeFH suffered a CVD event after more than 12 years of statin treatment. In patients taking a high intensity statin, CVD risk was low. However, as the number of classical risk factors increase, CVD risk also increases.

Current prevalence of CVD among HeFH is one third of that reported before the statins era. Early initiation and prolonged lipid-lowering treatment was associated with a reduction in CVD. New cases of CVD, in spite of HILLT, appeared mostly among patients accumulating risk factors and probably they may be considered for further lipid-lowering drugs.

Statin and clinical outcomes of primary prevention in individuals aged >75 years: The SCOPE-75 study

Advanced age is recognized as a definite and strong risk factor for atherosclerotic cardiovascular disease, regardless of an individual's ethnicity. The clinical benefit of statin use for secondary prevention, even in elderly patients are evident. Nevertheless, the statin prescription rates in elderly individuals are reportedly lower than those in younger individuals. The latest versions of major guidelines on lipid-lowering therapy recommend personalized prescription of statins for primary prevention in individuals aged >75 years. The restriction is partly related to the risks associated with frailty or geriatric-specific adverse events. Importantly, very limited data are available regarding the outcomes and safety of statins in this population. Kim et al. aimed to investigate whether statin for primary prevention is effective in lowering the cardiovascular risk and all-cause death in individuals aged >75 years.

They conducted a retrospective, propensity score-matched study and data were acquired between 2005 and 2016 in a tertiary university hospital. Of the 6414 patients screened, 1559 statin-naïve patients without a history of atherosclerotic cardiovascular disease before the index visit were included. After propensity score matching, 1278 patients (639 statin users, 639 statin non-users) were analysed. Primary outcome variables included major adverse cardiovascular and cerebrovascular events (MACCE) and all-cause death. MACCE included cardiovascular death, nonfatal myocardial infarction, coronary revascularization, and nonfatal stroke or transient ischemic attack.

At a median follow-up of 5.2 years, statin users had lower rates of MACCE and all-cause death, as well as lower levels of low-density lipoprotein-cholesterol than non-users. In addition, the incidence of myocardial infarction and coronary revascularization was lower in statin users.

Statin therapy for primary prevention was clearly associated with lower risk of cardiovascular events and all-cause death in individuals aged >75 years. These results support a more active statin use in this population.

Coronary atheroma regression and adverse cardiac events: A systematic review and meta-regression analysis

The relationship between plaque regression induced by dyslipidemia therapies and occurrence of major adverse cardiovascular events (MACE) is controversial. Bhindi et al. performed a systematic

review and meta-regression of dyslipidemia therapy studies reporting MACE and intravascular ultrasound (IVUS) measures of change in coronary atheroma.

Seventeen prospective studies (6333 patients) of dyslipidemia therapies reporting percent atheroma volume (PAV) measured by IVUS, death, myocardial infarction, stroke, unstable angina or transient ischemic attack, were included. The association between mean change in PAV and MACE was examined using meta-regression via mixed-effects binomial logistic regression models, unadjusted and adjusted for mean age, baseline PAV, baseline low density lipoprotein-cholesterol and study duration.

A 1% decrease in percent atheroma volume was associated with approximately a 20% reduction in the odds of incurring a major cardiovascular event. This result suggests that PAV changes represent a surrogate measure of cardiovascular events.

Decline in ankle-brachial index is stronger in poorly than in well controlled diabetes: Results from the Heinz Nixdorf Recall cohort study

An increase in HbA1c is associated with an increased risk of cardiovascular disease (CVD) in subjects with and without diabetes. The ankle-brachial index (ABI) is a marker of atherosclerosis and a diagnostic criterion for peripheral arterial disease (PAD). Patients with diabetes have a particular poor prognosis if they also suffer from PAD. In this study, Kowall et al. investigated whether glycemic control has an impact on ABI changes in patients with diabetes. Moreover, they used the HbA1c based diagnostic criterion for diabetes to assess whether subjects with HbA1c defined prediabetes and newly detected diabetes have a higher risk of ABI decline.

ABI was measured at baseline and at 5- and 10-year follow-up in patients from the Heinz Nixdorf Recall Study, a population-based cohort study in Germany. Subjects with ABI <0.9, ABI >1.4 or self-reported PAD at baseline were excluded. Using logistic and linear regression models, associations between HbA1c and incident PAD (ABI < 0.9) and change in ABI were assessed, respectively.

Compared to the reference group (subjects without diabetes, with HbA1c < 5.7%), 10-year decline in ABI was −0.066 and −0.021 in subjects with poorly and well controlled previously known diabetes; −0.010 in those with newly detected diabetes diagnosed by HbA1c ≥ 6.5%, and −0.005 in those without diabetes, with HbA1c 5.7–6.4%. For poorly controlled diabetes, odds ratios for low ABI were 3.5, and 3.1 after 5- and 10-year follow-up, respectively.

