Literature update week 42 (2019)

[1] *Shen X, DiMario S, Philip K*. **Gender Disparities in Health Resource Utilization in Patients with Atherosclerotic Cardiovascular Disease: A Retrospective Cross-Sectional Study**. Adv Ther 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31625131
ABSTRACT
INTRODUCTION: Gender disparities in access to healthcare have been documented, including disparities in access to care for cardiovascular diseases (CVDs). Disparities in access to cardiologists could disadvantage some patients to the newer lipid-lowering proprotein convertase subtilisin/kexin type 9 inhibitor (PCSK9i) antibodies, as utilization management criteria for PCSK9is often require step therapy with statins and/or ezetimibe and prescription by a cardiologist. To assess whether these utilization management criteria disproportionally limit access to patients with certain characteristics, we assessed the use of cardiologist care and receipt of statin and/or ezetimibe prescriptions from a cardiologist by gender and other patient demographic and clinical characteristics. METHODS: This cross-sectional study used administrative claims data from Inovalon's Medical Outcomes Research for Effectiveness and Economics Registry (MORE(2) Registry((R))) for patients enrolled in commercial and Medicare Advantage healthcare plans from January 1, 2014, through December 31, 2014. Provider data from the registry were linked to individual demographic and administrative claims data. Logistic regression models were used to assess characteristics associated with outpatient visits to a cardiologist and receipt of a prescription for statin and/or ezetimibe from a cardiologist. RESULTS: Data from 39,322 patients in commercial plans and 261,898 patients with Medicare Advantage were analyzed. Female gender (vs male) was associated with a significantly lower likelihood of visiting a cardiologist for patients in commercial plans (odds ratio [OR] 0.85; 95% confidence limit [CL] 0.81-0.88) and in Medicare Advantage plans (OR 0.82; 95% CL 0.81-0.83). Female gender was also associated with a lower likelihood of receiving a statin and/or ezetimibe prescription from a cardiologist for patients in commercial plans (OR 0.69; 95% CL 0.65-0.74) and in Medicare Advantage plans (OR 0.78; 95% CL 0.76-0.79). CONCLUSIONS: Compared with men, women were less likely to visit a cardiologist and less likely to receive a prescription for a statin and/or ezetimibe from a cardiologist. FUNDING: Amgen Inc.

[2] *D'Erasmo L, Di Costanzo A, Cassandra F et al.* **Spectrum of Mutations and Long-Term Clinical Outcomes in Genetic Chylomicronemia Syndromes**. Arteriosclerosis, thrombosis, and vascular biology 2019:Atvbaha119313401.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31619059
ABSTRACT
OBJECTIVE: Familial chylomicronemia syndrome (FCS) and multifactorial chylomicronemia syndrome (MCS) are the prototypes of monogenic and polygenic conditions underlying genetically based severe hypertriglyceridemia. These conditions have been only partially investigated so that a systematic comparison of their characteristics remains incomplete. We aim to compare genetic profiles and clinical outcomes in FCS and MCS. Approach and Results: Thirty-two patients with severe hypertriglyceridemia (triglyceride >1000 mg/dL despite lipid-lowering treatments with or without history of acute pancreatitis) were enrolled. Rare and common variants were screened using a panel of 18 triglyceride-raising genes, including the canonical LPL, APOC2, APOA5, GP1HBP1, and LMF1. Clinical information was collected

retrospectively for a median period of 44 months. Across the study population, 37.5% were classified as FCS due to the presence of biallelic, rare mutations and 59.4% as MCS due to homozygosity for nonpathogenic or heterozygosity for pathogenic variants in canonical genes, as well as for rare and low frequency variants in noncanonical genes. As compared with MCS, FCS patients showed a lower age of hypertriglyceridemia onset, higher levels of on-treatment triglycerides, and 3-fold higher incidence rate of acute pancreatitis. CONCLUSIONS: Our data indicate that the genetic architecture and natural history of FCS and MCS are different. FCS expressed the most severe clinical phenotype as determined by resistance to triglyceride-lowering medications and higher incidence of acute pancreatitis episodes. The most common genetic abnormality underlying FCS was represented by biallelic mutation in LPL while APOA5 variants, in combination with high rare polygenic burden, were the most frequent genotype of MCS.

