**Literature update week 08 (2020)**

[1] *Munjal A, Khandia R*. **Atherosclerosis: orchestrating cells and biomolecules involved in its activation and inhibition**. Advances in protein chemistry and structural biology 2020; 120:85-122.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=32085889

***ABSTRACT***

The term atherosclerosis refers to the condition of deposition of lipids and other substances in and on the artery walls, called as plaque that restricts the normal blood flow. The plaque may be stable or unstable in nature. Unstable plaque can burst and trigger clot formation adding further adversities. The process of plaque formation involves various stages including fatty streak, intermediate or fibro-fatty lesion and advanced lesion. The cells participating in the formation of atherosclerotic plaque include endothelial cells, vascular smooth muscle cells (VSMC), monocytes, monocytes derived macrophages, macrophages and dendritic cells and regulatory T cells (TREG). The role of a variety of cytokines and chemokines have been studied which either help in progression of atherosclerotic plaque or vice versa. The cytokines involved in atherosclerotic plaque formation include IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-9, IL-10, IL-12, IL-13, IL-15, IL-17, IL-18, IL-20, IL-25, IL-27, IL-33, IL-37, TNF-alpha, TGF-beta and IFN-gamma; whereas amongst the chemokines (family of small cytokines) are CCL2, CCL3, CXCL4, CCL5, CXCL1, CX3CL1, CCL17, CXCL8, CXCL10, CCL20, CCL19 and CCL21 and macrophage migration-inhibitory factor. These are involved in the atherosclerosis advancements, whereas the chemokine CXCL12 is play atheroprotective roles. Apart this, contradictory functions have been documented for few other chemokines such as CXCL16. Since the cytokines and chemokines are amongst the key molecules involved in orchestrating the atherosclerosis advancements, targeting them might be an effective strategy to encumber the atherosclerotic progression. Blockage of cytokines and chemokines via the means of broad-spectrum inhibitors, neutralizing antibodies, usage of decoy receptors or RNA interference have been proved to be useful intervention against atherosclerosis.

[2] *Tardif JC, Dube MP, Pfeffer MA et al.* **Study design of Dal-GenE, a pharmacogenetic trial targeting reduction of cardiovascular events with dalcetrapib**. American heart journal 2020; 222:157-165.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=32087417

***ABSTRACT***

The objectives of precision medicine are to better match patient characteristics with the therapeutic intervention to optimize the chances of beneficial actions while reducing the exposure to unneeded adverse drug experiences. In a retrospective genome-wide association study of the overall neutral placebo-controlled dal-Outcomes trial, the effect of the cholesteryl ester transfer protein (CETP) modulator dalcetrapib on the composite of cardiovascular death, myocardial infarction or stroke was found to be influenced by a polymorphism in the adenylate cyclase type 9 (ADCY9) gene. Whereas patients with the AA genotype at position rs1967309 experienced fewer cardiovascular events with dalcetrapib, those with the GG genotype had an increased rate and the heterozygous AG genotype exhibited no difference from placebo. Measurements of cholesterol efflux and C-reactive protein (CRP) offered directionally supportive genotype-specific findings. In a separate, smaller, placebo-controlled trial, regression of ultrasonography-determined carotid intimal-medial thickness was only observed in dalcetrapib-treated patients with the AA genotype. Collectively, these observations led to the hypothesis that the cardiovascular effects of dalcetrapib may be pharmacogenetically determined, with a favorable benefit-risk ratio only for patients with this specific genotype. We describe below the design of dal-GenE, a precision medicine, placebo-controlled clinical outcome trial of dalcetrapib in

patients with a recent acute myocardial infarction with the unique feature of selecting only those with the AA genotype at rs1967309 in the ADCY9 gene.

[3] *Li H, Wei Y, Yang Z et al.* **Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Alirocumab in Healthy Chinese Subjects: A Randomized, Double-Blind, Placebo-Controlled, Ascending Single-Dose Study**. American journal of cardiovascular drugs : drugs, devices, and other interventions 2020.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=32080823
***ABSTRACT***
BACKGROUND: The addition of alirocumab (a fully human monoclonal antibody to proprotein convertase subtilisin/kexin type 9 [PCSK9]) to background statin therapy provides significant incremental low-density lipoprotein cholesterol (LDL-C) lowering and cardiovascular event risk reduction. OBJECTIVES: Our objectives were to assess the safety, tolerability, pharmacokinetics, and pharmacodynamics of single ascending doses of alirocumab in healthy Chinese subjects. METHODS: In this double-blind, placebo-controlled, phase I study, 35 Chinese subjects (aged 21-45 years) with baseline LDL-C > 100 mg/dL (2.59 mmol/L) were randomized to receive a single 1 mL subcutaneous injection of alirocumab 75, 150, or 300 mg, or placebo, and followed up for ~ 12 weeks. RESULTS: Treatment-emergent adverse events, most frequently nasal congestion and dry throat, were reported in three of seven or eight subjects in each alirocumab dose group (two of seven in the placebo group). One patient receiving alirocumab 300 mg had a mild local injection-site reaction. No alirocumab recipients demonstrated antidrug antibodies. Maximum alirocumab serum concentrations (6-34 mg/dL) occurred at a median of 3-7 days across the dose groups. Maximum mean LDL-C reductions from baseline were observed on days 8, 15, and 22 with alirocumab 75 (55.3%), 150 (63.7%), and 300 mg (73.7%), respectively. Mean free PCSK9 levels were reduced to below the lower limit of quantification within 4 h of dosing. Total cholesterol, non-high-density lipoprotein cholesterol, and apolipoprotein B were reduced with alirocumab. CONCLUSIONS: In Chinese subjects, alirocumab 75, 150, and 300 mg was safe and well-tolerated. Pharmacokinetic/pharmacodynamic parameters, including clinically meaningful reductions in LDL-C and other lipids/lipoproteins, were consistent with data from Japanese and Western populations. Clinicaltrials.gov identifier: NCT02979015.

[4] *Croyal M, Blanchard V, Ouguerram K et al.* **VLDL (Very-Low-Density Lipoprotein)-Apo E (Apolipoprotein E) May Influence Lp(a) (Lipoprotein [a]) Synthesis or Assembly**. Arteriosclerosis, thrombosis, and vascular biology 2020; 40:819-829.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=32078365
***ABSTRACT***
OBJECTIVE: To clarify the association between PCSK9 (proprotein convertase subtilisin/kexin type 9) and Lp(a) (lipoprotein [a]), we studied Lp(a) kinetics in patients with loss-of-function and gain-of-function PCSK9 mutations and in patients in whom extended-release niacin reduced Lp(a) and PCSK9 concentrations. Approach and Results: Six healthy controls, 9 heterozygous patients with familial hypercholesterolemia (5 with low-density lipoprotein receptor [LDLR] mutations and 4 with PCSK9 gain-of-function mutations) and 3 patients with heterozygous dominant-negative PCSK9 loss-of-function mutations were included in the preliminary study. Eight patients were enrolled in a second study assessing the effects of 2 g/day extended-release niacin. Apolipoprotein kinetics in VLDL (very-low-density lipoprotein), LDL (low-density lipoprotein), and Lp(a) were studied using stable isotope

techniques. Plasma Lp(a) concentrations were increased in PCSK9-gain-of-function and familial hypercholesterolemia-LDLR groups compared with controls and PCSK9-loss-of-function groups (14+/-12 versus 5+/-4 mg/dL; P=0.04), but no change was observed in Lp(a) fractional catabolic rate. Subjects with PCSK9-loss-of-function mutations displayed reduced apoE (apolipoprotein E) concentrations associated with a VLDL-apoE absolute production rate reduction. Lp(a) and VLDL-apoE absolute production rates were correlated (r=0.50; P<0.05). ApoE-to-apolipoprotein (a) molar ratios in Lp(a) increased with plasma Lp(a) (r=0.96; P<0.001) but not with PCSK9 levels. Extended-release niacin-induced reductions in Lp(a) and VLDL-apoE absolute production rate were correlated (r=0.83; P=0.015). In contrast, PCSK9 reduction (-35%; P=0.008) was only correlated with that of VLDL-apoE absolute production rate (r=0.79; P=0.028). CONCLUSIONS: VLDL-apoE production could determine Lp(a) production and/or assembly. As PCSK9 inhibitors reduce plasma apoE and Lp(a) concentrations, apoE could be the link between PCSK9 and Lp(a).

[5] *Sanchez-Roa PM, Rees JI, Bartley L, Marshall C*. **Systemic atherosclerotic plaque vulnerability in patients with Coronary Artery Disease with a single Whole Body FDG PET-CT scan**. Asia Oceania journal of nuclear medicine & biology 2020; 8:18-26.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=32064279
***ABSTRACT***
Objectives: Cardiovascular disease is a leading cause of morbimortality with over half cardiovascular events occurring in the asymptomatic population by traditional risk stratification. This preliminary study aimed to evaluate systemic plaque vulnerability in patients with prior Coronary Artery Disease (CAD) with a single Whole Body [FDG] PET-CT scan in terms of plaque inflammation and calcifications. Methods: Twenty-two patients referred for oncological evaluation and with prior history of advanced CAD or age and gender matched controls without cardiovascular disease, underwent a Whole Body PET-CT scan 90 min after injection of (18)F-FDG. A total of 975 transaxial PET images were retrospectively analysed to assess plaque inflammation using a standardized method of analysis with averaged Target-to-Background Ratios (TBRs) at different levels, in the thoracic and abdominal aorta, carotids, LAD, common iliac and femoral arteries, and were correlated with calcium scores from the CT images. Results: TBRs from the thoracic aorta were higher in male patients than controls (1.49+/-0.11, p<0.05) and a gradient was observed (ascending > descending > aortic arch), and were also higher in the carotids in female patients (1.43+/-0.07) versus controls (p<0.05). A tendency for higher levels of plaque inflammation in the abdominal aorta was noted in all groups, but no significant FDG uptake was found either in the iliac or femoral arteries in any group. Plaque inflammation was also higher in the LAD in males but with large variations. Higher levels of calcifications were noted in the LAD, infra-renal abdominal aorta and common iliac arteries, but without significant correlation with plaque inflammation except sporadic overlapping. Conclusion: Patients with advanced CAD are at risk for vulnerable inflamed atheromas in other territories such as the thoracic aorta and carotid arteries, underpinning the systemic nature of the atherosclerotic disease. Coexistence with calcifications is rare, suggesting a different functional status of the plaques and different stages of the disease. Evaluation of subclinical systemic plaque vulnerability in CAD with a Whole Body [FDG] PET-CT scan is feasible and a potentially useful biomarker to assess subclinical vascular risk for risk stratification and treatment optimization, but further studies are needed.

