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Atherosclerosis newsletter

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Current guidelines for secondary prevention consider all patients with acute or chronic atherosclerotic cardiovascular disease (ASCVD) at very high risk for future fatal or non-fatal events. However, their risk is heterogeneous. This issue of *Atherosclerosis* contains several articles, which investigated the impact of demographic, clinical, circulating and imaging biomarkers for the sub-stratification of risk in patients with acute or chronic ASCVD

Risk-factors associated with extremely high cardiovascular risk of mid- and long-term mortality following myocardial infarction: Analysis of the Hyperlipidaemia Therapy in tERtiary Cardiological cEnTer (TERCET) registry

Despite sustained efforts to reduce the global burden of cardiovascular disease (CVD), the prevalence of CV risk factors along with cardiovascular and non-cardiovascular comorbidities has continued to rise. Risk-factor identification and risk stratification are prerequisites to the effective primary and secondary prevention of CVD. Patients at the highest risk benefit the most from the intensive risk-factor reduction. However, the high-risk patients' group is heterogeneous, and it is increasingly recognised that there is an 'extreme-risk' category of patients who may require particularly close attention and intensive therapeutic approach. Dyrbuś et al. aimed to identify subgroups of patients at the highest risk of death following myocardial infarction (MI) that might be considered as those at extremely high CVD risk.

Data from 19,582 participants of the Hyperlipidaemia Therapy in tERtiary Cardiological cEnTer (TERCET) Registry (NCT03065543) of patients with ischaemic heart disease in Poland from 2006 to present were used. Characteristics of 13,052 patients with chronic coronary syndromes (CCS) were compared with those of 4295 patients with myocardial infarction (STEMI and NSTEMI). Multivariable logistic regression with stepwise backward elimination was used to identify risk factors associated with mortality in the 12–36 months following the index hospitalisation.

The mortality rates were significantly higher in patients after MI than in patients with CCS. In the multivariable analysis, the risk factors most strongly associated with 12-month mortality in patients after MI were: left ventricular ejection fraction (LVEF) lower than 35%, age >75 years, multivessel coronary artery disease, atrial fibrillation, diabetes mellitus and increased LDL-C or creatinine levels.

The risk factors that influenced mortality after 24–36 months were consistent with those after 12 months, with additional low haemoglobin and chronic obstructive pulmonary disease.

The patients with these risk factors represent the population with the highest risk of death that should be considered the 'extreme risk' population and they are expected to derive the most benefit from intensive lipid-lowering combination therapy.

Coronary artery disease burden in women poorly explained by traditional risk factors: Sex disaggregated analyses from the BioHEART-CT study

Targeting the modifiable risk factors for coronary artery disease (CAD) has substantial impact at the community level. However, it is not uncommon for individuals to present with atherosclerosis related events without identified risk factors. Vernon et al. examined sex differences in the association of risk factors and atherosclerotic burden assessed by CT coronary angiography (CTCA).

The authors analysed clinical and imaging data in 1002 individuals in the BioHEART cohort, a prospective cohort study of patients having a clinically indicated CT coronary angiogram (CTCA) for suspected CAD, which collects imaging data, relevant clinical information and blood samples from each participant

45% were female, 35% had no CAD identified. Median coronary calcium score was 9.9 Agatston units, and median Gensini Score was 3.5. 26% had a calcified plaque predominant phenotype, and 18% had a non-calcified plaque predominant phenotype. There were no sex differences in the prevalence of risk factors. However, there were notable sex differences in the adjusted associations of risk factors with CAD. Age and hypercholesterolaemia were associated with the presence of CAD in both genders. Diabetes and smoking were associated with presence of CAD, calcified CAD, and non-calcified plaque in males but not females. In women, none of the standard modifiable risk factors were associated with the amount of plaque present when adjusted for age, BMI, and family history of premature CAD.

There are sex based differences in the association of traditional risk factor with coronary artery disease phenotypes. Traditional risk factors poorly explain coronary artery disease burden in women. CTCA provides an important opportunity for improving the stratification of cohorts to assess underlying biology and risk.

Serum apolipoprotein E levels predict residual cardiovascular risk in patients with chronic coronary syndrome undergoing first percutaneous coronary intervention and on-statin treatment

Little is known about the long-term impact of apolipoprotein E (apoE) on residual cardiovascular risk in patients with chronic coronary syndrome (CCS) receiving statin treatment. Fukase et al. aimed to evaluate the long-term impact of apoE on residual cardiovascular risk in patients with

CCS who underwent intervention treatment and successfully lowered low-density lipoprotein cholesterol (LDL-C) on statin treatment in real clinical practice.

A total of 1109 consecutive patients (mean age, 67 ± 10 years; 83% men) with CCS who underwent their first intervention between 2000 and 2016 were included in this study. All patients had achieved LDL-C <100 mg/dL on statin treatment and were divided into two groups based on median serum apoE values. The incidence of major adverse cardiovascular events (MACEs), including cardiovascular death, non-fatal acute coronary syndrome, and target vessel revascularization, was evaluated.

552 and 557 patients were categorized into the higher and lower apoE groups, respectively. There were significant relationships between apoE levels and total cholesterol levels, triglyceride levels, high-density lipoprotein cholesterol levels, and estimated remnant cholesterol, except for LDL-C levels. During the median follow-up period of 5.1 years, 195 patients developed MACEs. Kaplan-Meier analysis revealed that the cumulative incidence of MACEs in the higher apoE group was significantly higher than in the lower apoE group. Using multivariable Cox hazard analysis, serum apoE level was the strongest independent predictor of MACEs.