[3] *Sutton NR, Bouis D, Mann KM et al.* **CD73 Promotes Age-Dependent Accretion of Atherosclerosis**. Arteriosclerosis, thrombosis, and vascular biology 2019:Atvbaha119313002.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31619062
ABSTRACT
OBJECTIVE: CD73 is an ectonucleotidase which catalyzes the conversion of AMP to adenosine. Adenosine has been shown to be anti-inflammatory and vasorelaxant. The impact of ectonucleotidases on age-dependent atherosclerosis remains unclear. Our aim was to investigate the role of CD73 in age-dependent accumulation of atherosclerosis. Approach and results: Mice doubly deficient in CD73 and ApoE (apolipoprotein E; (cd73(-)(/-)/apoE(-/-)) were generated, and the extent of aortic atherosclerotic plaque was compared with apoE(-/-) controls at 12, 20, 32, and 52 weeks. By 12 weeks of age, cd73(-/-)/apoE(-/-) mice exhibited a significant increase in plaque (1.4+/-0.5% of the total vessel surface versus 0.4+/-0.1% in apoE(-/-) controls, P<0.005). By 20 weeks of age, this difference disappeared (2.9+/-0.4% versus 3.3+/-0.7%). A significant reversal in phenotype emerged at 32 weeks (9.8+/-1.2% versus 18.3+/-1.4%; P<0.0001) and persisted at the 52 week timepoint (22.4+/-2.1% versus 37.0+/-2.1%; P<0.0001). The inflammatory response to aging was found to be comparable between cd73(-/-)/apoE(-/-) mice and apoE(-/-) controls. A reduction in lipolysis in CD73 competent mice was observed, even with similar plasma lipid levels (cd73(-/-)/apoE(-/-) versus apoE(-/-) at 12 weeks [16.2+/-0.7 versus 9.5+/-1.4 nmol glycerol/well], 32 weeks [24.1+/-1.5 versus 7.4+/-0.4 nmol/well], and 52 weeks [13.8+/-0.62 versus 12.7+/-2.0 nmol/well], P<0.001). CONCLUSIONS: At early time points, CD73 exerts a subtle antiatherosclerotic influence, but with age, the pattern reverses, and the presence of CD73 promoted suppression of lipid catabolism.

[4] *Fassaert LMM, Timmerman N, van Koeverden ID et al.* **Preoperative hypertension is associated with atherosclerotic intraplaque hemorrhage in patients undergoing carotid endarterectomy**. Atherosclerosis 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31610883
ABSTRACT
BACKGROUND AND AIMS: Both hypertension and atherosclerotic plaque characteristics such as intraplaque hemorrhage (IPH) are associated with cardiovascular events (CVE). It is unknown if hypertension is associated with IPH. Therefore, we studied if hypertension is associated with

unstable atherosclerotic plaque characteristics in patients undergoing carotid endarterectomy (CEA). METHODS: Prospectively collected data of CEA-patients (2002-2014) were retrospectively analyzed. Blood pressure (BP) was the mean of 3 preoperative measurements. Preoperative hypertension was defined as systolic BP>/=160mmHg. Post-CEA, carotid atherosclerotic plaques were analyzed for the presence of calcifications, collagen, smooth muscle cells, macrophages, lipid core, IPH and microvessel density. Associations between BP (systolic and diastolic), patient characteristics and carotid plaque characteristics were assessed with univariate and multivariate analyses with correction for potential confounders. Results were replicated in a cohort of patients that underwent iliofemoral endarterectomy. RESULTS: Within CEA-patients (n=1684), 708 (42%) had preoperative hypertension. Increased systolic BP was associated with the presence of plaque calcifications (adjusted OR1.11 [95% CI 1.01-1.22], p=0.03), macrophages (adjusted OR1.12 [1.04-1.21], p < 0.01), lipid core >10% of plaque area (adjusted OR1.15 [1.05-1.25], p < 0.01), IPH (adjusted OR1.12 [1.03-1.21], p=0.01) and microvessels (adjusted beta 0.04 [0.00-0.08], p=0.03). Increased diastolic BP was associated with macrophages (adjusted OR1.36 [1.17-1.58], p < 0.01), lipid core (adjusted OR1.29 [1.10-1.53], p < 0.01) and IPH (adjusted OR1.25 [1.07-1.46], p < 0.01) but not with microvessels nor plaque calcifications. Replication in an iliofemoral-cohort (n=657) showed that increased diastolic BP was associated with the presence of macrophages (adjusted OR1.78 [1.13-2.91], p=0.01), lipid core (adjusted OR1.45 [1.06-1.98], p=0.02) and IPH (adjusted OR1.48 [1.14-1.93], p < 0.01). CONCLUSIONS: Preoperative hypertension in severely atherosclerotic patients is associated with the presence of carotid plaque macrophages, lipid core and IPH. IPH, as a plaque marker for CVE, is associated with increased systolic and diastolic BP in both the CEA and iliofemoral population.

[5] *Marie Hougaard Christensen M, Bruun Haastrup M, Ohlenschlaeger T et al.* **Interaction Potential between Clarithromycin and Individual Statins - a Systematic Review**. Basic & clinical pharmacology & toxicology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31628882

ABSTRACT

The high prevalence of statin and clarithromycin utilization creates potential for overlapping use. The objectives of this MiniReview were to investigate the evidence base for drug-drug interactions between clarithromycin and currently marketed statins and to present management strategies for these drug combinations. We conducted a systematic literature review following PRISMA guidelines with English language studies retrieved from PubMed and EMBASE (from inception through March 2019). We included 29 articles (16 case reports, 5 observational, 5 clinical pharmacokinetic and 3 in vitro studies). Based on mechanistic/clinical studies involving clarithromycin or the related macrolide erythromycin (both strong inhibitors of CYP3A4 and of hepatic statin uptake transporters OATP1B1 and OATP1B3), clarithromycin is expected to substantially increase systemic exposure to simvastatin and lovastatin (>5-fold increase in area under the plasma concentration time curve (AUC)), moderately increase AUCs of atorvastatin and pitavastatin (2-4-fold AUC increase) and slightly increase pravastatin exposure (approximately 2-fold AUC increase) while having little effect on fluvastatin or rosuvastatin. The 16 cases of statin-clarithromycin adverse drug reactions (rhabdomyolysis (n = 14) or less severe clinical myopathy) involved a CYP3A4-metabolized statin (simvastatin,