**Literature update week 08 (2020)**

[6] *De Nisco G, Hoogendoorn A, Chiastra C et al.* **The impact of helical flow on coronary atherosclerotic plaque development**. Atherosclerosis 2020.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=32085872
***ABSTRACT***
BACKGROUND AND AIMS: Atherosclerosis has been associated with near-wall hemodynamics and wall shear stress (WSS). However, the role of coronary intravascular hemodynamics, in particular of the helical flow (HF) patterns that physiologically develop in those arteries, is rarely considered. The purpose of this study was to assess how HF affects coronary plaque initiation and progression, definitively demonstrating its atheroprotective nature. METHODS: The three main coronary arteries of five adult hypercholesterolemic mini-pigs on a high fat diet were imaged by computed coronary tomography angiography (CCTA) and intravascular ultrasound (IVUS) at 3 (T1, baseline) and 9.4 +/- 1.9 (T2) months follow-up. The baseline geometries of imaged coronary arteries (n = 15) were reconstructed, and combined with pig-specific boundary conditions (based on in vivo Doppler blood flow measurements) to perform computational fluid dynamic simulations. Local wall thickness (WT) was measured on IVUS images at T1 and T2, and its temporal changes were assessed. Descriptors of HF and WSS nature were computed for each model, and statistically compared to WT data. RESULTS: HF intensity was strongly positively associated with WSS magnitude ($p < 0.001$). Overall, coronary segments exposed to high baseline levels of HF intensity exhibited a significantly lower WT growth ($p < 0.05$), compared to regions with either mid or low HF intensity. CONCLUSIONS: This study confirms the physiological significance of HF in coronary arteries, revealing its protective role against atherosclerotic WT growth and its potential in predicting regions undergoing WT development. These findings support future in vivo measurement of coronary HF as atherosclerotic risk marker, overcoming current limitations of in vivo WSS assessment.

[7] *Schreinlechner M, Noflatscher M, Reinstadler SJ et al.* **Early onset of menopause is associated with increased peripheral atherosclerotic plaque volume and progression**. Atherosclerosis 2020; 297:25-31.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=32062136
***ABSTRACT***
BACKGROUND AND AIMS: Cardiovascular disease (CVD) is the leading cause of death in western countries. One risk factor unique to women is the menopausal status. The aim of this study was to analyse the influence of the onset of menopause (MP) on the extent and progression of atherosclerotic plaque volume (PV). METHODS: Postmenopausal women with at least one cardiovascular risk factor (CVRF) but without established CVD were included. Quantification of PV was performed in peripheral arteries using a three - dimensional (3D) ultrasound (US) technique. Follow-up examination to assess PV progression was performed after 19 (+/-8) months. RESULTS: 110 consecutive postmenopausal women (mean age 65.5) were included. Females with an earlier onset of MP (<45 years) had a significantly higher PV than those with an intermediate (45-52 years) or later onset of menopause (>52 years), irrespective of other CVRF (244 mm(3) vs. 193 mm(3) vs. 73 mm(3), respectively, $p = 0.023$). In addition, women with an earlier onset of MP had a higher PV progression compared to women with an intermediate or late onset (40 mm(3) vs. 35 mm(3) vs. 8.5 mm(3); $p = 0.002$, respectively). Moreover, these results were confirmed in multivariate regression, where only onset of MP (OR 0.88; 95%CI 0.81-0.96; $p = 0.004$) and age (OR 1.06; 95%CI 1.08-1.13; $p = 0.025$) were significant predictors for a higher

atherosclerotic progression. CONCLUSIONS: An earlier onset of MP was associated with an increase in atherosclerotic PV and accelerated progression, independent of other CVRF.

[8] *Kwaifa IK, Bahari H, Yong YK, Noor SM*. **Endothelial Dysfunction in Obesity-Induced Inflammation: Molecular Mechanisms and Clinical Implications**. Biomolecules 2020; 10.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=32069832
***ABSTRACT***
Obesity is characterized by the excessive deposition of fat that may interfere with the normal metabolic process of the body. It is a chronic condition associated with various metabolic syndromes, whose prevalence is grossly increasing, and affects both children and adults. Accumulation of excessive macronutrients on the adipose tissues promotes the secretion and release of inflammatory mediators, including interleukin-6 (IL-6), interleukin 1beta, tumor necrotic factor-alpha (TNF-alpha), leptin, and stimulation of monocyte chemoattractant protein-1 (MCP-1), which subsequently reduce the production of adiponectin thereby initiating a proinflammatory state. During obesity, adipose tissue synthesizes and releases a large number of hormones and cytokines that alter the metabolic processes, with a profound influence on endothelial dysfunction, a situation associated with the formation of atherosclerotic plaque. Endothelial cells respond to inflammation and stimulation of MCP-1, which is described as the activation of adhesion molecules leading to proliferation and transmigration of leukocytes, which facilitates their increase in atherogenic and thromboembolic potentials. Endothelial dysfunction forms the cornerstone of this discussion, as it has been considered as the initiator in the progression of cardiovascular diseases in obesity. Overexpression of proinflammatory cytokines with subsequent reduction of anti-inflammatory markers in obesity, is considered to be the link between obesity-induced inflammation and endothelial dysfunction. Inhibition of inflammatory mechanisms and management and control of obesity can assist in reducing the risks associated with cardiovascular complications.

[9] *Chen S, Chen D, Yang H et al.* **Uric acid induced hepatocytes lipid accumulation through regulation of miR-149-5p/FGF21 axis**. BMC gastroenterology 2020; 20:39.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=32070295
***ABSTRACT***
BACKGROUND: Hyperuricemia is a major risk for non-alcoholic fatty liver disease. However, the mechanisms for this phenomenon are not fully understood. This study aimed to investigate whether microRNAs mediated the pathogenic effects of uric acid on non-alcoholic fatty liver disease. METHODS: Microarray was used to determine the hepatic miRNA expression profiles of male C57BL/6 mice fed on standard chow diet, high fat diet (HFD), and HFD combined with uric acid-lowering therapy by allopurinol. We validated the expression of the most significant differentially expressed microRNAs and explored its role and downstream target in uric acid-induced hepatocytes lipid accumulation. RESULTS: Microarray analysis and subsequent validation showed that miR-149-5p was significantly up-regulated in the livers of HFD-fed mice, while the expression was down-regulated by allopurinol therapy. MiR-149-5p expression was also significantly up-regulated in uric acid-stimulated hepatocytes. Over-expression of miR-149-5p significantly aggregated uric acid-induced triglyceride accumulation in hepatocytes, while inhibiting miR-149-5p ameliorated the triglyceride accumulation. Luciferase report assay confirmed that FGF21 is a target gene of miR-149-5p. Silencing FGF21 abolished the ameliorative effects of miR-149-5p inhibitor on uric acid-induced hepatocytes lipid accumulation, while

overexpression of FGF21 prevented the lipid accumulation induced by miR-149-5p mimics. CONCLUSIONS: Uric acid significantly up-regulated the expression of miR-149-5p in hepatocytes and induced hepatocytes lipid accumulation via regulation of miR-149-5p/FGF21 axis.

[10] *Byrne P, Cullinan J, Mintzes B, Smith SM*. **UK deal over inclisiran**. Bmj 2020; 368:m579.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=32071100
***ABSTRACT***

[11] *Llop-Talaveron JM, Leiva-Badosa E, Novak A et al.* **Phytosterolemia associated with parenteral nutrition administration in adult patients**. The British journal of nutrition 2020:1-26.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=32077392
***ABSTRACT***
Vegetable lipid emulsions (LE) contain non-declared phytosterols (PS). We aimed to determine PS content depending on the brand and LE batch; and in adult hospitalized patients treated with parenteral nutrition (PN), to establish the association between plasma and administered PS.I. LE study: Totals and fractions of PS in 3-4 non-consecutive batches from 6 LE were analysed. II. Patient study: randomized, double-blind study of patients with at least 7 previous days of PN with 0.8 g/kg/day of an olive/soybean LE, were randomized (Day 0) 1:1 to olive/soybean (O/S) or 100% fish oil (FO) at a dose of 0.4 g/kg/day for 7 days (Day 7). Plasma PS, its fractions, total cholesterol on Days 0 and 7, their clearance, and their association with PS administered by LE were studied.In part I. LE study: differences were found in the total PS, their fractions and cholesterol among different LE brands and batches. Exclusive soybean LE had the highest content of PS (422.36 +/- 130.46 mug/mL). II. Patient study: 19 patients were included. In the O/S group, PS levels were maintained (1.11+/-6.98 mug/mL) from Day 0 to 7, while in the FO group, significant decreases were seen in total PS (-6.21+/-4.73 mug/mL) and their fractions, except for campesterol and stigmasterol. Plasma PS on Day 7 were significantly associated with PS administered (R2=0.443).PS content in different LE brands had great variability. PS administered during PN resulted in accumulation and could be prevented with the exclusive administration of FO LE.

