atherosclerosis

Atherosclerosis newsletter

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From January 2020 on, *Atherosclerosis* appears on a biweekly rather than monthly basis. Newsletters will hence appear more frequently, but with smaller content.

This issue of *Atherosclerosis* contains several articles evaluating the prognostic performance of novel biomarkers in the prediction of cardiovascular events including stroke and mortality.

Association between serum ferritin and acute coronary heart disease: A population-based cohort study

Cardiovascular disease (CVD) is the leading cause of death and disability worldwide. In Europe, it is responsible for over 4 million deaths/year, of which coronary heart disease (CHD) accounts for almost half of them. Recent research has focused on the identification of non-traditional risk factors, such as iron biomarkers, which could contribute to reduce the rates of CHD in the next decades. Among the available iron biomarkers, serum ferritin has gained importance, since it is the most common measure of body iron status and correlates well with body iron stores. Several studies aiming to determine the association between iron stores and coronary heart disease (CHD) have reported conflicting results. None of them has been performed in a Mediterranean region. Reyes et al. assessed the association between the level of serum ferritin and the incidence of CHD in a Mediterranean region.

A cohort study using a primary health care population database was conducted. Primary outcome was incidence of CHD. Subjects aged between 35 and 74 years with serum ferritin measurements at baseline were included. Cox regression models were used to calculate hazard ratios and 95%CIs for the association between serum ferritin and time until CHD outcome. Participants were observed for a median of 8.4 years.

During follow-up, 1106 incident cases of CHD were identified. No increased CHD risk at follow-up was observed in subjects with elevated serum ferritin suggesting questioning its role as a risk factor for this disease.

High betatrophin in coronary patients protects from cardiovascular events

Betatrophin, also known as angiopoietin-like protein 8 (ANGPTL8) or lipasin, is a nutritionally-regulated mammalian-specific protein secreted by the liver and adipose tissue. Many conflicting data exist with respect to its association with type 2 diabetes mellitus (T2DM), insulin resistance, and lipid markers, but no data are available on its association with cardiovascular risk. Leiherer et al. measured betatrophin in 553 coronary patients undergoing coronary angiography for the evaluation of established or suspected stable coronary artery disease (CAD) and prospectively recorded cardiovascular events during a follow-up of 8 years.

Two hundred and one patients suffered a cardiovascular event and 64 died from cardiovascular causes. High betatrophin was significantly and inversely associated with cardiovascular events both univariately and after full adjustment including the status of CAD and T2DM. The inclusion of betatrophin into a basic prediction model for the cardiovascular event risk significantly improved the model performance.

This study shows that betatrophin predicts cardiovascular events independently of conventional risk factors including the presence of CAD and T2DM.

ALCAM predicts future cardiovascular death in acute coronary syndromes: Insights from the PLATO trial

Activated leukocyte cell adhesion molecule (ALCAM) is upregulated during inflammation and involved in transmigration of leukocytes and T-cell activation. Ueland et al. previously detected consistently higher serum levels of ALCAM in the first days following acute ischemic stroke in patients who subsequently suffered an adverse event and serum ALCAM remained an independent predictor of outcome in adjusted analysis. However, there are currently no data on ALCAM in relation to acute coronary syndromes (ACS). Based on its role in inflammation, the authors hypothesized that ALCAM might be associated with recurrent events in patients with ACS.

To test this hypothesis, ALCAM was measured in serum obtained on admission, at discharge, 1 month and 6 months in a subgroup of 5165 patients with ACS included in the PLATelet inhibition and

patient Outcomes (PLATO) trial. The association between ALCAM and the composite endpoint and its components, including cardiovascular (CV) death, non-procedural spontaneous myocardial infarction (MI) or stroke during 1-year follow-up, was assessed by Cox proportional hazards models with incremental addition of clinical risk factors and biomarkers (including high-sensitivity troponin T, N-terminal pro−B-type natriuretic peptide and growth differentiation factor-15).

The median concentration of ALCAM at admission was 97 ng/mL. A 50% higher level of ALCAM on admission was associated with a hazard ratio of 1.16 for the composite endpoint in fully adjusted analysis, mainly driven by the association with CV death.