lovastatin or atorvastatin). In line, a cohort study found concurrent use of clarithromycin and CYP3A4-metabolized statins to be associated with a doubled risk of hospitalisation with rhabdomyolysis or other statin-related adverse events as compared with azithromycin-statin co-administration. If clarithromycin is necessary, we recommend 1) avoiding co-administration with simvastatin, lovastatin or atorvastatin; 2) withholding or dose-reducing pitavastatin; 3) continuing pravastatin therapy with caution, limiting pravastatin dose to 40 mg daily and 4) continuing fluvastatin or rosuvastatin with caution.

[6] *Hashizume-Takizawa T, Yamaguchi Y, Kobayashi R et al.* **Oral challenge with Streptococcus sanguinis induces aortic inflammation and accelerates atherosclerosis in spontaneously hyperlipidemic mice**. Biochem Biophys Res Commun 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31610917
ABSTRACT
Atherosclerosis is exacerbated by periodontal pathogens, which induce vascular inflammation after entering the bloodstream. Among oral indigenous bacteria, Streptococcus sanguinis and S. anginosus are related to systemic disorders, such as infective endocarditis and abscess, and are sometimes detected in human atherosclerotic plaques or blood. Thus, these oral streptococci may contribute to the progression of atherosclerosis. To test this hypothesis, apolipoprotein E-deficient spontaneously hyperlipidemic mice were intraorally challenged with S. sanguinis or S. anginosus. Atherosclerotic plaque formation increased significantly in the S. sanguinis-challenged group compared with the carboxymethylcellulose-treated control group. Expression levels of mRNAs of proinflammatory cytokines in the aorta and levels of atherosclerosis-related mediators in blood increased upon S. sanguinis challenge. Adaptor molecule TNF receptor-associated factor 6 was also enhanced in the aorta when mice were challenged with S. sanguinis. Furthermore, challenge with S. anginosus induced systemic inflammation, but inflammation-related mRNA expression levels in the aorta only increased slightly and were accompanied by minimal expansion of the lesion area. By contrast, with the exception of IL-1alpha, the expression levels of inflammation-related genes did not change in gingival tissues of both bacteria- and sham-challenged groups. These results reveal that S. sanguinis causes aortic inflammation that leads to accelerated progression of atherosclerosis.

[7] *Kim YH, Jang WG, Oh SH et al.* **Fenofibrate induces PPARalpha and BMP2 expression to stimulate osteoblast differentiation**. Biochem Biophys Res Commun 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31607484
ABSTRACT
The peroxisome proliferator-activated receptor (PPAR)-alpha agonist fenofibrate is used as a lipid-lowering agent to reduce cholesterol and triglyceride in blood. In this study, we investigated whether fenofibrate affects osteoblast differentiation of osteogenic precursor cells. Quantitative real-time PCR and alkaline phosphatase (ALP) staining assays revealed that fenofibrate can enhance the osteoblast differentiation of C3H10T1/2 and MC3T3-E1 cells. In contrast with fenofibrate, the PPARgamma agonist rosiglitazone decreased or did not affect the expression of osteogenic genes in these cells. Fenofibrate dose- and time-dependently increased PPARalpha expression, and concomitantly increased the expression of bone morphogenetic protein 2 (BMP2). Knockdown of PPARalpha abolished fenofibrate-induced

BMP2 expression, activity of the BMP2 promoter gene, and calcium deposition. The chromatin immunoprecipitation assay demonstrated that fenofibrate increased BMP2 expression by inducing direct binding of PPARalpha to the BMP2 promoter region. Taken together, we suggest that fenofibrate has a stimulatory effect on osteoblast differentiation via the elevation of PPARalpha levels and the PPARalpha-mediated BMP2 expression. Our findings provide fenofibrate as a useful agent for controlling hypercholesterolemic patients with osteoporosis.

[8] *Shao L, Bai Y, Wang Q et al.* **Design, synthesis and evaluation of 5-(4-hydroxyphenyl)-3H-1,2-dithiole-3-thione-Based fibrates as potential hypolipidemic and hepatoprotective agents**. Bioorganic & medicinal chemistry letters 2019:126723.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31624042
ABSTRACT
Six novel target compounds 5-(4-hydroxyphenyl)-3H-1,2-dithiole-3-thione (ADT) based fibrates were synthesized and evaluated. All the synthesized compounds were preliminarily screened by using the Triton WR-1339-induecd hyperlipidemia model, in which T1 exhibited more potent hypolipidemic property than positive drug fenofibrate (FF). T1 also significantly decreased serum triglycerides (TG), total cholesterol (TC) and low density lipoprotein cholesterin (LDL) in methionine solution (Mets) induced hyperlipidemic mice. Moreover, hepatic transaminases (AST and ALT) were obviously ameliorated after treatment with T1 and the histological observation indicated that T1 ameliorated the injury in liver tissue and inhibited the hepatic lipid accumulation. In the livers of T1-administrated rat, the levels of PPARalpha related to lipids metabolism were up-regulated. Additional effects such as antioxidant, anti-inflammatory and H2S releasing action confirmed and reinforced the activity of T1 as a potential multifunctional hypolipidemic and hepatoprotective agent.

