

Atherosclerosis newsletter

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This issue of *Atherosclerosis* contains the novel ESC/EAS guidelines for the management of dyslipidemias, as well as a statement of UK-Heart on the management of familial hypercholesterolemia in children and adolescents. A registry study from UK presents data on the efficacy of LDL apheresis in patients who are not adequately treated with lipid lowering drugs. Finally, several original articles report on the quality of state of the art risk prediction tools and on the quality of various imaging strategies for optimized risk prediction.

[Volume 290, Issue November 2019](#)

2019 ESC/EAS guidelines for the management of dyslipidaemias: Lipid modification to reduce cardiovascular risk

The previous European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) lipid Guidelines were published in August 2016. In order to be aligned with the emergence of a substantial body of novel evidence gained over the last few years, the ESC/EAS Task Force members have updated and revised the Guidelines on the management of dyslipidemias. Among several novel recommendations, lower target levels for low density lipoprotein cholesterol (LDL-C) as well as modified criteria for the definition of moderate, high or very high risk are the most prominent changes. These novel ESC/EAS Guidelines on lipids provide important advice on patient management, which should enable more clinicians to efficiently and safely reduce cardiovascular risk through lipid modification.

Current management of children and young people with heterozygous familial hypercholesterolaemia - HEART UK statement of care

This consensus statement by Ramaswami et al. addresses the management of children and young people with heterozygous familial hypercholesterolaemia (FH) in the UK. It concerns children and adolescents identified by cascade testing when a parent is diagnosed with FH and those diagnosed by incidental lipid testing. This statement of care provides advice for lifestyle and diet, suggests LDL-C targets, and the most appropriate lipid-lowering therapies to achieve them. Assuming a prevalence of ~1/250 for FH, in UK approximately 50,000 children under the age of 18 years are estimated to suffer from FH. Currently, only about 550 of these children and young people have been identified and taken care.

Lipoprotein apheresis efficacy, challenges and outcomes: A descriptive analysis from the UK Lipoprotein Apheresis Registry, 1989–2017

Lipoprotein apheresis (LA) is a well-established extracorporeal technique, which removes apolipoprotein B containing particles from the circulation. Patients with homozygous familial hypercholesterolaemia (HoFH), severe heterozygous familial hypercholesterolaemia (HeFH) with progressive cardiovascular disease, and some patients with hyper-lipoproteinaemia (a) (hyper-Lp(a)) benefit from this procedure through lowering of LDL-C and Lp(a) and the consequent reduction in cardiovascular events. In 2008, the National Institute of Health and Care Excellence in the UK recommended that patients undergoing LA should be included in an anonymised registry, providing a record of lipid levels and cardiovascular events. The UK Lipoprotein Apheresis Registry was subsequently established in 2011. Pottle et al. conducted a descriptive analysis of the data collected in the registry to assess the outcomes and challenges of LA as therapeutic option for the management of HoFH in the UK.

Between 2011 and 2017, data was entered retrospectively and prospectively by seven LA centres in the UK for 151 patients. Twenty-two patients involved in a research study were excluded, leaving 129 patients for the analysis.

Most patients had HeFH (45.0%); 23.3% HoFH, 7.8% hyper-Lp(a) and 24.0% other forms of dyslipidaemia. Detailed treatment data is available for 63 patients relating to 348 years of LA treatment. The number of years of treatment per patient ranged from 1 to 15. The mean reduction in interval mean LDL-C from the pre-procedure baseline was 43.14%. The mean reduction in interval mean Lp(a) from baseline was 37.95%. The registry data also shows a 62.5% reduction in major

adverse cardiovascular events (MACE) between the 2 years prior to, and the first 2 years following introduction of LA.

The data demonstrates that LA is a very efficient method for reducing LDL-C and Lp(a) and lowering the incidence rate of MACE. It is an important tool in the management of selected patients with HoFH and drug-resistant dyslipidaemias.

Predictive validity of the risk SCORE model in a Mediterranean population with dyslipidemia

Hypercholesterolemia is one of the main cardiovascular risk factors. Recommendations on the initiation of lipid-lowering treatment depend on the level of cardiovascular risk, as calculated using the SCORE (Systematic COronary Risk Evaluation) scale. Bertomeu-González et al. aimed to assess the predictive value and clinical utility of the SCORE scale for preventing cardiovascular events and all-cause mortality in subjects with dyslipidemia and no lipid-lowering treatment.