[12] *Heeba GH, El-Deen R, Abdel-Latif RG, Khalifa MMA*. **Combined treatments with metformin and phosphodiesterase inhibitors alleviate non-alcoholic fatty liver disease in high-fat diet-fed rats: A comparative study**. Canadian journal of physiology and pharmacology 2020.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=32083947
***ABSTRACT***
Nonalcoholic fatty liver disease (NAFLD) is an excessive accumulation of fats in the liver resulted in hepatic inflammation and fibrous tissue formation along with insulin resistance. This study was designed to investigate the possible protective effects of metformin alone and in combination with different phosphodiesterase inhibitors (PDEIs). Rats were fed a high-fat diet (HFD) for sixteen weeks to induce NAFLD. Starting from week 12, rats received metformin alone or in combination with pentoxifylline, cilostazol or sildenafil. HFD administration resulted in hepatic steatosis and inflammation in rats. In addition, liver index, body composition index, activities of liver enzymes, and serum lipids deviated from normal. Further, significant elevations were recorded compared to control in terms of serum glucose, insulin and HOMA-IR, oxidative stress parameters, hepatic TNF-alpha and NF-small ka, CyrillicB gene expression and iNOS protein expression. Rats treated with metformin

showed a significant improvement in the aforementioned parameters. However, the addition of pentoxifylline to metformin treatment synergized its action and produced a fortified effect against HFD-induced NAFLD better than other PDEIs. Data from this study indicated that combined treatment of metformin and pentoxifylline had the most remarkable ameliorated effects against HFD-induced NAFLD; further clinical investigations are in-need to approve PDEIs for NAFLD treatment.

[13] *Kuwabara M, Sasaki J, Saikawa T, Ouchi Y*. **Response by Kuwabara et al to Letter Regarding Article, "Ezetimibe Lipid-Lowering Trial on Prevention of Atherosclerotic Cardiovascular Disease in 75 or Older (EWTOPIA 75): A Randomized Controlled Trial"**. Circulation 2020; 141:e67-e68.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=32078428
***ABSTRACT***

[14] *Weingartner O, Sijbrands E, Lutjohann D*. **Letter by Weingartner et al Regarding Article, "Ezetimibe Lipid-Lowering Trial on Prevention of Atherosclerotic Cardiovascular Disease in 75 or Older (EWTOPIA 75): A Randomized, Controlled Trial"**. Circulation 2020; 141:e65-e66.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=32078427
***ABSTRACT***

[15] *Xia S, Du X, Guo L et al.* **Sex Differences in Primary and Secondary Prevention of Cardiovascular Disease in China**. Circulation 2020; 141:530-539.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=32065775
***ABSTRACT***
BACKGROUND: Despite improvements in diagnostic and therapeutic interventions to combat cardiovascular disease (CVD) in recent decades, there are significant ongoing access gaps and sex disparities in prevention that have not been adequately quantified in China. METHODS: A representative, cross-sectional, community-based survey of adults (aged >/=45 years) was conducted in 7 geographic regions of China between 2014 and 2016. Logistic regression models were used to determine sex differences in primary and secondary CVD prevention, and any interaction by age, education level, and area of residence. Data are presented as adjusted odds ratios (ORs) and 95% CIs. RESULTS: Of 47 841 participants (61.3% women), 5454 (57.2% women) had established CVD and 9532 (70.5% women) had a high estimated 10-year CVD risk (>/=10%). Only 48.5% and 48.6% of women and 39.3% and 59.8% of men were on any kind of blood pressure (BP)-lowering medication, lipid-lowering medication, or antiplatelet therapy for primary and secondary prevention, respectively. Women with established CVD were significantly less likely than men to receive BP-lowering medications (OR, 0.79 [95% CI, 0.65-0.95]), lipid-lowering medications (OR, 0.69 [95% CI, 0.56-0.84]), antiplatelets (OR, 0.53 [95% CI, 0.45-0.62]), or any CVD prevention medication (OR, 0.62 [95% CI, 0.52-0.73]). Women with established CVD, however, had better BP control (OR, 1.31 [95% CI, 1.14-1.50]) but less well-controlled low-density lipoprotein cholesterol (OR, 0.66 [95% CI, 0.57-0.76]), and were less likely to smoke (OR, 13.89 [95% CI, 11.24-17.15]) and achieve physical activity targets (OR, 1.92 [95% CI, 1.61-2.29]). Conversely, women with high CVD risk were less likely than men to have their BP, low-density lipoprotein cholesterol, and bodyweight controlled (OR, 0.46 [95% CI, 0.38-0.55]; OR, 0.60 [95% CI, 0.52-0.69]; OR, 0.55 [95% CI, 0.48-0.63], respectively), despite a higher use of BP-lowering medications (OR, 1.21 [95% CI, 1.01-1.45]). Younger patients (<65 years) with established CVD were less likely to be taking CVD preventive medications, but there were no sex differences by area of residence or

education level. CONCLUSIONS: Large and variable gaps in primary and secondary CVD prevention exist in China, particularly for women. Effective CVD prevention requires an improved overall nationwide strategy and a special emphasis on women with established CVD, who have the greatest disparity and the most to benefit.

[16] *Zhang X, Wu M, Zhang Y et al.* **Molecular imaging of atherosclerotic plaque with lipid nanobubbles as targeted ultrasound contrast agents**. Colloids and surfaces. B, Biointerfaces 2020; 189:110861.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=32070864
***ABSTRACT***
Molecularly-targeted nanobubbles (NBs) offer opportunities to improve the ability of ultrasound imaging to identify specific pathological tissue from healthy tissue. In this work, we aimed to design ligands-conjugated, nanosized, lipid ultrasound contrast agents (UCAs) and apply the agents in the ultrasound imaging of atherosclerotic plaque. Anti-VEGFR-2 ligands were conjugated to UCAs using the noncovalent biotin-avidin linker method. Several investigations were used to determine the morphology and performance of the targeted UCAs, including surface morphology, size distribution and ligands conjunction efficiency. The prepared targeted UCAs were utilized in vivo ultrasound imaging to detect rabbit abdominal aorta atherosclerotic plaque and to investigate the acoustic behavior in a rabbit kidney model. The results implied that the nanosized UCAs carrying anti-VEGFR-2 ligands would facilitate site-specific recognition of atherosclerosis and can provide unique advantages in targeted ultrasound molecular imaging.

[17] *Ingles DP, Cruz Rodriguez JB, Garcia H*. **Supplemental Vitamins and Minerals for Cardiovascular Disease Prevention and Treatment**. Current cardiology reports 2020; 22:22.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=32067177
***ABSTRACT***
PURPOSE OF REVIEW: The objective of this study is to explore the current literature supporting the use oral multivitamins and multi/minerals (OMVMs) for cardiovascular diseases (CVD) treatment and prevention. RECENT FINDINGS: Data on multivitamins, vitamin C and D, coenzyme Q, calcium, and selenium, has showed no consistent benefit for the prevention of CVD, myocardial infarction, or stroke, nor was there a benefit for all-cause mortality to support their routine supplementation. Folic acid alone and B vitamins with folic acid, B6 and B12, reduce stroke, whereas niacin and antioxidants are associated with an increased risk of all-cause mortality. Iron deficiency should be avoided and treated if found, but routine supplementation to those without deficiency is not evidence based. Despite the high supplement use by the general public, there is no evidence to support the routine supplementation of oral multivitamins and multi/minerals (OVMN) for CVD prevention or treatment.

[18] *Vallejo-Vaz AJ, Corral P, Schreier L, Ray KK*. **Triglycerides and residual risk**. Current opinion in endocrinology, diabetes, and obesity 2020; 27:95-103.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=32073428
***ABSTRACT***
PURPOSE OF REVIEW: To review the recent evidence from observational/genetic/interventional studies addressing triglycerides and residual cardiovascular risk (CVRisk). RECENT FINDINGS: Large population-based and secondary prevention studies consistently show an association of higher

triglycerides with increased CVRisk. This is compounded by genetic studies demonstrating an independent relationship between triglyceride raising or lowering genetic variants affecting triglyceride-rich lipoproteins (TRL) metabolism and CVRisk. Mendelian randomization analysis suggests the benefit of genetic lowering of triglycerides and LDL-cholesterol is similar per unit change in apolipoprotein-B. Among cholesterol-lowering trials, more intensive statin therapy produced greater CVRisk reductions in patients with higher TRL-cholesterol or triglycerides; proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibition led to similar triglycerides reduction but greater non-HDL-C or apolipoprotein-B reductions than fibrates or fish oils. Regarding n-3 fatty acids, A Study of Cardiovascular Events in Diabetes (ASCEND) and Vitamin D and Omega-3 Trial (VITAL) primary prevention trials with eicosapentaenoic acid (EPA) and docosahexaenoic acid failed to demonstrate cardiovascular benefits, Conversely, Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial (REDUCE-IT) using high-dose icosapent-ethyl (purified EPA) in primary (diabetes) and secondary prevention with hypertriglyceridemia showed significant cardiovascular events reductions (greater than expected by the observed triglycerides or apolipoprotein-B reductions, suggesting potential benefits through non-lipid pathways). SUMMARY: Evidence suggests higher triglycerides are a marker of CVRisk and may help identify patients who benefit from intensification of therapy. Moreover, genetic studies support a causal link between TRL/triglycerides and cardiovascular disease. Treatment with high-dose EPA may be of benefit in high-risk patients with hypertriglyceridemia to reduce CVRisk.

