atherosclerosis

Atherosclerosis newsletter

Simona Negrini and Arnold von Eckardstein

Volume 308, Issue September 2020

Volume 307, Issue August 2020

Volume 306, Issue August 2020

Familial hypercholesterolemia (FH) is an inherited autosomal dominant disease characterised by high plasma levels of low-density lipoprotein cholesterol (LDL-C) and premature atherosclerosis. In fact, it is the prototype condition indicating the causality of hypercholesterolemia in the pathogenesis of atherosclerotic cardiovascular disease (ASCVD). Although known for decades, the systematic collection of family data combined with molecular diagnostics led to the appreciation of the higher than anticipated prevalence, the externalization of the high cardiovascular risk in untreated FH, the recognition of residual risk in treated FH, and the development of FH-specific risk scores. The three issues of *Atherosclerosis* contain three articles on systematic research in large FH populations. Additional articles compare the prognostic value of family history and polygenic risk scores and investigate the protective effects of genetic variants at the *ASGR1* locus.

Prevalence Of familial hypercholeSTerolaemia (FH) in Italian Patients with coronary artERy disease: The POSTER study

Familial hypercholesterolaemia (FH) is a powerful risk factor for cardiovascular (CV) events. High levels of low-density lipoprotein cholesterol (LDL-C) since birth are linked to the early onset of atherosclerotic disease. A genetic mutation determining FH is present in about one subject out of 250; FH should be more represented among subjects with a documented diagnosis of coronary artery disease (CAD). Gulizia et al. aimed at establishing the prevalence of FH in patients with a documented CAD event, referring to a large number of cardiology centres representative of the whole Italian territory.

Eighty-two cardiology centres enrolled patients with a documented CAD event. CV risk profile, drug therapy and biochemical parameters were collected. Dutch Lipid Clinic Network (DLCN) criteria were used to define patients with a potential FH diagnosis and these patients underwent molecular testing for genetic diagnosis of FH.

Overall, 5415 patients were enrolled and the main index events were myocardial infarction with ST-elevation, non ST-elevation acute coronary syndrome (ACS), or a recent coronary revascularization. Mean age was 66 ± 11 years, 78% were male and about 40% were already treated with statins. Based on the DLCN score, the prevalence of potential FH was 5.1%, 0.9% of them had a diagnosis of definite FH. These patients were younger than patients with a score <6, and LDL-C levels were in most of them >190 mg/dL. FH was genetically confirmed in 42 subjects; genetic diagnosis was defined as not conclusive for FH in 63 patients. Finally, in 159 subjects, no pathogenic mutations in the tested genes were identified, defining them as negative for monogenic familial hypercholesterolemia.

The results underscore a relatively high prevalence of potential FH in patients with a recent CAD event. Therefore, an early identification of these subjects may help improve the management of their high CV risk and, by cascade screening, identify possible FH relatives.

Long term follow-up of genetically confirmed patients with familial hypercholesterolemia treated with first and second-generation statins and then with PCSK9 monoclonal antibodies

In Italy, the clinical and genetic characteristics of FH have been extensively assessed in various lipid clinics, although no studies on long-term cardiovascular outcomes in heterozygous patients (He-FH) have been conducted. Pasta et al. evaluated the incidence of atherosclerotic cardiovascular disease (ASCVD) in He-FH before and after long-term lipid-lowering treatments to ascertain the interference of other risk factors.

A total of 294 He-FH subjects genetically characterized between 1989 to 2019 were retrospectively analysed. General characteristics, lipid profiles, ASCVD prevalence were evaluated, and ultrasound carotid atherosclerosis assessment was performed. Primary end points were ASCVD outcomes and the percentage of patients reaching recommended LDL-C targets.

During follow-up, despite a significant improvement in plasma lipid profiles, the European Society of Cardiology (ESC) European Atherosclerosis Society (ESC/EAS) 2016 and 2019 recommended LDL-C goals were attained in only a few patients treated with anti-PCSK9 monoclonal antibodies added to the maximum tolerated oral therapy with statins plus ezetimibe. Forty-seven subjects had an ASCVD event before starting lipid-lowering therapy (LLT). During follow-up on LLT, 28 patients had a first ASCVD event and 16 had recurrent ASCVD. In basal conditions and during follow-up, higher LDL-C levels were associated with increased ASCVD risk. Prevention of recurrent ASCVD events was recorded with a long-term reduction of LDL-C below 100 mg/dl with statins plus ezetimibe.

PCSK9 inhibition is the only therapeutic option to achieve LDL-C goals as recommended for He-FH and can prevent ASCVD events as reported in large clinical trials. Long-term treatment with

statins and ezetimibe seems to be effective at preventing ASCVD recurrence when LDL-C is maintained below 130 and 100 mg/dL for primary and secondary prevention, respectively.