[9] *Teixeira RS, Arriaga MB, Terse-Ramos R et al.* **Higher values of triglycerides:HDL-cholesterol ratio hallmark disease severity in children and adolescents with sickle cell anemia**. Brazilian journal of medical and biological research = Revista brasileira de pesquisas medicas e biologicas / Sociedade Brasileira de Biofisica ... [et al.] 2019; 52:e8833.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31618296
ABSTRACT
Dyslipidemia has been described in sickle cell anemia (SCA) but its association with increased disease severity is unknown. Here, we examined 55 children and adolescents with SCA as well as 41 healthy controls to test the association between the lipid profiles in peripheral blood and markers of hemolysis, inflammation, endothelial function, and SCA-related clinical outcomes. SCA patients exhibited lower levels of total cholesterol (P<0.001), low-density lipoprotein cholesterol (LDL-c) (P<0.001), and high-density lipoprotein cholesterol (HDL-c) (P<0.001), while displaying higher triglyceride (TG) levels and TG/HDL-c ratio values (P<0.001). TG/HDL-c values were positively correlated with lactate dehydrogenase (P=0.047), leukocyte count (P=0.006), and blood flow velocity in the right (P=0.02) and left (P=0.05) cerebral artery, while being negatively correlated with hemoglobin levels (P<0.04). Acute chest syndrome (ACS) and vaso-occlusive events (VOE) were more frequent in SCA patients exhibiting higher TG/HDL-c values (odds ratio: 3.77, P=0.027). Multivariate logistic regression analysis confirmed independent associations between elevated TG/HDL-c values and SCA. Thus, children and adolescents with

SCA exhibited a lipid profile associated with hemolysis and inflammatory parameters, with increased risk of ACS and VOE. TG/HDL-c is a potential biomarker of severity of disease.

[10] *Li Q, Wang H, Peng H et al.* **Exosomes: Versatile Nano Mediators of Immune Regulation**. Cancers 2019; 11.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31615107
ABSTRACT
One of many types of extracellular vesicles (EVs), exosomes are nanovesicle structures that are released by almost all living cells that can perform a wide range of critical biological functions. Exosomes play important roles in both normal and pathological conditions by regulating cell-cell communication in cancer, angiogenesis, cellular differentiation, osteogenesis, and inflammation. Exosomes are stable in vivo and they can regulate biological processes by transferring lipids, proteins, nucleic acids, and even entire signaling pathways through the circulation to cells at distal sites. Recent advances in the identification, production, and purification of exosomes have created opportunities to exploit these structures as novel drug delivery systems, modulators of cell signaling, mediators of antigen presentation, as well as biological targeting agents and diagnostic tools in cancer therapy. This review will examine the functions of immunocyte-derived exosomes and their roles in the immune response under physiological and pathological conditions. The use of immunocyte exosomes in immunotherapy and vaccine development is discussed.

[11] *Cano Cevallos EJ, Shaikh DH, Gonzalez J et al.* **Tendon rupture associated with concomitant simvastatin and gemfibrozil use: Biological and pharmacokinetic implications**. Clinical case reports 2019; 7:1919-1922.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31624609
ABSTRACT
Tendon or muscle rupture is a rare complication of statins that could potentially be disabling and result in a significant burden to patients. The co-administration of statin and gemfibrozil should warrant prescribers' awareness of tendon-related complications of statin use, particularly in high-risk populations with poor renal function or musculoskeletal comorbidities.

[12] *Packard CJ*. **Strategies to alter the trajectory of atherosclerotic cardiovascular disease**. Current opinion in lipidology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31609725
ABSTRACT
PURPOSE OF REVIEW: Cardiovascular disease prevention trials of lipid lowering with statins have shown unexpected long-term benefits after the formal randomized treatment stopped. This finding needs further exploration because it raises the possibility that the trajectory of the disease can be modified. RECENT FINDINGS: Extended follow up data are now available from further major primary prevention studies and from meta-analyses of the legacy effect of statin trials. New outcome studies have been proposed and launched to test the ability of early intervention to slow or regress atherosclerosis. SUMMARY: Legacy effects are apparent in trials of LDL lowering in hypercholesterolemic and hypertensive patient cohorts. Over follow up periods of decades, both cardiovascular mortality and all-cause mortality are reduced in

individuals who received 3 to 5 years of statin therapy. The phenomenon is observed also in studies of intensive glycemic control suggesting that it is possible to impact plaque development with long-term beneficial consequences. Novel strategies for primary prevention are being devised that include the early use of both prolonged-moderate and short-term aggressive LDL lowering.

