atherosclerosis

Atherosclerosis newsletter

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Volume 318, Issue February 2021

Volume 319, Issue February 2021

Volume 320, Issue March 2021

Volume 321, Issue March 2021

Familial hypercholesterolemia (FH) is an autosomal dominantly inherited disorder estimated to affect an average of 1:300 individuals. Pathogenic mutations in either the low-density lipoprotein receptor gene (*LDLR*), apolipoprotein B100 gene (*APOB*), or proprotein convertase substilisin kexin type 9 gene (*PCSK9*) result in high circulating levels of LDL cholesterol (LDL-C) from birth and early atherosclerotic cardiovascular disease (ASCVD). About 40 years after the Nobel Prize awarded elucidation of FH's metabolic and molecular basis by Goldstein ad Brown, FH is still a rich source of scientific progress. We here summarize several articles published in the March and February issues of *Atherosclerosis*.

Intronic variant screening with targeted next-generation sequencing reveals first pseudoexon in *LDLR* in familial hypercholesterolemia

Depending on the severity of the phenotype, an FH-causing mutation in the three canonical FH genes (*LDLR, APOB, PCSK9*) is found in 40 to 88% of patients with clinically suspected FH (designated FH+) but not in 12–60% of clinical FH patients (designated FH-). In this study, Reeskamp et al. investigated whether variants in intronic regions of *LDLR* can be attributed to FH by affecting pre-mRNA splicing.

LDLR introns are partly covered in routine sequencing of clinical FH patients using next-generation sequencing. Deep intronic variants, >20 bp from intron-exon boundary, were considered of interest in this study if (a) present in FH- patients (n = 909) with LDL-C >7 mmol/L (severe FH-) or after *in silico* analysis in patients with LDL-C >5 mmol/L (moderate FH-) and (b) absent in FH+ patients (control group). cDNA and co-segregation analyses were performed to assess pathogenicity of the identified variants.

Three unique variants were present in the severe FH- group. One of these was the previously described likely pathogenic variant c.2140+103G>T. Three additional variants were selected based on *in silico* analyses in the moderate FH- group. One of these variants, c.2141-218G>A, was found to result in a pseudo-exon inclusion, producing a premature stop codon. This variant co-segregated with the hypercholesterolemic phenotype.

This finding emphasizes the need to consider a whole *LDLR* gene analysis in FH- patients.

2.5-fold increased risk of recurrent acute myocardial infarction with familial hypercholesterolemia

Individuals with genetically verified FH have increased risk of suffering from an early incident acute myocardial infarction (AMI) event or premature death compared with the general population. A first-time acute myocardial infarction (AMI) is a severe diagnosis that leads to initiation or intensification of lipid-lowering medication to prevent recurrent events. Individuals with familial hypercholesterolemia (FH) already use high-intensity lipid-lowering medication at the time of an incident AMI due to their diagnosis. Hence, Svendsen et al. aimed to strengthen existing findings by comparing the risk of incident and recurrent AMI and mortality after the incident AMI between individuals with genetically verified FH and age and sex matched controls.

The study population comprised 4871 subjects with genetically verified FH, and 96,251 age and sex matched controls randomly selected from the Norwegian population. Data were obtained from the Cardiovascular Disease in Norway Project, the Norwegian Patient Registry and the Norwegian Cause of Death Registry. Incidence of AMI, all-cause mortality and recurrent AMI after incident AMI were analyzed for the period 2001–2017. Incidence and mortality were compared using hazard ratios (HR) from Cox regression. Risk of recurrent AMI was compared using sub-hazard ratios (SHR) from competing risk regression with death as a competing event.

232 individuals with FH and 2118 controls with an incident AMI were identified. Among survivors ≥29 days after the incident AMI, both mortality and recurrent AMI were significantly increased among individuals with FH compared with non-FH controls.

These findings call for intensive follow-up of individuals with FH following an AMI.

LDL-cholesterol lowering and clinical outcomes in hypercholesterolemic subjects with and without a familial hypercholesterolemia phenotype: Analysis from the secondary prevention 4S trial

Trial evidence for the benefits of cholesterol-lowering is limited for FH patients, since they have not been the focus of large outcome trials. Vallejo-Vaz et al. assessed statin use in CAD subjects with LDL-C ≥4.9 mmol/L with or without an FH phenotype in a *post-hoc* analysis of the 4S (Scandinavian Simvastatin Survival Study) trial that randomized hypercholesterolemic CAD patients to simvastatin or placebo.

The authors first stratified participants into baseline LDL-C <4.9 and ≥ 4.9 mmol/L; next, based on the Dutch Lipid Clinic Network (DLCN) criteria for FH, the latter group was stratified into four subgroups by presence of none, one or both of “premature CAD” and “family history of CAD”. Participants having both were defined as having an FH phenotype.

2267 and 2164 participants had LDL-C <4.9 and ≥ 4.9 mmol/L, respectively. Mortality endpoints and major coronary events (MCE) were significantly reduced with simvastatin *versus* placebo in both groups over 5.4 years, but the latter derived greater absolute risk reductions (ARR).
LDL-C reductions were similar among the 4 subgroups with levels ≥4.9 mmol/L. Participants with FH phenotype appeared to derive greater relative benefits with simvastatin than the other three subgroups; statistical interaction was non-significant. Participants with FH phenotype derived greater ARR than any other group with simvastatin *versus* placebo.

Subjects with FH phenotype appear to be associated with greater relative and absolute benefit from the same magnitude of LDL-C lowering as compared to individuals without FH phenotype.