This observational cohort study included patients from the ESCARVAL-RISK study, a prospective cohort study of subjects with cardiovascular risk factors (arterial hypertension, hypercholesterolemia, or diabetes mellitus) but without established cardiovascular disease. Cardiovascular risk was calculated by means of the SCORE scale. All deaths and cardiovascular events were recorded for up to five years of follow-up. Sensitivity, specificity and other predictive values for different cut-off points were measured and the effect of different risk factors on the diagnostic accuracy of the SCORE charts was assessed.

In the final cohort of 18,853 patients, there were 1565 cardiovascular events and 268 deaths. The risk value, recommended to initiate pharmacological treatment (5%), presented a specificity of 86% for death and 90% for cardiovascular events, and a sensitivity of 53% for death and 32% for cardiovascular events. In addition, low risk was estimated in 62.8% of the patients who experienced a cardiovascular event and in 46.6% of those who died. Antithrombotic treatment, diabetes, hypertension, heart failure, peripheral artery disease and chronic kidney disease were associated with a reduction in the predictive capability of the SCORE scale, whereas metabolic syndrome was related to better risk prediction.

The results show that SCORE does not accurately predict the occurrence of cardiovascular events in patients with hypercholesterolemia and without lipid-lowering treatment. Using SCORE in clinical practice can lead to undertreatment of patients with hypercholesterolemia.

Risk stratification of non-obstructive coronary artery disease for guidance of preventive medical therapy

Coronary computed tomography angiography (CCTA) is increasingly used for risk stratification and decision-making in the management of patients with suspected coronary artery disease (CAD). Compared with traditional approaches that focus on the evaluation of myocardial ischemia, CCTA directly visualizes coronary atherosclerosis and allows for detection of non-obstructive and obstructive CAD. Due to the lack of an obstructive lesion limiting coronary blood flow, non-obstructive CAD has often been regarded as “non-significant” in the medical literature. However, recent studies using CCTA have shown that the presence of non-obstructive CAD contributes to a higher risk of myocardial infarction (MI) and mortality. Given the potential benefit of medical therapy in patients with non-obstructive CAD, there is a need for risk stratification and treatment strategy for these patients. Hwang et al. aimed to develop a risk prediction model for non-obstructive CAD patients for risk stratification and guidance of statin and aspirin therapy.

From a cohort of 25,087 consecutive patients who underwent CCTA, the authors identified 6243 with non-obstructive CAD of 1–49% diameter-stenosis and developed a risk prediction model for 5-year occurrence of a composite of all-cause mortality, myocardial infarction, and late coronary revascularization using a derivation cohort (n = 4391).

Age, sex, hypertension, diabetes, anemia, C-reactive protein, and the extent of non-obstructive CAD were incorporated in the prediction model. Patients were categorized into 4 groups: risk score of 0–3 (low-risk), 4–6 (intermediate-risk), 7–9 (high-risk), and ≥ 10 (very high-risk). Patients with very high-risk demonstrated unfavorable outcome comparable to patients with obstructive CAD. The low-risk group exhibited favorable outcome similar to those with no CAD. While statin therapy was associated with better outcomes in the high- or very high-risk groups, aspirin use was associated with an increased risk in this category of patients.

The results show that a dedicated risk scoring system for non-obstructive CAD can guide preventive medical therapy in these patients.

Intravascular optical coherence tomography method for automated detection of macrophage infiltration within atherosclerotic coronary plaques

The infiltration of macrophages in advanced atherosclerotic plaques promotes acute coronary events. Hence, the clinical imaging of macrophage content in coronary atherosclerotic plaques could potentially help identify patients at highest risk of future acute coronary events. In this study, Rico-Jimenez et al. introduced and validated an intravascular optical coherence tomography (IV-OCT) image

processing method for automated detection of macrophage infiltration within coronary atherosclerotic plaques.

This method calculates the ratio of the normalized-intensity standard deviation (NSD) values estimated over two axially-adjacent regions of interest in an IV-OCT cross-sectional image (B-scan). When applied to entire IV-OCT B-scans, this method highlights plaque areas with high NSD ratio values (NSDRatio), which was demonstrated to be correlated with the degree of coronary plaque macrophage infiltration.