[13] *Kim J, Lee JY, Ham NS et al.* **Association Between Carotid Ultrasonography Findings and Colorectal Adenoma in Asymptomatic Adults**. Digestive diseases and sciences 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31624981
ABSTRACT
BACKGROUND: Coexistence of colorectal neoplasia and atherosclerotic cardiovascular disease has been reported. Subclinical atherosclerosis can be evaluated noninvasively and easily by assessing carotid intima-media thickness (CIMT) and carotid plaque using ultrasonography. AIMS: We aimed to evaluate the association between carotid ultrasonography findings and colorectal conventional adenoma (AD) in health checkup examinees. METHODS: We retrospectively reviewed the medical records of health checkup examinees >/= 40 years old who had undergone both carotid ultrasonography and colonoscopies at a single hospital between January 2012 and December 2016. RESULTS: The median age of 4871 eligible participants was 54 years (range, 40-89). AD was found in 2009 individuals (41.2%), with a mean number of 1.9 +/- 1.7 lesions. Abnormal CIMT (>/= 1 mm) and carotid plaque were found in 1366 (28.0%) and 1255 (25.8%) individuals, respectively. AD and high-risk adenoma (HRA) were observed more frequently in those with abnormal CIMT or plaque. Moreover, abnormal CIMT and plaque were independent risk factors for the presence of AD (odds ratio [OR]: 1.21, 95% confidence interval [CI]: 1.06-1.39, P = 0.006; OR: 1.24, 95% CI: 1.08-1.43, P = 0.002) and HRA (OR: 1.24, 95% CI: 1.05-1.52, P = 0.034; OR: 1.35, 95% CI: 1.10-1.65, P = 0.004), respectively. CONCLUSIONS: Abnormal CIMT and the presence of carotid plaque were significantly associated with AD and HRA, and each was an independent risk factor for AD and HRA. More careful observation might be needed during colonoscopies in individuals with abnormal carotid ultrasonographic findings.

[14] *Riaz H, Khan SU, Lateef N et al.* **Residual Inflammatory Risk After Contemporary Lipid Lowering Therapy**. European heart journal. Quality of care & clinical outcomes 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31609450
ABSTRACT

[15] *Lee HY, Lee EG, Hur J et al.* **Pravastatin alleviates allergic airway inflammation in obesity-related asthma mouse model**. Experimental lung research 2019:1-13.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31608695
ABSTRACT
Background: Obesity is one of the factors associated with severe, uncontrolled asthma. The effect of pravastatin on asthmatic airway inflammation in obesity has not been evaluated. Methods: C57BL/6 mice were fed a high-fat diet (HFD) to induce obesity with or without ovalbumin (OVA) sensitization and challenge. Pravastatin was administered intraperitoneally during the OVA treatment. Airway inflammation and airway hyper-responsiveness (AHR) were

analyzed and lung tissues were examined. The changes in mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase (PI3K)/Akt signaling pathways were measured in the lung tissues. Results: HFD with OVA sensitization and challenge exacerbated eosinophilic and neutrophilic airway inflammation and increased AHR compared to lean asthma mice. The levels of cytokines examined in bronchoalveolar lavage fluid (BALF) revealed that the expressions of IL-4, 5, and 17 were elevated in the obese asthmatic group and decreased after pravastatin treatment, indicating that both the Th2 and Th17 pathways were stimulated by HFD-induced obesity and OVA challenge and suppressed by pravastatin treatment. Moreover, the serum leptin and adiponectin ratio was elevated only in obese asthmatic mice and decreased with pravastatin administration. Pravastatin successfully alleviated the airway inflammation of lung tissues and AHR in both obese and lean asthmatic mice, however, treatment with pravastatin had no effects on BALF cell counts and cytokines in lean asthma mice. In lung tissues, the phosphorylation of p38 MAPK was significantly decreased in lean as well as obese asthmatic mice. Conclusions: Pravastatin treatment in obese asthmatic mice suppressed allergic airway infiltration and AHR by inhibition of Th2 and Th17-associated signaling pathways, decreasing the leptin expression and downstream p38 MAPK signaling pathways. The effect on lean asthmatic mice was different, independent of airway cell counts and cytokines.

[16] *Iqbal Z, Dhage S, Mohamad JB et al.* **Efficacy and safety of PCSK9 monoclonal antibodies**. Expert opinion on drug safety 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31623472
ABSTRACT
Introduction: Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are novel drugs that have been developed since the discovery of the PCSK9 protein in 2003. In addition to background statin treatment they reduce low density lipoprotein cholesterol (LDL-C) to unprecedented levels and have shown encouraging results in improving cardiovascular events. Concerns regarding the safety of PCSK9 inhibitors and very low LDL-C have somewhat been allayed after several longer-term prospective studies. Areas covered: A comprehensive literature search was carried out including article searches in electronic databases (EMBASE, PUBMED, OVID) and reference lists of relevant articles. This review examines novel research concerning PCSK9 monoclonal antibodies and cardiovascular outcomes with a special focus on their safety and tolerability. The safety of very low LDL-C concentrations and the link between LDL-C lowering and diabetes is also discussed. Expert opinion: PCSK9 monoclonal antibodies when added to background statin therapy, lowers LDL-C to previously unattainable levels. This is safe with little undesirable effects and impacts positively on cardiovascular disease. Current guidance limits their use to primary prevention. Cost effectiveness should be taken into consideration before allowing a wider use of this new class of cholesterol lowering therapy and more data on their long-term safety is welcome.