[19] *Lee J, Hwang YC, Lee WJ et al.* **Comparison of the Efficacy and Safety of Rosuvastatin/Ezetimibe Combination Therapy and Rosuvastatin Monotherapy on Lipoprotein in Patients With Type 2 Diabetes: Multicenter Randomized Controlled Study**. Diabetes Ther 2020.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=32065359

***ABSTRACT***

INTRODUCTION: Ezetimibe/statin combination therapy has been reported to provide additional cardioprotective effects compared to statin monotherapy. The apolipoprotein B/A1 (apoB/A1) ratio is an effective predictor of cardiovascular diseases. The aim of this study was to compare the efficacy and safety of rosuvastatin/ezetimibe combination therapy versus rosuvastatin monotherapy using the apoB/A1 ratio in patients with diabetes and hypercholesterolemia. METHODS: In this randomized, multicenter, open-label, parallel-group study, patients were randomly assigned to receive the combination therapy of rosuvastatin 5 mg/ezetimibe 10 mg once daily (n = 68) or monotherapy with rosuvastatin 10 mg once daily (n = 68), for 8 weeks. RESULTS: After the 8-week treatment, percentage change (least-square means +/- standard error) in the apoB/A1 ratio in the rosuvastatin/ezetimibe group was significantly decreased compared to the rosuvastatin group (- 46.14 +/- 1.58% vs. - 41.30 +/- 1.58%, respectively; P = 0.03). In addition, the proportion of patients achieving > 50% reduction in low-density lipoprotein-cholesterol (LDL-C) and in the comprehensive lipid target (LDL-C < 70 mg/dL, non-HDL-cholesterol [non-HDL-C] < 100 mg/dL, and apoB < 80 mg/dL) was significantly different between the two groups (76.5 and 73.5% in the rosuvastatin/ezetimibe group and 47.1 and 45.6% in the rosuvastatin group, respectively; P < 0.001). The reduction in total cholesterol, non-HDL-C, LDL-C, and apoB were greater in the rosuvastatin/ezetimibe group than in the rosuvastatin group. Both treatments were well tolerated, and no between-group differences in drug-related adverse events were observed. CONCLUSION: The apoB/A1 ratio was significantly reduced in patients receiving combination therapy with ezetimibe and rosuvastatin compared to those receiving rosuvastatin

monotherapy. Both treatments were well tolerated in patients with type 2 diabetes and hypercholesterolemia. TRIAL REGISTRATION: NCT03446261.

[20] *Ottenhoff MJ, Krab LC, Elgersma Y*. **Considerations for clinical therapeutic development of statins for neurodevelopmental disorders**. eNeuro 2020.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=32071072
***ABSTRACT***
Significance statementThe HMG-CoA reductase inhibitors lovastatin and simvastatin have both been investigated in clinical trials designed to treat the cognitive deficits associated with neurodevelopmental disorders such as Neurofibromatosis type 1, Fragile X and autism. In a recent study, the therapeutic efficacy of lovastatin and simvastatin were compared in a Fragile X (Fmr1) mouse model. The authors concluded that lovastatin was superior to simvastatin in rescuing the Fmr1 phenotypes, and cautioned against considering simvastatin as treatment for neurodevelopmental disorders. We discuss these findings in the context of published literature and argue that more support is needed for this potentially far-reaching conclusion. We further provide recommendations to improve the translation of pre-clinical studies of cognitive disorders into the clinical domain.

[21] *Allahyari A, Jernberg T, Hagstrom E et al.* **Application of the 2019 ESC/EAS dyslipidaemia guidelines to nationwide data of patients with a recent myocardial infarction: a simulation study**. European heart journal 2020.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=32072178
***ABSTRACT***
AIMS: To estimate the proportion of patients with a recent myocardial infarction (MI) who would be eligible for additional lipid-lowering therapy according to the 2019 European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) guidelines for the management of dyslipidaemias, and to simulate the effects of expanded lipid-lowering therapy on attainment of the low-density lipoprotein cholesterol (LDL-C) target as recommended by the guidelines. METHODS AND RESULTS: Using the nationwide SWEDEHEART register, we included 25 466 patients who had attended a follow-up visit 6-10 weeks after an MI event, 2013-17. While most patients (86.6%) were receiving high-intensity statins, 82.9% of the patients would be eligible for expanded lipid-lowering therapy, as they had not attained the target of an LDL-C level of <1.4 mmol and a >/=50% LDL-C level reduction. When maximized use of high-intensity statins followed by add-on therapy with ezetimibe was simulated using a Monte Carlo model, the LDL-C target was reached in 19.9% using high-intensity statin monotherapy and in another 28.5% with high-intensity statins and ezetimibe, while 50.7% would still be eligible for proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors. When use of alirocumab or evolocumab was simulated in those who were eligible for PCSK9 inhibitors, around 90% of all patients attained the LDL-C target. CONCLUSION : Our study suggests that, even with maximized use of high-intensity statins and ezetimibe, around half of patients with MI would be eligible for treatment with PCSK9 inhibitors according to the 2019 ESC/EAS guidelines. Considering the current cost of PCSK9 inhibitors, the financial implications of the new guidelines may be substantial.

[22] *Nazarzadeh M, Pinho-Gomes AC, Bidel Z et al.* **Plasma lipids and risk of aortic valve stenosis: a Mendelian randomization study**. European heart journal 2020.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=32076698

***ABSTRACT***
AIMS: Aortic valve stenosis is commonly considered a degenerative disorder with no recommended preventive intervention, with only valve replacement surgery or catheter intervention as treatment options. We sought to assess the causal association between exposure to lipid levels and risk of aortic stenosis. METHODS AND RESULTS: Causality of association was assessed using two-sample Mendelian randomization framework through different statistical methods. We retrieved summary estimations of 157 genetic variants that have been shown to be associated with plasma lipid levels in the Global Lipids Genetics Consortium that included 188 577 participants, mostly European ancestry, and genetic association with aortic stenosis as the main outcome from a total of 432 173 participants in the UK Biobank. Secondary negative control outcomes included aortic regurgitation and mitral regurgitation. The odds ratio for developing aortic stenosis per unit increase in lipid parameter was 1.52 [95% confidence interval (CI) 1.22-1.90; per 0.98 mmol/L] for low density lipoprotein (LDL)-cholesterol, 1.03 (95% CI 0.80-1.31; per 0.41 mmol/L) for high density lipoprotein (HDL)-cholesterol, and 1.38 (95% CI 0.92-2.07; per 1 mmol/L) for triglycerides. There was no evidence of a causal association between any of the lipid parameters and aortic or mitral regurgitation. CONCLUSION: Lifelong exposure to high LDL-cholesterol increases the risk of symptomatic aortic stenosis, suggesting that LDL-lowering treatment may be effective in its prevention.

[23] *van Rosendael AR, Bax AM, Smit JM et al.* **Clinical risk factors and atherosclerotic plaque extent to define risk for major events in patients without obstructive coronary artery disease: the long-term coronary computed tomography angiography CONFIRM registry**. European heart journal cardiovascular Imaging 2020.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=32065624

***ABSTRACT***
AIMS: In patients without obstructive coronary artery disease (CAD), we examined the prognostic value of risk factors and atherosclerotic extent. METHODS AND RESULTS: Patients from the long-term CONFIRM registry without prior CAD and without obstructive (>/=50%) stenosis were included. Within the groups of normal coronary computed tomography angiography (CCTA) (N = 1849) and non-obstructive CAD (N = 1698), the prognostic value of traditional clinical risk factors and atherosclerotic extent (segment involvement score, SIS) was assessed with Cox models. Major adverse cardiac events (MACE) were defined as all-cause mortality, non-fatal myocardial infarction, or late revascularization. In total, 3547 patients were included (age 57.9 +/- 12.1 years, 57.8% male), experiencing 460 MACE during 5.4 years of follow-up. Age, body mass index, hypertension, and diabetes were the clinical variables associated with increased MACE risk, but the magnitude of risk was higher for CCTA defined atherosclerotic extent; adjusted hazard ratio (HR) for SIS >5 was 3.4 (95% confidence interval [CI] 2.3-4.9) while HR for diabetes and hypertension were 1.7 (95% CI 1.3-2.2) and 1.4 (95% CI 1.1-1.7), respectively. Exclusion of revascularization as endpoint did not modify the results. In normal CCTA, presence of >/=1 traditional risk factors did not worsen prognosis (log-rank P = 0.248), while it did in non-obstructive CAD (log-rank P = 0.025). Adjusted for SIS, hypertension and diabetes predicted MACE risk in non-obstructive CAD, while diabetes did not increase risk in absence of CAD (P-interaction = 0.004). CONCLUSION: Among patients without obstructive CAD, the extent of CAD provides more prognostic information for MACE than traditional cardiovascular risk factors. An interaction was observed between risk factors and CAD burden, suggesting synergistic effects of both.

**Literature update week 08 (2020)**

[24] *Ponticelli C, Arnaboldi L, Moroni G, Corsini A*. **Treatment of dyslipidemia in kidney transplantation**. Expert opinion on drug safety 2020:1-11.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=32073914
***ABSTRACT***
Introduction: Lipid disorders are frequent after kidney transplantation (KT) and KT recipients are considered at high- or very-high cardiovascular risk. Among many concurring factors, a major role is played by immunosuppressants.Areas covered: General measures to manage lipid disorders first include physical activity and diet counseling. Modulating the doses of immunosuppressants also improves dyslipidemia. When lipid-lowering drugs are necessary to control elevated plasma cholesterol and/or triglycerides, statins are the cornerstone for managing hypercholesterolemia. However, side-effects (e.g. myopathy, new-onset diabetes, and kidney graft dysfunction) may occur. In these cases, ezetimibe (which does not affect kidney function) alone or on top of statins for the severe cases, is suggested by the most recent Guidelines. Proprotein convertase subtilisin/kexin type9 inhibitors are promising but expensive and their use in KT is still limited.Expert opinion: In KT recipients, statins should be used cautiously. Rather than using high-dose statin in difficult patients, an association with ezetimibe is suggested. While fibrates, niacin, and resins do not play a relevant role due to their erratic efficacy and common side-effects, new lipid-lowering drugs are emerging but their safety and efficacy in KT patients still need to be assessed.