Serum apoE level could be a strong predictor of residual cardiovascular risk in patients with CCS long-term, even if LDL-C levels are controlled with statin treatment.

Autoimmune diseases in patients undergoing percutaneous coronary intervention: A risk factor for in-stent restenosis?

The interplay between cellular and humoral components of the immune system and atherosclerosis is established and proved by the presence of T cells and autoantibodies in atherosclerotic vessel walls, as well as by the role of macrophages and cytokines notoriously involved in atherogenesis. However, beyond the known relationship between autoimmune diseases and increased atherosclerotic risk, the particular influence of autoimmune disorders on in-stent restenosis (ISR) after percutaneous coronary intervention (PCI) is only partly understood. ISR is an aberrant reparative process mainly characterized by an increased number of vascular smooth muscle cells and excessive deposition of extracellular proteoglycans and type III collagen. Chronic inflammation, always present in autoimmune diseases, modulates the endothelial response to PCI. In this study, Pepe et al. aimed to summarize the current evidence on the association between ISR and autoimmune diseases, focusing on pathogenic mechanisms and therapeutic targets.

They conducted a comprehensive review of the literature on the relationship between ISR and insulin-dependent diabetes mellitus (IDDM), rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), antiphospholipid-antibodies syndrome (APS), inflammatory bowel diseases (IBD), and Hashimoto's thyroiditis (HT).

The results show that patients with IDDM, RA, SLE, APS, IBD and HT face higher rates of ISR compared to the general population. The endothelial dysfunction seems the principal common pathogenic pathway for ISR and is attributed to the immune system disorder and the systemic inflammation. Some evidence suggests that methotrexate and anti-tumor necrosis factor treatments can be effective in reducing ISR, while antibodies against vascular cell adhesion molecule-1 and intercellular adhesion molecule-1 reduce neointimal hyperplasia in animal models.

Autoimmune diseases are a risk factor for ISR. The study of the potential cardiovascular benefits of the current therapies, mainly anti-inflammatory drugs, and the pursuit of innovative treatments appear of paramount interest.

$CD34^+$ progenitors are predictive of mortality and are associated with physical activity in cardiovascular disease patients

Circulating progenitor cells (CPC) are a heterogenous group of cells, which have tissue regenerative potential. They play an important role in vascular repair and can influence cardiovascular (CV) health and longevity. Exercise is known to modulate these cells via mobilization from the bone marrow. Muggeridge et al. aimed to evaluate the association of CPCs with mortality and explore the association between physical activity (PA) and CPCs.

1751 individuals from the Framingham Offspring cohort were included in the study. This cohort was included from 1971 in the Framingham Heart Study (FHS), a longitudinal community-based cohort set up in 1948 under the direction of the National Heart, Lung, and Blood Institute (NHLBI) aimed to determine factors that contribute to the onset and progression of cardiovascular disease (CVD). CPCs (CD34+, CD34+CD133+, CD34+CD133+KDR+) were measured by flow cytometry. Multivariable Cox regression analyses were performed to investigate relationship of CPCs with future CV event and mortality. Multivariate regression analyses were performed to determine the relationship between self-reported PA and CPC counts.

Following adjustment for standard risk factors, there was an inverse association between CD34+ CPCs and all-cause mortality. CD34+CD133+ CPCs were inversely associated with CV mortality. Associations of CD34+ and CD34+CD133+ with mortality were strongest in participants with pre-existing CVD. PA was associated with CD34+ CPCs only in CVD participants. This relationship was maintained after adjustment for confounding variables.

A higher number of CD34+ and CD34+ CD133+ CPCs was inversely associated with all-cause and CV mortality. These associations were strongest in participants with CVD. PA is independently associated with CD34+ CPCs in individuals with CVD only, suggestive of greater benefit for this population group.

Phenylacetylglutamine is associated with the degree of coronary atherosclerotic severity assessed by coronary computed tomographic angiography in patients with suspected coronary artery disease

Recently, the role of gut microbiota in the pathological process underlying various diseases has become a new research hotspot. Through untargeted metabolomics, it has been found that phenylacetylglutamine (PAG), a compound produced by the gut microbial metabolism of phenylalanine, has a serious impact on the incidence and prognosis of 3-year major adverse cardiac events (MACEs) after adjusting for traditional cardiac risk factors. In this study, Liu et al. analyzed the relationship between plasma PAG and coronary atherosclerotic severity assessed by coronary computed tomographic angiography (CCTA).

Consecutive patients with suspected coronary artery disease (CAD) who underwent CCTA were enrolled. Plasma PAG was measured by mass spectrometry. Coronary atherosclerotic severity was evaluated based on plaque burden and plaque vulnerability. Plaque burden was quantified as percent atheroma volume (PAV), CCTA-derived SYNTAX score (CT-SYNTAX) and CAD reporting and data system score (CAD-RADS). Plaque vulnerability was evaluated by the presence of adverse characteristics.

A total of 686 patients were enrolled. The patients were divided into two groups based on median plasma PAG (3.25 μM). A correlation was found between plasma PAG and PAV. Patients with obstructive CAD and high coronary lesion complexity had higher plasma PAG. After adjustment for confounding factors, plasma PAG remained associated with PAV, and patients in the higher PAG group had higher risks of obstructive CAD and high coronary lesion complexity. In addition, a high plasma PAG level was not an independent predictor of the presence of high-risk plaques.

There was an independent association between plasma PAG levels and the coronary atherosclerotic burden among patients with suspected CAD, which may have implications for prevention and treatment of coronary atherosclerosis.