[17] *Li X, Bi X, Wang S et al.* **Therapeutic Potential of omega-3 Polyunsaturated Fatty Acids in Human Autoimmune Diseases**. Frontiers in immunology 2019; 10:2241.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31611873
ABSTRACT

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The recognition of omega-3 polyunsaturated acids (PUFAs) as essential fatty acids to normal growth and health was realized more than 80 years ago. However, the awareness of the long-term nutritional intake of omega-3 PUFAs in lowering the risk of a variety of chronic human diseases has grown exponentially only since the 1980s (1, 2). Despite the overwhelming epidemiological evidence, many attempts of using fish-oil supplementation to intervene human diseases have generated conflicting and often ambiguous outcomes; null or weak supporting conclusions were sometimes derived in the subsequent META analysis. Different dosages, as well as the sources of fish-oil, may have contributed to the conflicting outcomes of intervention carried out at different clinics. However, over the past decade, mounting evidence generated from genetic mouse models and clinical studies has shed new light on the functions and the underlying mechanisms of omega-3 PUFAs and their metabolites in the prevention and treatment of rheumatoid arthritis, systemic lupus erythematosus (SLE), multiple sclerosis, and type 1 diabetes. In this review, we have summarized the current understanding of the effects as well as the underlying mechanisms of omega-3 PUFAs on autoimmune diseases.

[18] *Cai P, Zhong W, Wang Y, Wang X*. **Effects of white-coat, masked and sustained hypertension on coronary artery stenosis and cardiac arrhythmia**. Hypertension research : official journal of the Japanese Society of Hypertension 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31624353
ABSTRACT
This study aimed to investigate whether hypertension phenotypes such as white-coat hypertension (WCHT), diagnosed with the addition of nighttime blood pressure (BP) criteria, are related to coronary artery stenosis (CAS) and cardiac arrhythmia. In this cross-sectional observational study, 844 participants who did not use antihypertensive, lipid-lowering, and antiplatelet drugs were selected. The subjects were divided into normotensive (NT), WCHT, masked hypertension (MHT), and sustained hypertension (SHT) groups based on the results of clinic BP measurement and ambulatory BP monitoring. Coronary angiography and ambulatory electrocardiography were performed to determine the participants' CAS and cardiac arrhythmia status. Coronary angiography revealed 556 patients with CAS and 288 participants with normal coronary arteries. The chi-squared test showed that the incidence of CAS was higher in the MHT and SHT groups than in the NT group, while no significant change was found in the WCHT group ($P = 0.003$, $P < 0.001$, $P = 0.119$). The logarithm of the Gensini score was used to compare the degree of CAS between the groups. Multiple linear regression analysis showed that the degree of CAS was higher in the WCHT, MHT, and SHT groups than in the NT group ($P < 0.05$). The incidences of frequent atrial premature beats, atrial tachycardia, and ventricular cardiac arrhythmia were significantly higher in the WCHT and SHT groups than in the NT group, while only ventricular cardiac arrhythmia changes were observed in the MHT group. This study found that hypertension phenotypes such as WCHT were closely associated with CAS and cardiac arrhythmia.

[19] *Li Y, Zhu G, Ding V et al.* **Carotid Artery Imaging Is More Strongly Associated With the 10-Year Atherosclerotic Cardiovascular Disease Score Than Coronary Artery Imaging**. Journal of computer assisted tomography 2019; 43:679-685.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31609291

ABSTRACT
PURPOSE: The aim of this study was to compare coronary and carotid artery imaging and determine which one shows the strongest association with atherosclerotic cardiovascular disease (ASCVD) score. PATIENTS AND METHODS: Two separate series patients who underwent either coronary computed tomography angiography (CTA) or carotid CTA were included. We recorded the ASCVD scores and assessed the CTA imaging. Two thirds were used to build predictive models, and the remaining one third generated predicted ASCVD scores. The Bland-Altman analysis analyzed the concordance. RESULTS: A total of 110 patients were included in each group. There was no significant difference between clinical characteristics. Three imaging variables were included in the carotid model. Two coronary models (presence of calcium or Agatston score) were created. The bias between true and predicted ASCVD scores was 0.37 +/- 5.72% on the carotid model, and 2.07 +/- 7.18% and 2.47 +/- 7.82% on coronary artery models, respectively. CONCLUSIONS: Both carotid and coronary artery imaging features can predict ASCVD score. The carotid artery was more associated to the ASCVD score than the coronary artery.