SAFEHEART risk-equation and cholesterol-year-score are powerful predictors of cardiovascular events in French patients with familial hypercholesterolemia

Patients with heterozygous familial hypercholesterolemia (HeFH) present elevated cardiovascular (CV) risk. Current CV risk stratification algorithms developed for the general population are not adapted for HeFH patients. It is therefore important to develop and validate CV prediction tools for the this population. Gallo et al. aimed at validating the Spanish SAFEHEART-risk equation (RE) in the French HeFH cohort (REFERCHOL), and at comparing SAFEHEART-RE with the low-density-lipoprotein-cholesterol (LDL-C)-year-score for the prediction of CV events in the HeFH French population.

They included HeFH patients with a genetic or clinical diagnosis. Among them, 512 patients with a 5-year follow-up were included to validate the 5 year-CV-RE. A total of 152 events occurred in the entire population of 1473 patients during a mean follow-up of 3.9 years. Over the five-year follow-up, non-fatal CV events occurred in 103 patients. Almost all the parameters used in the SAFEHEART-RE were confirmed as strong predictors of CV events in the REFERCHOL cohort. The C-statistic revealed a satisfactory performance of both the SAFEHEART-RE and LDL-C-year-scores in predicting CV events for all the patients (primary and secondary prevention), as well as for those in primary prevention at inclusion.

This analysis represents the first external validation of the SAFEHEART-RE and demonstrated that both SAFEHEART-RE and LDL-C-year-score are good predictors of CV events in primary prevention HeFH patients.

Family history and polygenic risk of cardiovascular disease: Independent factors associated with secondary cardiovascular events in patients undergoing carotid endarterectomy

Family history (FHx) of cardiovascular disease (CVD) is a risk factor for CVD and a proxy for cardiovascular heritability. Polygenic risk scores (PRS) summarizing >1 million variants for coronary artery disease (CAD) are associated with incident and recurrent CAD events. However, little is known about the influence of FHx or PRS on secondary cardiovascular events (sCVE) in patients undergoing carotid endarterectomy (CEA). Timmerman et al. investigated the association between MetaGRS (a genomic risk score for CAD consisting of 1.7 million genetic variants) and sCVE in patients undergoing CEA and explored possible underlying pathophysiological mechanisms by studying the impact of

MetaGRS on carotid histological plaque characteristics. Given that FHx is used in clinical practice as a derivative of genetic background, they also examined the association between FHx, sCVE and plaque characteristics.

1788 CEA patients from the Athero-Express Biobank were included. The composite endpoint of sCVE during three years of follow-up included coronary, cerebrovascular and peripheral events and cardiovascular death.

Positive FHx was associated with a higher 3-year risk of sCVE independent of cardiovascular risk factors and MetaGRS. Patients in the highest MetaGRS quintile had a higher 3-year risk of sCVE compared to the rest of the cohort independent of cardiovascular risk factors including FHx, and their atherosclerotic plaques contained more fat and more macrophages.

In CEA patients, both positive FHx and higher MetaGRS were independently associated with increased risk of sCVE. Moreover, higher MetaGRS was associated with vulnerable plaque characteristics. Future studies should unravel underlying mechanisms and focus on the added value of PRS and FHx in individual risk prediction for sCVE.

Common gene variants in *ASGR1* gene locus associate with reduced cardiovascular risk in absence of pleiotropic effects

The Asialoglycoprotein receptor (ASGPR) is a highly conserved transmembrane receptor consisting of two subunits, ASGR1 and ASGR2. The rare *ASGR1* del12 variant is associated with a beneficial effect on coronary artery disease (CAD) that is disproportionate to the small reductions in plasma LDL cholesterol (LDLc). This unexplained benefit has sparked the debate on potential additional pleiotropic effects of *ASGR1* variants. Since ASGR1 has also been implicated in platelet homeostasis, Ali et al. evaluated platelet function in heterozygous *ASGR1* del12 carriers and controls, and they compared the magnitude of various LDLc lowering genetic scores in the UK-Biobank using Mendelian randomization.

Desialylation of platelet surface glycoproteins and platelet aggregation capacity were measured in 12 carriers and 10 controls. Three common genetic variants in the *ASGR1* locus significantly associated with plasma LDLc were selected and the association with coronary artery disease (CAD) was assessed and compared with the effects of *HMCGR, LDLR, NCI1L1* and *PCSK9* gene scores.

Platelet surface N-acetylglucosamine (GlcNAC) residues were significantly lower in carriers but platelet aggregation did not differ. The relative risk reduction of *ASGR1* genetic risk score (GRS) on CAD and myocardial infarction per 10 mg/dl LDLc reduction was 23%. This risk reduction was proportionally similar to the gene risk scores in *HMCGR, NPC1L1, PCSK9,* and *LDLR*.

Unlike previous reports, no evidence was found for a pleiotropic effect of the rare del12 variant at the *ASGR1* locus on CAD, as platelet function did not differ between carriers and controls. Moreover, the observed effect of ASGR1 variants on CAD risk was proportional to the reduction in plasma LDLc levels.