The results show that in patients with ACS, admission levels of ALCAM were independently associated with adverse outcome, including CV death, even after adjustment for established inflammatory and cardiac biomarkers.

Endostatin as a novel prognostic biomarker in acute ischemic stroke

Endostatin is a potent endogenous inhibitor of angiogenesis. It can inhibit ischemia-induced neovascularization by blocking the proliferation and migration of endothelial cells. It is suggested to participate in the growth of the atherosclerotic plaque and to serve as an important predictive biomarker of cardiovascular disease and mortality in the setting of primary prevention or in several pathophysiological conditions including heart failure, myocardial infarction and chronic kidney disease. Animal experiments and human studies suggested the expression of endostatin in brain tissue significantly increased in cerebral ischemia. Increased plasma endostatin is associated with a greater extent of intracranial atherosclerosis and predicts new cerebral ischemic events and functional outcomes in stroke patients. Despite this, the clinical significance of plasma endostatin for ischemic stroke needs to be explored. Zhang et al. aimed to examine the association between endostatin and mortality and disability after ischemic stroke.

A total of 3463 acute ischemic stroke patients with measured plasma endostatin from the China Antihypertensive Trial in Acute Ischemic Stroke were included in the study. The primary outcome was death or severe disability, and secondary outcomes included death and vascular events.

After 3-month follow-up, 402 participants experienced severe disability or died. Compared with the lowest quartile of endostatin, odds ratios or hazard ratios for the highest quartile were 1.47 for the primary outcome, and 2.36 for death after adjustment for multiple covariates, including age, sex, admission NIH Stroke Scale score and systolic blood pressure. Each 1-SD higher log-transformed endostatin was associated with a 20% increased risk for primary outcome. Adding plasma endostatin to the basic model constructed with conventional factors significantly improved risk stratification of

the primary outcome, as observed by the category-free net reclassification index of 20.5% and integrated discrimination improvement of 0.3%.

The results of association between increased baseline plasma endostatin levels in acute ischemic stroke and increased risk of mortality and severe disability at 3 months suggest that plasma endostatin may serve as an important prognostic marker for risk stratification in patients with ischemic stroke.

Reduced bile acid excretion is an independent risk factor for stroke and mortality: A prospective follow-up study

Hypercholesterolemia is a major risk factor for atherosclerosis, which is a cornerstone of coronary artery disease (CAD), stroke, peripheral vascular disease, aortic aneurysm and renal artery stenosis. Cholesterol is the substrate for bile acids. Bile acid excretion (BAE) is one of the natural mechanisms for elimination of cholesterol and sub-endothelial deposition. Primary bile acids, cholic acid and chenodeoxycholic acid are synthetized in the liver. Secondary bile acids, deoxycholic acid and lithocholic acid are the result of conjugation of primary bile acids by the intestinal bacteria. These bile acids play a major role in cholesterol homeostasis in humans. Previous studies found an inverse relationship between the prevalence of CAD, manifested as ischemic heart disease, and BAE. Charach et al. investigated the association of BAE with stroke incidence and mortality.

Patients admitted to the hospital due to chest pain and suspected CAD were enrolled and followed from 1998 to 2018. Patients received a standard in-hospital diet containing 490 mg/day cholesterol and performed a 24-h stool collection. A continuous, non-absorbable marker was used to evaluate the amount of BAE.

Mean BAE at first admission was higher among survivors than non-survivors. Total cholesterol, LDL cholesterol and triglyceride levels at baseline did not differ significantly. The main fractions of deoxycholic, lithocholic, and cholic acids were significantly different in the two groups and higher in the survivors. Total BAE was higher in stroke-free patients compared to those who developed stroke: 561.6 mg/24h and 231.2 mg/24h, respectively. Patients with BAE <262.4 developed stroke in 75% of cases. None of the patients with BAE >622 mg/24h developed stroke.

This retrospective cohort follow-up study adjusting for main potential confounders showed a significant association between lower amounts of total bile acid, deoxycholic acid and lithocholic acid excretion and stroke. Low BAE may be an independent risk factor for stroke.