[20] *Lytrivi M, Anne-Laure C, Poitout V, Cnop M*. **Recent insights into mechanisms of beta-cell lipo- and glucolipotoxicity in type 2 diabetes**. Journal of molecular biology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31628942
ABSTRACT
The deleterious effects of chronically elevated free fatty acid (FFA) levels on glucose homeostasis are referred to as lipotoxicity, and the concurrent exposure to high glucose may cause synergistic glucolipotoxicity. Lipo- and glucolipotoxicity have been studied for over 25 years. Here, we review the current evidence supporting the role of pancreatic beta-cell lipo- and glucolipotoxicity in type 2 diabetes, including lipid-based interventions in humans, prospective epidemiological studies and human genetic findings. In addition to total FFA quantity, the quality of FFAs (saturation and chain length) is a key determinant of lipotoxicity. We discuss in vitro and in vivo experimental models to investigate lipo- and glucolipotoxicity in beta-cells and describe experimental pitfalls. Lipo- and glucolipotoxicity adversely affect many steps of the insulin production and secretion process. The molecular mechanisms underpinning lipo- and glucolipotoxic beta-cell dysfunction and death comprise endoplasmic reticulum stress, oxidative stress and mitochondrial dysfunction, impaired autophagy and inflammation. Crosstalk between these stress pathways exists at multiple levels and may aggravate beta-cell lipo- and glucolipotoxicity. Lipo- and glucolipotoxicity are therapeutic targets as several drugs impact the underlying stress responses in beta-cells, potentially contributing to their glucose-lowering effects in type 2 diabetes.

[21] *Toghi M, Bitarafan S*. **Simvastatin Therapy in Multiple Sclerosis Patients with Respect to Gut Microbiome-Friend or Foe?** Journal of neuroimmune pharmacology : the official journal of the Society on NeuroImmune Pharmacology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31628587
ABSTRACT

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[22] *Wang L, Tao L, Hao L et al.* **A Moderate-Fat Diet with One Avocado per Day Increases Plasma Antioxidants and Decreases the Oxidation of Small, Dense LDL in Adults with Overweight and Obesity: A Randomized Controlled Trial**. The Journal of nutrition 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31616932

ABSTRACT

BACKGROUND: Avocados are a nutrient-dense source of MUFAs and are rich in antioxidants. Avocados have an additional LDL cholesterol (LDL-C) lowering effect beyond that observed when their MUFAs are substituted for SFAs, especially on small, dense LDL (sdLDL) particles, which are susceptible to in vivo oxidation and associated with increased risk of cardiovascular disease (CVD). OBJECTIVES: We investigated whether a healthy diet with 1 avocado daily decreased the following secondary outcomes: circulating oxidized LDL (oxLDL) and related oxidative stress markers. METHODS: A randomized, crossover, controlled feeding trial was conducted with 45 men and women, aged 21-70 y, with overweight or obesity and elevated LDL-C (25th-90th percentile). Three cholesterol-lowering diets were provided (5 wk each) in random sequences: a lower-fat (LF) diet (24% calories from fat-7% SFAs, 11% MUFAs, 6% PUFAs) and 2 moderate-fat (MF) diets (34% calories from fat-6% SFAs, 17% MUFAs, 9% PUFAs): the avocado (AV) diet included 1 Hass avocado (approximately 136 g) per day, and the MF diet used high oleic acid oils to match the fatty acid profile of 1 avocado. A general linear mixed model was used to analyze the treatment effects. RESULTS: Compared with baseline, the AV diet significantly decreased circulating oxLDL (-7.0 U/L, -8.8%, P = 0.0004) and increased plasma lutein concentration (19.6 nmol/L, 68.7%, P < 0.0001), and both changes differed significantly from that after the MF and LF diets (P </= 0.05). The change in oxLDL caused by the AV diet was significantly correlated with the changes in the number of sdLDL particles (r = 0.32, P = 0.0002) but not large, buoyant LDL particles. CONCLUSIONS: One avocado a day in a heart-healthy diet decreased oxLDL in adults with overweight and obesity, and the effect was associated with the reduction in sdLDL. This trial was registered at http://www.clinicaltrials.gov as NCT01235832.

[23] *Mundal LJ, Hovland A, Igland J et al.* **Association of Low-Density Lipoprotein Cholesterol With Risk of Aortic Valve Stenosis in Familial Hypercholesterolemia**. JAMA cardiology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31617858

ABSTRACT

Importance: Aortic valve stenosis (AS) is the most common valve disease. Elevated levels of low-density lipoprotein (LDL) cholesterol are a risk factor; however, lipid-lowering treatment seems not to prevent progression of AS. The importance of LDL cholesterol in the development of AS thus remains unclear. People with familial hypercholesterolemia (FH) have elevated LDL cholesterol levels from birth and until lipid-lowering treatment starts. Thus, FH may serve as a model disease to study the importance of LDL cholesterol for the development of AS. Objective: To compare the incidence of AS per year in all genetically proven patients with FH in Norway with the incidence of these diseases in the total Norwegian population of about 5 million people. Design, Setting, and Participants: This is a registry-based prospective cohort study of all Norwegian patients with FH with regard to first-time AS between 2001 and 2009. All genotyped patients with FH in Norway were compared with the total Norwegian populations through linkage with the Cardiovascular Disease in Norway project and the Norwegian Cause of Death Registry regarding occurrence of first-time AS. Data were analyzed between January 1, 2018,

and December 31, 2018. Main Outcomes and Measures: Standardized incidence ratios. Results: In total, 53 cases of AS occurred among 3161 persons (1473 men [46.6%]) with FH during 18300 person-years of follow-up. Mean age at inclusion and at time of AS were 39.9 years (range, 8-91 years) and 65 years (range, 44-88 years), respectively. Total standardized incidence ratios were 7.9 (95% CI, 6.1-10.4) for men and women combined, 8.5 (95% CI, 5.8-12.4) in women, and 7.4 (95% CI, 5.0-10.9) in men, respectively, indicating marked increased risk of AS compared with the general Norwegian population. Conclusions and Relevance: In this prospective registry study, we demonstrate a marked increase in risk of AS in persons with FH.