Familial hypercholesterolemia and cardiovascular disease in older individuals

With a lipid lowering therapy (LLT), most individuals with FH may have a longer ASCVD-free survival. However, data on older individuals (≥60 years old) with FH are scarce, with previous studies enrolling a very small number of older subjects, other studies including only FH individuals without confirmed molecular diagnosis, and some others without the use of contemporary lipid lowering therapies. In this study, Coutinho et al. compared characteristics of genetically defined FH older individuals with age-matched non-FH counterparts.

From 4111 genotyped individuals, 462 older than 60 years were included (198 positive and 264 negative for FH variants). There were no differences regarding median age for FH and non-FH. In the FH group, there was a higher frequency of males. No differences were seen between FH and non-FH in LLT use. Despite a longer LLT duration in FH patients, treatment was started late in both groups. FH subjects had greater frequencies of previous and early ASCVD. In FH, male sex and LLT onset age were independently associated with ASCVD.

Among hypercholesterolemic older individuals, the genetic diagnosis of FH was associated with higher ASCVD rates, emphasizing the relevance of a monogenic defect as the cause of long-lasting hypercholesterolemia and ASCVD risk.

Combination of bempedoic acid, ezetimibe, and atorvastatin in patients with hypercholesterolemia: A randomized clinical trial

Many patients with hypercholesterolemia fail to achieve sufficient LDL-C lowering despite use of guideline-recommended lipid-lowering therapies. The residual cardiovascular risk associated with elevated LDL-C in these patients underscores the need to develop additional lipid-lowering therapies that can be used in combination with statins and/or other lipid-lowering agents. In a phase 2, randomized, double-blind, placebo-controlled study, Rubino et al. evaluated LDL-C lowering with the combination of bempedoic acid, ezetimibe, and atorvastatin.

After washout of lipid-lowering drugs, patients were randomized 2:1 to triple therapy (bempedoic acid 180 mg, ezetimibe 10 mg, and atorvastatin 20 mg) or placebo once daily for 6 weeks. The primary endpoint was percent change from baseline in LDL-C at week 6.

At week 6, mean LDL-C lowering with triple therapy (−63.6%) was significantly greater than with placebo (–3.1%). Significant reductions with triple therapy *vs.* placebo were also observed for non–high-density lipoprotein cholesterol, total cholesterol, apolipoprotein B, and high-sensitivity C-reactive protein. With triple-therapy, 90% of patients achieved LDL-C <70 mg/dL and 95% of patients had ≥50% lower LDL-C from baseline to week 6; no patients in the placebo group met either goal. The majority of treatment-emergent adverse events were mild to moderate in severity. No patients experienced clinically relevant elevations in aminotransferase or creatine kinase levels.

The combination of bempedoic acid, ezetimibe, and atorvastatin significantly lowered LDL-C in patients with hypercholesterolemia, allowing more than 90% of patients to reach guideline-recommended LDL-C goals.

The study is discussed in details in Banach and Penson editorial.

Maternally inherited hypercholesterolemia does not modify the cardiovascular phenotype in familial hypercholesterolemia

There is a large variability in the clinical presentation in heterozygous subjects (HeFH). Maternal hypercholesterolemia has been proposed as a cardiometabolic risk factor later in life. Whether this phenotype variability depends on the mother or father origin of hypercholesterolemia is unknown. Marco-Benedí et al. assessed potential differences in anthropometry, superficial lipid deposits, comorbidities, and lipid concentrations depending on the parental origin of hypercholesterolemia within a large group of HeFH.

They performed a cross-sectional observational, multicenter, nation-wide study in Spain and recruited adults with HeFH to study clinical differences according to the parental origin. Data on HeFH patients were obtained from the Dyslipidemia Registry of the Spanish Atherosclerosis Society.

HeFH patients were grouped in 1231 HeFH-mother-offspring aged 45.7 (16.3) years and 1174 HeFH-father-offspring aged 44.8 (16.7) years. No difference in lipid parameters (total cholesterol, triglycerides, low density lipoprotein cholesterol (LDLc), high density lipoprotein cholesterol (HDLc), and lipoprotein a Lp(a)), nor in the comorbidities studied (cardiovascular disease prevalence, age of onset of cardiovascular disease, obesity, diabetes, and hypertension) was found between groups. Lipid-lowering treatment did not differ between groups. The prevalence of comorbidities did not show differences when studied by age groups.

The results do not support any relevant effect of maternal hypercholesterolemia in the offspring. This implies that severe maternal hypercholesterolemia during pregnancy is not associated with additional risk in the FH affected offspring.

Familial hypercholesterolaemia and COVID-19: A two-hit scenario for endothelial dysfunction amenable to treatment

Patients with FH are likely at increased risk for COVID-19 complications in the acute phase of the infection, and for a long time thereafter. This is because the exposure of heterozygous FH (HeFH) and even more so homozygous FH (HoFH) patients to very high LDL-C from birth causes a dysfunctional endothelium prone to further damage by the direct viral attack and the hyper-inflammatory reaction typical of severe COVID-19. Evidence to date shows the benefit of statin use in patients with COVID-19. In FH patients, the focus should therefore be on the effective lowering of LDL-C levels, the root cause of the expected excess vulnerability to COVID-19 infection in these patients. Moreover, the ongoing use of statins and other lipid-lowering therapies should be encouraged during the COVID pandemic to mitigate the risk of cardiovascular complications from COVID-19. For the reduction of the excess risk in FH patients with COVID-19, stringent adherence to the guideline-determined LDL-C levels for FH patients are advocated. Unfortunately, epidemiologic data are lacking on the severity of COVID-19 infections, as well as the number of acute cardiac events that have occurred in FH subjects during the COVID-19 pandemic. Such data need to be urgently gathered to learn how much the risk for, and the severity of COVID-19 in FH are increased.