[25] *Innes JK, Calder PC*. **Marine Omega-3 (N-3) Fatty Acids for Cardiovascular Health: An Update for 2020**. International journal of molecular sciences 2020; 21.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=32085487
***ABSTRACT***
The omega-3 (n-3) fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are found in seafood (especially fatty fish), supplements and concentrated pharmaceutical preparations. Long-term prospective cohort studies consistently demonstrate an association between higher intakes of fish, fatty fish and marine n-3 fatty acids (EPA + DHA) or higher levels of EPA and DHA in the body and lower risk of developing cardiovascular disease (CVD), especially coronary heart disease (CHD) and myocardial infarction (MI), and cardiovascular mortality in the general population. This cardioprotective effect of EPA and DHA is most likely due to the beneficial modulation of a number of known risk factors for CVD, such as blood lipids, blood pressure, heart rate and heart rate variability, platelet aggregation, endothelial function, and inflammation. Evidence for primary prevention of CVD through randomised controlled trials (RCTs) is relatively weak. In high-risk patients, especially in the secondary prevention setting (e.g., post-MI), a number of large RCTs support the use of EPA + DHA (or EPA alone) as confirmed through a recent meta-analysis. This review presents some of the key studies that have investigated EPA and DHA in the primary and secondary prevention of CVD, describes potential mechanisms for their cardioprotective effect, and evaluates the more recently published RCTs in the context of existing scientific literature.

[26] *Tommasi S, Yoon JI, Besaratinia A*. **Secondhand Smoke Induces Liver Steatosis through Deregulation of Genes Involved in Hepatic Lipid Metabolism**. International journal of molecular sciences 2020; 21.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=32075112
***ABSTRACT***

We investigated the role of secondhand smoke (SHS) exposure, independently of diet, in the development of chronic liver disease. Standard diet-fed mice were exposed to SHS (5 h/day, 5 days/week for 4 months). Genome-wide gene expression analysis, together with molecular pathways and gene network analyses, and histological examination for lipid accumulation, inflammation, fibrosis, and glycogen deposition were performed on the liver of SHS-exposed mice and controls, upon termination of exposure and after one-month recovery in clean air. Aberrantly expressed transcripts were found in the liver of SHS-exposed mice both pre- and post-recovery in clean air (n = 473 vs. 222). The persistent deregulated transcripts (n = 210) predominantly affected genes and functional networks involved in lipid metabolism as well as in the regulation of the endoplasmic reticulum where manufacturing of lipids occurs. Significant hepatic fat accumulation (steatosis) was observed in the SHS-exposed mice, which progressively increased as the animals underwent recovery in clean air. Moderate increases in lobular inflammation infiltrates and collagen deposition as well as loss of glycogen were also detectable in the liver of SHS-exposed mice. A more pronounced phenotype, manifested as a disrupted cord-like architecture with foci of necrosis, apoptosis, inflammation, and macrovesicular steatosis, was observed in the liver of SHS-exposed mice post-recovery. The progressive accumulation of hepatic fat and other adverse histological changes in the SHS-exposed mice are highly consistent with the perturbation of key lipid genes and associated pathways in the corresponding animals. Our data support a role for SHS in the genesis and progression of metabolic liver disease through deregulation of genes and molecular pathways and functional networks involved in lipid homeostasis.

[27] *Sun Y, Liu Y, Guan X et al.* **Atorvastatin inhibits renal inflammatory response induced by calcium oxalate crystals via inhibiting the activation of TLR4/NF-kappaB and NLRP3 inflammasome**. IUBMB life 2020.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=32083808
***ABSTRACT***
This study aimed to investigate the renal protective effect of atorvastatin (ATV) on the kidney inflammation induced by calcium oxalate (CaOx) crystals. A cell model of cell-crystal interactions and a rat model of CaOx kidney stone were established. The expressions of TLR4, NF-kappaB, NLRP3, and cleaved caspase-1 in cells and rat kidney tissues were detected using Western blot, immunohistochemical, and/or immunofluorescence. The concentrations of malondialdehyde (MDA), superoxide dismutase (SOD), reactive oxygen species (ROS) in cells, and lactic acid dehydrogenase (LDH) in the culture medium were measured. The secreted levels of interleukin (IL)-1beta, IL-18, IL-6, and tumor necrosis factor-alpha (TNF-alpha) were examined by ELISA. The serum levels of creatinine (CRE) and blood urea nitrogen (BUN) were measured. von Kossa staining was used for the evaluation of renal lens deposition. The CaOx model group showed significantly decreased SOD level; increased concentrations of MDA; ROS and LDH; elevated expressions of TLR4, NF-kappaB, NLRP3, and cleaved caspase-1; and the elevated release of IL-1beta, IL-18, IL-6, and TNF- alpha as compared to the control group. The treatment with ATV significantly inhibited the formation of CaOx kidney stone by increasing the level of SOD; downregulating MDA, ROS, and LDH; inhibiting the expressions of TLR4, NF-kappaB, NLRP3 and cleaved caspase-1; and blocking the secretion of inflammatory cytokines. In addition, the serum levels of CRE and BUN, and the intrarenal crystal deposition were also significantly decreased in ATV-treated rats. In summary, oxidative stress, TLR4/NF-kappaB, and NLRP3 inflammasome pathways are involved in renal inflammatory responses induced by CaOx crystals. ATV treatment significantly

suppressed oxidative stress, inhibited the activation of TLR4/NF-kappaB and NLRP3 inflammasome pathways, and decreased the release of inflammatory mediators, thereby ameliorating CaOx crystal-induced damage and crystal deposition in HK-2 cells and rat kidney tissues.

[28] *Nanna MG, Navar AM, Giugliano RP et al.* **Muscle Complaints or Events in Patients Randomized to Simvastatin or Ezetimibe/Simvastatin**. Journal of the American College of Cardiology 2020; 75:835-837.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=32081289
***ABSTRACT***

[29] *PV ES, Borges CDS, Rosa JL et al.* **Effects of isolated or combined exposure to sibutramine and rosuvastatin on reproductive parameters of adult male rats**. Journal of applied toxicology : JAT 2020.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=32072669
***ABSTRACT***
Many obese patients are exposed to hypolipidemic and serotonin-norepinephrine reuptake inhibitor (SNRI) drugs. Statins are one of the most marketed drugs in the world to treat dyslipidemia, while sibutramine, a SNRI drug, is prescribed in some countries to treat obesity and is detected as an additive in many adulterated weight loss supplements marketed worldwide. Previous studies reported adverse effects of isolated exposure to these drugs on male rat reproductive parameters. In the present work, we further investigated male reproductive toxicity of these drugs, administered in isolation or combination in adult rats for a longer period of treatment. Adult male rats (90 days) were treated (gavage) for 70 days with saline and dimethyl sulfoxide (control), sibutramine (10 mg/kg), rosuvastatin (5 mg/kg), or rosuvastatin combined with sibutramine. Sibutramine alone or with rosuvastatin, promoted a reduction in food intake and body weight gain, weight of the epididymis, ventral prostate and seminal vesicle; as well as decreased sperm reserves and transit time through the epididymis; androgen depletion; and increased index of cytoplasmic droplet. The rosuvastatin-treated group showed reduced frequency of ejaculation. Exposure to this drug alone or combined with sibutramine impaired epididymal morphology. Co-exposed rats had altered epididymal morphometry, and seminal vesicle and testis weights. The rats also showed decreased fertility after natural mating and a trend toward a delay in ejaculation, suggesting a small synergistic effect of these drugs. Given the greater reproductive efficiency of rodents, the results obtained in the present study raise concern regarding possible fertility impairment in men taking statins and SNRI drugs.

[30] *van Rosendael AR, Lin FY, Ma X et al.* **Percent atheroma volume: Optimal variable to report whole-heart atherosclerotic plaque burden with coronary CTA, the PARADIGM study**. Journal of cardiovascular computed tomography 2020.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=32063545
***ABSTRACT***
BACKGROUND AND AIMS: Different methodologies to report whole-heart atherosclerotic plaque on coronary computed tomography angiography (CCTA) have been utilized. We examined which of the three commonly used plaque burden definitions was least affected by differences in body surface area (BSA) and sex. METHODS: The PARADIGM study includes symptomatic patients with suspected coronary atherosclerosis who underwent serial CCTA >2 years apart. Coronary lumen, vessel, and plaque were quantified from the coronary tree on a 0.5 mm cross-sectional basis by a core-lab, and

summed to per-patient. Three quantitative methods of plaque burden were employed: (1) total plaque volume (PV) in mm(3), (2) percent atheroma volume (PAV) in % [which equaled: PV/vessel volume * 100%], and (3) normalized total atheroma volume (TAVnorm) in mm(3) [which equaled: PV/vessel length * mean population vessel length]. Only data from the baseline CCTA were used. PV, PAV, and TAVnorm were compared between patients in the top quartile of BSA vs the remaining, and between sexes. Associations between vessel volume, BSA, and the three plaque burden methodologies were assessed. RESULTS: The study population comprised 1479 patients (age 60.7 +/- 9.3 years, 58.4% male) who underwent CCTA. A total of 17,649 coronary artery segments were evaluated with a median of 12 (IQR 11-13) segments per-patient (from a 16-segment coronary tree). Patients with a large BSA (top quartile), compared with the remaining patients, had a larger PV and TAVnorm, but similar PAV. The relation between larger BSA and larger absolute plaque volume (PV and TAVnorm) was mediated by the coronary vessel volume. Independent from the atherosclerotic cardiovascular disease risk (ASCVD) score, vessel volume correlated with PV (P < 0.001), and TAVnorm (P = 0.003), but not with PAV (P = 0.201). The three plaque burden methods were equally affected by sex. CONCLUSIONS: PAV was less affected by patient's body surface area then PV and TAVnorm and may be the preferred method to report coronary atherosclerotic burden.