Using an optimized NSDRatio threshold value, coronary plaque macrophage infiltration could be detected with ~88% sensitivity and specificity in a database of 28 IV-OCT scans from postmortem coronary segments. For comparison, using an optimized NSD threshold value, considered the standard IV-OCT signature for macrophages, coronary plaque macrophage infiltration could be detected with only ~55% sensitivity and specificity.

The proposed NSDRatio method significantly increases the sensitivity and specificity for the detection of coronary plaque macrophage infiltration compared to the standard NSD method. This method can be implemented within standard IV-OCT imaging systems for *in-vivo* real-time imaging of macrophage content in coronary plaques, which could potentially help identify patients most at risk of future acute coronary events.

Visceral adipose tissue volume is associated with premature atherosclerosis in early type 2 diabetes mellitus independent of traditional risk factors

Type 2 diabetes mellitus (T2DM) is commonly associated with abdominal obesity, predominantly with high visceral adipose tissue (VAT), and is accompanied by premature atherosclerosis. However, the association between VAT and subcutaneous adipose tissue (SAT) with premature atherosclerosis and inflammation is not completely understood. To provide more insight into this association, Reijrink et al. investigated the association between arterial ¹⁸F-fluorodeoxyglucose (FDG) positron emission tomography (PET) uptake, as a measure of arterial inflammation, and metabolic syndrome (MetS) markers in early T2DM patients.

Forty-four patients with early T2DM, without glucose lowering medication, were studied. Arterial inflammation was quantified using glucose corrected maximum standardized uptake value (SUVmax) FDG of the aorta, carotid, iliac, and femoral arteries, and corrected for background activity (blood pool) as target-to-background ratio (meanTBR). VAT and SAT volumes were automatically segmented using computed tomography (CT) between levels L1-L5. Non-alcoholic fatty liver disease (NAFLD) was assessed by liver function test and CT.

VAT volume, but not SAT volume, correlated with meanTBR. Linear regression models showed a significant association, even after sequential adjustment for potentially influencing MetS components. Interaction term VAT volume * sex and additional components, including HbA1c, insulin resistance, NAFLD, adiponectin, leptin, and C- reactive protein (CRP), did not change the independent association between VAT volume and meanTBR.

CT-assessed VAT volume is positively associated with FDG-PET assessed arterial inflammation, independently of factors thought to potentially mediate these effects. These findings suggest that VAT in contrast to SAT is linked with early atherosclerotic changes in T2DM patients.

Preoperative hypertension is associated with atherosclerotic intraplaque hemorrhage in patients undergoing carotid endarterectomy

Both hypertension and atherosclerotic plaque characteristics such as intraplaque hemorrhage (IPH) are associated with cardiovascular events (CVE). It is unknown if hypertension is associated with IPH. In this study, Fassaert et al. investigated whether hypertension is associated with unstable atherosclerotic plaque characteristics in patients undergoing carotid endarterectomy (CEA).

Prospectively collected data of CEA patients (2002–2014) were retrospectively analyzed. Blood pressure (BP) was the mean of three preoperative measurements. Preoperative hypertension was defined as systolic BP \geq 160 mmHg. Post-CEA, carotid atherosclerotic plaques were analyzed for the presence of calcifications, collagen, smooth muscle cells, macrophages, lipid core, IPH and microvessel density. Associations between BP (systolic and diastolic), patient characteristics and carotid plaque characteristics were assessed with univariate and multivariate analyses, with correction for potential confounders. Results were replicated in a cohort of patients who underwent iliofemoral endarterectomy.

Forty-two percent of CEA patients had preoperative hypertension. Increased systolic BP was associated with the presence of plaque calcifications, macrophages, lipid core $>10\%$ of plaque area, IPH and microvessels. Increased diastolic BP was associated with macrophages, lipid core and IPH but not with microvessels nor plaque calcifications. Similar associations were found for diastolic BP in the iliofemoral cohort.

The results show that preoperative hypertension in severely atherosclerotic patients is associated with more vulnerable carotid plaques. IPH, as a plaque marker for CVE, is associated with increased systolic and diastolic BP in the CEA and iliofemoral cohorts studied.