In conclusion, decline in ABI was stronger in poorly than well-controlled diabetes. Subjects with newly detected diabetes diagnosed by the new HbA1c criterion did not show an increased decline in ABI over 10 years.

Maternal obesity and gestational diabetes: Impact on arterial wall layer thickness and stiffness in early childhood - RADIEL study six-year follow-up

Gestational diabetes (GDM) and maternal obesity are linked to weight gain in childhood and an increased risk of cardiovascular disease later in life. Sundholm et al. assessed the effects of GDM and maternal obesity on arterial function and morphology in relation to body anthropometrics and composition in early childhood.

Body size and composition, blood pressure (BP), arterial morphology and stiffness in 201 pairs of obese mothers and their children at 6.1 years were measured.

Child BMI and common carotid intima-media thickness were increased compared with a healthy Finnish reference population. No associations with maternal GDM was found. Carotid IMT and pulse wave velocity were unrelated to child sex, anthropometrics, body composition, BP, as well as maternal anthropometrics and body composition. Carotid stiffness was independently predicted by second trimester fasting glucose. Child lean body mass was the strongest independent predictor for radial (RA), and brachial artery (BA) lumen diameter (LD) and BA IMT and carotid LD.

Children of obese mothers have increased BMI, blood pressure and carotid IMT suggesting a transgenerational effect of maternal obesity and clustering of cardiovascular risk factors in the population. Arterial dimensions were mainly predicted by child LBM, and not associated with maternal or child adiposity or GDM. There was a weak association with maternal gestational fasting glucose and increased carotid artery stiffness.

Identification of novel serum markers for the progression of coronary atherosclerosis in WHHLMI rabbits, an animal model of familial hypercholesterolemia

The development of serum markers specific for coronary lesions is important to prevent coronary events. However, analyses of serum markers in humans are affected by environmental factors and non-target diseases. Using an appropriate model animal can reduce these effects, by keeping confounding factors constant. Shiomi et al. analysed the serum of WHHLMI rabbits, which spontaneously develop coronary atherosclerosis, to identify specific markers for coronary atherosclerosis.

Serum and plasma were collected under fasting (at intervals of 4 months) from female WHHLMI rabbits fed a standard chow, and a total of 313 lipid molecules, 59 metabolites, lipoprotein lipid levels, and various plasma biochemical parameters were analysed. The severity of coronary lesions was evaluated with cross-sectional narrowing (CSN) corrected with a frequency of 75%–89% CSN and CSN> 90%.

There was a large variation in the severity of coronary lesions in WHHLMI rabbits despite almost no differences in plasma biochemical parameters and aortic lesion area between rabbits with severe

and mild coronary lesions. The metabolites and lipid molecules selected as serum markers for coronary atherosclerosis were lysophosphatidylcholine (LPC) 22:4 and diacylglycerol 18:0–18:0 at 4 months old, LPC 20:4 (sn-2), ceramide d18:1–18:2, citric acid plus isocitric acid, and pyroglutamic acid at 8 months old, and phosphatidylethanolamine plasminogen 16:1p-22:2 at 16 months old.

These serum markers were coronary lesion-specific markers independent of cholesterol levels and aortic lesions and may be useful to detect patients who develop cardiovascular disease.

A peptide antagonist of F11R/JAM-A reduces plaque formation and prolongs survival in an animal model of atherosclerosis

The F11 Receptor (F11R), AKA Junctional Adhesion Molecule-A (JAM-A) (F11R/JAM-A), is an adhesion protein constitutively expressed on the membrane surface of circulating platelets and the luminal surface of inflamed endothelial cells (EC).

Platelet adhesion to an inflamed endothelium is one of the early steps of atherosclerotic plaque formation. Previous studies from Babinska et al., with cultured EC *in vitro*, have demonstrated the expression of F11R/JAM-A on the luminal surface of inflamed EC, platelet adhesion to inflamed EC through F11R/JAM-A interactions, and inhibition of this interaction by the presence of F11R/JAM-A antagonistic peptide (F11Rpeptide 4D). In this study, the authors examined the effects of F11Rpeptide 4D on cardiovascular health and atherosclerotic plaque of *ApoE*$^{-/-}$ mice.

Twenty *ApoE*$^{-/-}$ mice were assigned to daily treatment with peptide 4D and compared to control mice for wellness and survival. Plaque size in the aorta and heart was measured using histological analysis. The effects of peptide 4D on platelet adhesion to the inflamed endothelium were measured by intravital microscopy.

In *ApoE*$^{-/-}$mice, the F11R peptide 4D reduced plaque formation and prolonged survival, with overall better health. Moreover, it inhibited adhesion of platelets to the cytokine-inflamed aortic endothelium.

These results suggest that peptide 4D is a potential drug for the prevention and treatment of thrombosis and atherosclerosis triggered by inflammation.