[31] *Bair TL, May HT, Knowlton KU et al.* **Predictors of Statin Intolerance in Patients with a New Diagnosis of Atherosclerotic Cardiovascular Disease Within a Large Integrated Healthcare Institution: The IMPRES Study**. Journal of cardiovascular pharmacology 2020.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=32079856
***ABSTRACT***
Statins are among the most prescribed medications due to well-documented benefits of safely lowering LDL cholesterol. However, many patients are unable or unwilling to continue statin therapy because of real or perceived adverse effects. This study sought to increase understanding about which patients are unlikely to tolerate statin therapy. The Intermountain Healthcare electronic data repository was queried from January 1, 1999 to December 31, 2013 to identify all adults who survived their first encounter of coronary artery disease (CAD), cerebral vascular disease (CVD), or peripheral artery disease (PAD), and received statin therapy during follow-up. Statin intolerance (SI) was identified by documentation of clinician-noted intolerance or allergy or the use of pitavastatin. Patients were followed for >/=3 years or until death. Of the 48,997 patients evaluated, 3,049 (6.2%) were documented with SI. Of those with SI, 9.8% were prescribed a low, 73.4% moderate, and 16.8% high-intensity statin dose, respectively. After adjustment for covariables, significant predictors of SI were female sex (OR=1.47, p<0.0001), age (65-74 vs. <65: OR=1.15, p=0.002; >/=75 vs. <65: OR=0.90, p=0.03), hypertension (OR=1.11, p=0.01), hyperlipidemia (OR=1.31, p<0.0001), smoking (OR=0.88, p=0.001), renal failure (OR=1.20, p=0.009), heart failure (OR=1.26, p<0.0001), sleep apnea (OR=1.22, p<0.0001), prior malignancy (OR=1.18, p=0.007), depression (OR=1.13, p=0.04), and index ASCVD diagnosis (CAD vs. CVD: OR=1.71, p<0.0001; CAD vs. PAD: OR=1.23, p=0.02). In this study, the strongest identified clinical predictor of future SI was female sex. Many standard CV risk factors were also associated with SI, suggesting that patients with multiple comorbidities are more likely to be vulnerable.

[32] *Board C, Kelly MS, Shapiro MD, Dixon DL*. **PCSK9 inhibitors in secondary prevention - an opportunity for personalized therapy**. Journal of cardiovascular pharmacology 2020.

**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=32073537

***ABSTRACT***

Atherosclerotic cardiovascular disease (ASCVD) remains the leading cause of death worldwide. Low-density lipoprotein cholesterol (LDL-C) is the primary cause of ASCVD and reducing LDL-C levels with statin therapy significantly reduces ASCVD risk; however, significant residual risk remains. Two monoclonal antibodies (mAbs), alirocumab and evolocumab, that target proprotein convertase subtilisin/kexin-type 9 (PCSK9), reduce LDL-C levels by up to 60% when used in combination with statins and significantly reduce the risk of recurrent ASCVD events in both stable secondary prevention and acute coronary syndrome populations. Pre-specified analyses of recent randomized controlled trials have shed light on how best to prioritize these therapies to maximize their value in select high risk groups. These data have also informed recent clinical practice guidelines and scientific statements resulting in an expanded role for PCSK9-mAbs compared to previous guidelines, albeit there are notable differences between these recommendations. Ongoing research is exploring the long-term safety of PCSK9-mAbs and their role in the acute setting as well as patients without prior myocardial infarction or stroke. Novel therapies that inhibit PCSK9 synthesis via small interfering RNA, such as inclisiran, are also in development and may reduce LDL-C levels similar to PCSK9-mAbs but with less frequent administration. Nonetheless, the PCSK9-mAbs are a breakthrough therapy and warrant consideration in very-high risk patients who are most likely to benefit. Such a personalized approach can help to ensure cost-effectiveness and maximize their value.

[33] *Merolle L, Marraccini C, Latorrata A et al.* **Heparin-induced lipoprotein precipitation apheresis in dyslipidemic patients: A multiparametric assessment**. Journal of clinical apheresis 2020.

**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=32087045

***ABSTRACT***

Low-density lipoprotein (LDL) apheresis (LA) selectively eliminates lipoproteins containing apolipoprotein B 100 (ApoB100) on patients affected by severe dyslipidemia. In addition to lowering lipids, LA is thought to exert pleiotropic effects altering a number of other compounds associated with atherosclerosis, such as pro- and anti-inflammatory cytokines or pro-thrombotic factors. More knowledge needs to be gathered on the effects of LA, and particularly on its ability to modify blood components other than lipids. We performed a multiparametric assessment of the inflammatory, metabolic and proteomic profile changes after Heparin-induced lipoprotein precipitation (H.E.L.P.) apheresis on serum samples from nine dyslipidemic patients evaluating cholesterol and lipoproteins, plasma viscosity and density, metabolites, cytokines, PCSK9 levels and other proteins selectively removed after the treatment. Our results show that H.E.L.P. apheresis is effective in lowering lipoprotein and PCSK9 levels. Although not significantly, complement and inflammation-related proteins are also affected, indicating a possible transient epiphenomenon induced by the extracorporeal procedure.

[34] *Vella CA, Nelson MC, Unkart JT et al.* **Skeletal muscle area and density are associated with lipid and lipoprotein cholesterol levels: The Multi-Ethnic Study of Atherosclerosis**. Journal of clinical lipidology 2020.

**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=32061531

***ABSTRACT***

BACKGROUND: Loss of muscle mass with age may be a key player in metabolic dysregulation. We examined the associations between abdominal muscle area and density with lipids and lipoproteins. METHODS: One thousand eight hundred and sixty eight adults completed health history and physical activity questionnaires, provided venous blood samples for lipids and inflammatory biomarkers, and underwent computed tomography to quantify body composition. Associations between muscle area and density with multiple lipid measures were assessed with multivariable linear and logistic regression. RESULTS: The mean age and body mass index of participants was 65 years and 28 kg/m(2), respectively, and 50% were female. After adjustment for demographics, cardiovascular disease risk factors, lipid-lowering medications, physical activity, sedentary behavior, inflammatory biomarkers, and central obesity, a 1-standard deviation increase in total abdominal, stability, and locomotor muscle areas was associated with a 13%, 11%, and 8% lower high-density lipoprotein cholesterol level, respectively ($P < .05$). With similar adjustment, a 1-standard deviation increase in total abdominal and stability muscle area was associated with a 13% and 12% lower total cholesterol level, respectively ($P < .01$). Compared to the lowest quartiles of total, stability, and locomotor muscle area, those in the higher quartiles of muscle area had over a 40% reduction in the odds of triglyceride levels greater than 150 mg/dL ($P < .05$). Total abdominal muscle density was positively associated with total cholesterol ($P < .05$) but was not associated with the other lipid outcomes. CONCLUSION: Maintaining adequate skeletal muscle mass with age may decrease specific lipid levels related to hyperlipidemia and development of cardiometabolic disease.

[35] *Piper K, Garelnabi M*. **Eicosanoids: Atherosclerosis and cardiometabolic health**. Journal of clinical & translational endocrinology 2020; 19:100216.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=32071878
***ABSTRACT***
Cardiovascular diseases (CVD) have been the leading causes of death in the U.S. for nearly a century. Numerous studies have linked eicosanoids to cardiometabolic disease. Objectives and Methods: This review summaries recent advances and innovative research in eicosanoids and CVD. Numerous review articles and their original human or animal studies were assessed in the relevant and recent studies. Outcome: We identified and discussed recent trends in eicosanoids known for their roles in CVD. Their subsequent relationships were assessed for any possible implications associated with consumption of different dietary lipids, essentially omega fatty acids. Eicosanoids have been heavily sought after over recent decades for their direct role in mediating the enhancement and resolution of acute immune responses. Given the short half-life of these oxidized lipid metabolites, studies on atherosclerosis have had to rely on the metabolites that are actively involved in eicosanoid production, signaling or redox reactions as markers for atherosclerosis-related molecular behaviors. Conclusion: Further investigations expending current knowledge, should be applied to narrow the specific class and species of eicosanoids responsible for inciting inflammation especially in the context of recent clinical studies assessing the role of dietary lipid in cardiovascular diseases.

[36] *Gouni-Berthold I*. **Significant Quality of Life Improvement Observed in a Patient With FCS Associated With a Marked Reduction in Triglycerides**. Journal of the Endocrine Society 2020; 4:bvz035.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=32083235
***ABSTRACT***

Familial chylomicronemia syndrome (FCS) is a rare genetic disorder characterized by severely high triglycerides (TGs). It is associated with a marked increase in risk of recurrent, potentially fatal acute pancreatitis (AP), and symptoms including abdominal pain, fatigue, and anxiety that may substantially reduce quality of life (QoL). A 46-year-old woman with FCS and severely high TGs initially presented with necrotizing pancreatitis with pseudocysts, having previously experienced recurrent AP. The patient reported constant abdominal pain and fatigue, which were evident in her demeanor. Initial management included maximum doses of omega-3 fatty acids and fibrates, plus an extremely restricted diet (reduced intake: calories, fats, simple sugars; no alcohol). Despite adherence to all management strategies, TGs remained at approximately 2800 mg/dL (31.6 mmol/L) and symptoms persisted. The patient was enrolled in COMPASS, a phase 3, placebo-controlled trial to evaluate the effect of an investigational drug, volanesorsen, on fasting TGs in patients with hypertriglyceridemia (fasting TGs >/= 500 mg/dL [>/=5.7 mmol/L]). The woman, a confirmed FCS patient, continued into the open-label extension study, during which fasting TGs decreased to 146 mg/dL (1.7 mmol/L) following 4 months of treatment. The restrictive diet was maintained throughout treatment and no serious adverse events were reported. Along with sustained TG reduction, the patient experienced progressive, perceived improvements in observable QoL measures and a marked reduction in symptom severity and frequency. In a patient with FCS, reduction in TGs following volanesorsen therapy appeared to be associated with marked improvement in clinical symptoms and observed QoL.

[37] *Rossi A, Hoogeveen IJ, Bastek VB et al.* **Dietary lipids in glycogen storage disease type III: A systematic literature study, case studies, and future recommendations**. Journal of inherited metabolic disease 2020.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=32064649
***ABSTRACT***
A potential role of dietary lipids in the management of hepatic glycogen storage diseases (GSDs) has been proposed, but no consensus on management guidelines exists. The aim of this study was to describe current experiences with dietary lipid manipulations in hepatic GSD patients. An international study was set up to identify published and unpublished cases describing hepatic GSD patients with a dietary lipid manipulation. A literature search was performed according to the Cochrane Collaboration methodology through PubMed and EMBASE (up to December 2018). All delegates who attended the dietetics session at the IGSD2017, Groningen were invited to share unpublished cases. Due to multiple biases, only data on GSDIII were presented. A total of 28 cases with GSDIII and a dietary lipid manipulation were identified. Main indications were cardiomyopathy and/or myopathy. A high fat diet was the most common dietary lipid manipulation. A decline in creatine kinase concentrations (n = 19, P < .001) and a decrease in cardiac hypertrophy in paediatric GSDIIIa patients (n = 7, P < .01) were observed after the introduction with a high fat diet. This study presents an international cohort of GSDIII patients with different dietary lipid manipulations. High fat diet may be beneficial in paediatric GSDIIIa patients with cardiac hypertrophy, but careful long-term monitoring for potential complications is warranted, such as growth restriction, liver inflammation, and hepatocellular carcinoma development.

[38] *Pontremoli R, Bellizzi V, Bianchi S et al.* **Management of dyslipidaemia in patients with chronic kidney disease: a position paper endorsed by the Italian Society of Nephrology**. Journal of nephrology 2020.

**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=32065354

***ABSTRACT***

Chronic kidney disease (CKD) represents a major public health issue worldwide and entails a high burden of cardiovascular events and mortality. Dyslipidaemia is common in patients with CKD and it is characterized by a highly atherogenic profile with relatively low levels of HDL-cholesterol and high levels of triglyceride and oxidized LDL-cholesterol. Overall, current literature indicates that lowering LDL-cholesterol is beneficial for preventing major atherosclerotic events in patients with CKD and in kidney transplant recipients while the evidence is less clear in patients on dialysis. Lipid lowering treatment is recommended in all patients with stage 3 CKD or worse, independently of baseline LDL-cholesterol levels. Statin and ezetimibe are the cornerstones in the management of dyslipidaemia in patients with CKD, however alternative and emerging lipid-lowering therapies may acquire a central role in near future. This position paper endorsed by the Italian Society of Nephrology aims at providing useful information on the topic of dyslipidaemia in CKD and at assisting decision making in the management of these patients.

[39] *Calkins KL, Thamotharan S, Ghosh S et al.* **MicroRNA 122 Reflects Liver Injury in Children with Intestinal Failure-Associated Liver Disease Treated with Intravenous Fish Oil**. The Journal of nutrition 2020.

**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=32072161

***ABSTRACT***

BACKGROUND: There is evidence that microRNA (MIR) 122 is a biomarker for various liver diseases in adults and children. To date, MIR122 has not been explored in children with intestinal failure-associated liver disease (IFALD, or hyperbilirubinemia associated with prolonged parenteral nutrition). OBJECTIVES: This study's purpose was to investigate changes in plasma miR-122, correlate miR-122 with serum liver function tests and enzymes, and investigate changes in whole blood transcripts including miR-122 targets in a group of children with IFALD who received pure intravenous fish oil (FO) as a treatment for cholestasis. METHODS: This was a prospective, observational study that enrolled children with IFALD who received intravenous FO (1 g/kg/d) and whose cholestasis resolved with FO. Plasma miR-122 was measured using reverse transcription-quantitative real-time PCR, and whole blood miR-122 targets were quantified using RNA sequencing. RESULTS: Fourteen subjects with median age 6 mo (IQR: 3-65 mo) were enrolled. RNA sequence data were available for 4 subjects. When compared with the start of FO, median miR-122 concentrations at 6 mo of FO therapy decreased [1.0 (IQR: 1.0-1.0) compared with 0.04 (IQR: 0.01-0.6), P = 0.009]. At the start of FO, miR-122 correlated with conjugated bilirubin (r = 0.56; P = 0.038). At approximately 3 mo of FO, miR-122 correlated with conjugated bilirubin (r = 0.56; P = 0.045). Reactive oxygen species, heme metabolism, coagulation, adipogenesis, IL-6-Janus kinase-signal transducer and activator of transcription (JAK-STAT) 3, IL-2-STAT5, transforming growth factor-beta, TNF-alpha, inflammatory response, mammalian target of rapamycin gene families (normalized enrichment scores < -1.4), and miR-122 target genes were significantly downregulated with FO. CONCLUSIONS: In this small cohort of young children with IFALD, miR-122 decreased with FO therapy and correlated with conjugated bilirubin. Key pathways involving oxidation, inflammation, cellular differentiation, and nutrient regulation were downregulated. Data from this study provide information about IFALD and FO. This trial was registered at www.clinicaltrials.gov as NCT00969332.

**Literature update week 08 (2020)**

[40] *Yaghobee S, Panjnoush M, Rafiei SC et al.* **Effect of Simvastatin on Bone Regeneration: A Histologic and Histomorphometric Analysis**. Journal of oral and maxillofacial surgery : official journal of the American Association of Oral and Maxillofacial Surgeons 2020.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=32084353
***ABSTRACT***
PURPOSE: The purpose of the present study was to evaluate the efficacy of simvastatin administration as an osteoinductive agent combined with bovine bone material (BBM) for augmentation of human maxillary sinuses. MATERIALS AND METHODS: In the present randomized clinical trial with a split-mouth design, 24 maxillary sinuses in 12 patients were augmented using BBM alone or BBM combined with simvastatin. Biopsy samples were taken 9 months after maxillary sinus floor augmentation for histologic and histomorphometric analyses. A total of 44 implants were placed in the augmented bone. RESULTS: The results of the microscopic assessment of most samples revealed no inflammation or only mild chronic inflammation. Lamellation was detectable in old bone trabeculae under polarized light microscopy but was not observed in newly formed bone. Osteocytes were found with a lower frequency in the lacunae of newly formed bone compared with normal bone. No significant differences were found in the amount of newly formed bone and the amount of residual particles between the 2 groups. CONCLUSIONS: Despite the greater mean percentage of newly formed bone in the test group, the histomorphometric analysis results did not show a significant positive effect for the use of simvastatin in maxillary sinus augmentation.

[41] *Benekos T, Kosmeri C, Vlahos A, Milionis H*. **Nine-year overview of dyslipidemia management in children with heterozygous familial hypercholesterolemia: a university hospital outpatient lipid clinic project in Northwestern Greece**. J Pediatr Endocrinol Metab 2020.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=32084003
***ABSTRACT***
Background To assess the efficacy and safety of lipid-lowering treatment in children with heterozygous familial hypercholesterolemia (HeFH) aged </=12 years attending a tertiary hospital-based outpatient lipid clinic. Methods Data in 318 children from the University Hospital of Ioannina (Northwestern Greece) Outpatient Lipid Clinic Project for Children and Adolescents with Dyslipidemia from March 2009 to December 2018 were analyzed. We assessed the efficacy and safety treatment alongside any possible predictors of the achievement of the treatment target. Results Of 318 children with hyperlipidemia, 72 were diagnosed having HeFH based on clinical criteria and genetic confirmation. Compared with non-familial hypercholesterolemia (non-FH) children, those with FH had a higher occurrence of positive family history of premature cardiovascular disease, and higher levels of total, low-density lipoprotein-cholesterol (LDL-C), apolipoprotein B (apoB) and lipoprotein (a) (Lp(a)). Treatment regimens included either atorvastatin 10-20 mg/day, rosuvastatin 5-10 mg/day, pitavastatin 2-4 mg/day monotherapy or in combination with ezetimibe. The treatment goal of LDL-C (<135 mg/dL, 3.5 mmol/L) was achieved in 69% of children treated. The achievement of the treatment targets correlated positively with male sex and inversely with the Dutch Lipid Clinic Network Score, baseline total, LDL-C and apoB levels. No clinically significant changes in liver or muscle-related laboratory tests were reported; no effect on growth or sexual maturation was noted. Conclusions This study confirms that lipid-lowering treatment in HeFH children initiated in the setting of a specialized tertiary hospital-based outpatient lipid clinic is efficacious and safe. Children of male sex and low baseline lipid values had a better achievement of treatment target.

[42] *Shoman ME, Aboelez MO, Shaykhon MSA et al.* **New nicotinic acid-based 3,5-diphenylpyrazoles: design, synthesis and antihyperlipidemic activity with potential NPC1L1 inhibitory activity**. Molecular diversity 2020.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=32067133
***ABSTRACT***
Nicotinic acid hydrazide was incorporated into new 4,5-dihydro-5-hydroxy-3,5-diphenylpyrazol-1-yl derivatives. Compounds 6a-h were synthesized, and their antihyperlipidemic activity was evaluated in high cholesterol diet-fed rat model. Compounds 6e, 6f were found to decrease the levels of serum total cholesterol by 14-19% compared to control group. Total triglycerides were also reduced by 24-28% and LDL cholesterol by 16%. As expected from parent niacin, compounds 6e and 6f caused an elevation of HDL cholesterol by 33-41%. Docking study supported the ability of designed compounds to block NPC1L1 active site in a manner similar to that observed with ezetimibe.

[43] *Vitturi BK, Gagliardi RJ*. **The influence of statins on the risk of post-stroke epilepsy**. Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology 2020.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=32086686
***ABSTRACT***
BACKGROUND: Currently, statins are widely used for secondary prevention of stroke due to their pleiotropic neuroprotective effects. Epilepsy is a common complication of cerebrovascular diseases. The purpose of this study was to evaluate the effect of statin therapy on the occurrence of post-stroke epilepsy (PSE). METHODS: In this prospective cohort study, patients who suffered an ischemic stroke and without history of epilepsy before stroke were enrolled. At baseline, patients were classified according to the particularities of statin therapy. Statin use onset and adherence to treatment were registered as well. After a follow-up period of 1 year, we assessed the occurrence of seizures and PSE. RESULTS: Among the 477 patients included in our cohort, there were 91 (19.1%) patients without statins, 160 (33.5%) with simvastatin 20 mg, 180 (37.7%) with simvastatin 40 mg, and 46 (9.6%) with high-potency statins. Overall, PSE emerged in 53 (11.1%) patients. PSE was significantly more prevalent among those who did not receive statins and those with lower doses of simvastatin. Acute onset of statin use was associated with reduced odds of having PSE. CONCLUSION: Adequate treatment with statins after stroke may lower the risk of PSE.

[44] *Hayat M, Kerr R, Bentley AR et al.* **Genetic associations between serum low LDL-cholesterol levels and variants in LDLR, APOB, PCSK9 and LDLRAP1 in African populations**. PloS one 2020; 15:e0229098.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=32084179
***ABSTRACT***
Non-communicable diseases, including cardiovascular diseases (CVDs), are increasing in African populations. High serum low density lipoprotein cholesterol (LDL-cholesterol) levels are a known risk factor for CVDs in European populations, but the link remains poorly understood among Africans. This study investigated the associations between serum LDL-cholesterol levels and selected variants in the low density lipoprotein receptor (LDLR), apolipoprotein B (APOB), proprotein convertase subtilisin/kexin type 9 (PCSK9) and low density lipoprotein receptor adaptor protein 1 (LDLRAP1) genes in some selected African populations. Nineteen SNPs were selected from publicly available African

whole genome sequence data based on functional prediction and allele frequency. SNPs were genotyped in 1000 participants from the AWI-Gen, study selected from the extremes of LDL-cholesterol level distribution (500 with LDL-cholesterol>3.5 mmol/L and 500 with LDL-cholesterol<1.1 mmol/L). The minor alleles at five of the six associated SNPs were significantly associated (P<0.05) with lower LDL-cholesterol levels: LDLRAP1 rs12071264 (OR 0.56, 95% CI: 0.39-0.75, P = 2.73x10-4) and rs35910270 (OR 0.78, 95% CI: 0.64-0.94, P = 0.008); APOB rs6752026 (OR 0. 55, 95% CI: 0.41-0.72, P = 2.82x10-5); LDLR: rs72568855 (OR 0.47, 95% CI: 0.27-0.82, P = 0.008); and PCSK9 rs45613943 (OR = 0.72, 95% CI: 0.58-0.88, P = 0.001). The minor allele of the sixth variant was associated with higher LDL-cholesterol levels: APOB rs679899 (OR 1.41, 95% CI: 1.06-1.86, P = 0.016). A replication analysis in the Africa America Diabetes Mellitus (AADM) study found the PCSK9 variant to be significantly associated with low LDL-cholesterol levels (Beta = -0.10). Since Africans generally have lower LDL-cholesterol levels, these LDL-cholesterol associated variants may be involved in adaptation due to unique gene-environment interactions. In conclusion, using a limited number of potentially functional variants in four genes, we identified significant associations with lower LDL-cholesterol levels in sub-Saharan Africans.

[45] *Heo GS, Sultan D, Liu Y*. **Current and novel radiopharmaceuticals for imaging cardiovascular inflammation**. The quarterly journal of nuclear medicine and molecular imaging : official publication of the Italian Association of Nuclear Medicine (AIMN) [and] the International Association of Radiopharmacology (IAR), [and] Section of the So 2020.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=32077667
***ABSTRACT***
Cardiovascular disease (CVD) remains the leading cause of death worldwide despite advances in diagnostic technologies and treatment strategies. The underlying cause of most CVD is atherosclerosis, a chronic disease driven by inflammatory reactions. Atherosclerotic plaque rupture could cause arterial occlusion leading to ischemic tissue injuries such as myocardial infarction (MI) and stroke. Clinically, most imaging modalities are based on anatomy and provide limited information about the on-going molecular activities affecting the vulnerability of atherosclerotic lesion for risk stratification of patients. Thus, the ability to differentiate stable plaques from those that are vulnerable is an unmet clinical need. Of various imaging techniques, the radionuclide-based molecular imaging modalities including positron emission tomography (PET) and single-photon emission computerized tomography (SPECT) provide superior ability to noninvasively visualize molecular activities in vivo and may serve as a useful tool in tackling this challenge. Moreover, the well-established translational pathway of radiopharmaceuticals may also facilitate the translation of discoveries from benchtop to clinical investigation in contrast to other imaging modalities to fulfill the goal of precision medicine. The relationship between inflammation occurring within the plaque and its proneness to rupture has been well documented. Therefore, an active effort has been significantly devoted to develop radiopharmaceuticals specifically to measure CVD inflammatory status, and potentially elucidate those plaques which are prone to rupture. In the following review, molecular imaging of inflammatory biomarkers will be briefly discussed.

[46] *Vigne J, Hyafil F*. **Inflammation imaging to define vulnerable plaque or vulnerable patient**. The quarterly journal of nuclear medicine and molecular imaging : official publication of the Italian

Association of Nuclear Medicine (AIMN) [and] the International Association of Radiopharmacology (IAR), [and] Section of the So 2020.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=32077668
***ABSTRACT***
The role of nuclear imaging in the characterization of high risk atherosclerotic plaque is increasing thanks to its high sensitivity to detect radiopharmaceuticals signal in tissues. Currently, 2-deoxy-2-[18F]fluoro-D-glucose ([18F]FDG) is the most studied and widely used radiopharmaceutical for the molecular imaging of atherosclerotic plaques with positron emission tomography (PET). [18F]FDG PET is a valuable tool to non-invasively detect, monitor and quantify inflammatory processes occurring in atherosclerotic plaques. The aim of this review is to gather insights provided by [18F]FDG PET to better understand the role of inflammation in the definitions of the vulnerable plaque and the vulnerable patient. Alternatives radiopharmaceuticals targeting inflammation and other potential high risk plaque related processed are also discussed.

[47] *Amarenco P, Kim JS, Labreuche J et al.* **Benefit of Targeting a LDL (Low-Density Lipoprotein) Cholesterol <70 mg/dL During 5 Years After Ischemic Stroke**. Stroke 2020:Strokeaha119028718.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=32078484
***ABSTRACT***
Background and Purpose- The TST trial (Treat Stroke to Target) evaluated the benefit of targeting a LDL (low-density lipoprotein) cholesterol of <70 mg/dL to reduce the risk of cardiovascular events in 2860 patients with ischemic stroke with atherosclerotic stenosis of cerebral vasculature or aortic arch plaque >4 mm, in a French and Korean population. The follow-up lasted a median of 5.3 years in French patients (similar to the median follow-up time in the SPARCL trial [Stroke Prevention by Aggressive Reduction in Cholesterol Level]) and 2.0 years in Korean patients. Exposure duration to statin is a well-known driver for cardiovascular risk reduction. We report here the TST results in the French cohort. Methods- One thousand seventy-three French patients were assigned to <70 mg/dL (1.8 mmol/L) and 1075 to 100+/-10 mg/dL (90-110 mg/dL, 2.3-2.8 mmol/L). To achieve these goals, investigators used the statin and dosage of their choice and added ezetimibe on top if needed. The primary outcome was the composite of ischemic stroke, myocardial infarction, new symptoms requiring urgent coronary or carotid revascularization and vascular death. Results- After a median follow-up of 5.3 years, the achieved LDL cholesterol was 66 (1.69 mmol/L) and 96 mg/dL (2.46 mmol/L) on average, respectively. The primary end point occurred in 9.6% and 12.9% of patients, respectively (HR, 0.74 [95% CI, 0.57-0.94]; P=0.019). Cerebral infarction or urgent carotid revascularization following transient ischemic attack was reduced by 27% (P=0.046). Cerebral infarction or intracranial hemorrhage was reduced by 28% (P=0.023). The primary outcome or intracranial hemorrhage was reduced by 25% (P=0.021). Intracranial hemorrhages occurred in 13 and 11 patients, respectively (HR, 1.17 [95% CI, 0.53-2.62]; P=0.70). Conclusions- After an ischemic stroke of documented atherosclerotic origin, targeting a LDL cholesterol of <70 mg/dL during 5.3 years avoided 1 subsequent major vascular event in 4 (number needed to treat of 30) and no increase in intracranial hemorrhage. Registration- URL: https://www.clinicaltrials.gov. Unique identifier: NCT01252875.

[48] *Xiao P, Cheng H, Hou DQ et al.* **[A comparative study on diagnostic cut points of dyslipidemia in children and adolescents in China]**. Zhonghua liu xing bing xue za zhi = Zhonghua liuxingbingxue zazhi 2020; 41:62-67.

**Literature update week 08 (2020)**

**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=32062944

***ABSTRACT***

Objective: To compare the power of dyslipidemia diagnosis by different sets of cut points in the prediction of cardiovascular metabolic risk factors and identify the appropriate cut points for the diagnosis of dyslipidemia in children and adolescents in China. Methods: Data were obtained from the baseline survey of 'School-based Cardiovascular and Bone Health Promotion Program' in Beijing in 2017. Dyslipidemia was diagnosed by using two set of cut points. Receiver operating characteristic curve analysis was conducted to assess the power of dyslipidemia diagnosis by the two set of cut points to predict the prevalence of hypertension, obesity, high fat mass percentage and impaired fasting glucose. Results: A total of 14 390 children and adolescents were in included in the study. The prevalence rates of high TC, high LDL-C, low HDL-C, and high TG in the participants were 2.7%, 2.7%, 14.4%, and 3.7% according to 'Chinese Reference Standard', and 5.0%, 3.7%, 13.3%, and 3.5% according to 'China Expert Consensus'. Low HDL-C and high TG defined by the 'Chinese Reference Standard' had better performance for the prediction of high fat mass percentage and obesity in boys, but worse performance in girls ($P<0.001$). Conclusions: Using 'China Reference Standard' can increase the true positive rate in the prediction of obesity or high fat mass percentage in boys, and reduce the false positive rate in girls. The cut points for the diagnosis of dyslipidemia in Chinese children and adolescents need to be further validated by using national representative sample and in longitudinal study.