[24] *Pose E, Napoleone L, Amin A et al.* **Safety of two different doses of simvastatin plus rifaximin in decompensated cirrhosis (LIVERHOPE-SAFETY): a randomised, double-blind, placebo-controlled, phase 2 trial**. The lancet. Gastroenterology & hepatology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31607677

ABSTRACT

BACKGROUND: Statins have beneficial effects on intrahepatic circulation and decrease portal hypertension and rifaximin modulates the gut microbiome and might prevent bacterial translocation in patients with cirrhosis. Therefore, this drug combination might be of therapeutic benefit in patients with decompensated cirrhosis. However, there is concern regarding the safety of statins in patients with decompensated cirrhosis. We assessed the safety of two different doses of simvastatin, in combination with rifaximin, in patients with decompensated cirrhosis. METHODS: We did a double-blind, randomised, placebo-controlled, phase 2 trial in patients with decompensated cirrhosis and moderate-to-severe liver failure from nine university hospitals in six European countries (Italy, France, Holland, Germany, the UK, and Spain). Patients older than 18 years with Child-Pugh class B or C disease were eligible. We randomly assigned patients (1:1:1) to receive either simvastatin 40 mg/day plus rifaximin 1200 mg/day, simvastatin 20 mg/day plus rifaximin 1200 mg/day, or placebo of both medications for 12 weeks. Randomisation was stratified according to Child-Pugh class (B vs C) and restricted using blocks of multiples of three. The primary endpoint was development of liver or muscle toxicity, as defined by changes in liver aminotransferases (aspartate aminotransferase [AST] and alanine aminotransferase [ALT]), alkaline phosphastase, and creatine kinase. The study is registered with the European Union Clinical Trials Register, 2016-004499-23, and with ClinicalTrials.gov, NCT03150459. FINDINGS: The study recruitment period was between July 28, 2017, and Jan 2, 2018. Follow-up finished on March 12, 2018. 50 patients were randomly assigned to simvastatin 40 mg/day plus rifaximin 1200 mg/day (n=18), simvastatin 20 mg/day plus rifaximin 1200 mg/day (n=16), or placebo of both medications (n=16). Six patients (two from each group) were excluded. Therefore, the full analysis set included 44 patients (16 in the simvastatin 40 mg/day plus rifaximin 1200 mg/day group, 14 in the simvastatin 20 mg/day plus rifaximin mg/day group, and 14 in the placebo group). After a safety analyses when the first ten patients completed treatment, treatment was stopped prematurely in the simvastatin 40 mg/day plus rifaximin group due to recommendations by the data safety monitoring board. Patients in the simvastatin 40 mg/day plus rifaximin group showed a significant increase in AST and ALT compared with the placebo group (mean differences between the groups at the end of treatment for AST 130 IU/L [95% CI 54 to 205; p=0.0009] and for ALT 61 IU/L [22 to 100; p=0.0025]. We observed no significant differences at

12 weeks in AST and ALT between the simvastatin 20 mg/day plus rifaximin and placebo group (for AST -14 IU/L [-91 to 64; p=0.728] and for ALT -8 IU/L [-49 to 33; p=0.698]). We observed no significant differences in alkaline phosphatase between the the simvastatin 40 mg/day plus rifaximin or the simvastatin 20 mg/day plus rifaximin groups compared with placebo. Patients in the simvastatin 40 mg/day plus rifaximin group showed an increase in creatine kinase at the end of treatment compared with patients in the placebo group (1009 IU/L [208 to 1809]; p=0.014). We observed no significant changes in creatine kinase in the simvastatin 20 mg/day plus rifaximin group (4.2 IU/L [-804 to 813]; p=0.992). Three (19%) patients in the simvastatin 40 mg/day group developed liver and muscle toxicity consistent with rhabdomyolysis. The number of patients who stopped treatment because of adverse events was significantly higher in the simvastatin 40 mg/day plus rifaximin group (nine [56%] of 16 patients) compared with the other two groups (two [14%] of 14 for both groups; p=0.017). There were no serious unexpected adverse reactions reported during the study. INTERPRETATION: Treatment with simvastatin 40 mg/day plus rifaximin in patients with decompensated cirrhosis was associated with a significant increase in adverse events requiring treatment withdrawal, particularly rhabdomyolysis, compared with simvastatin 20 mg/day plus rifaximin. We recommend simvastatin 20 mg/day as the dose to be used in studies investigating the role of statins in patients with decompensated cirrhosis. FUNDING: Horizon 20/20 European programme.

[25] *Simon TG*. **When less is more: dosing simvastatin in decompensated cirrhosis**. The lancet. Gastroenterology & hepatology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31607676
ABSTRACT

[26] *O'Keefe EL, Harris WS, DiNicolantonio JJ et al.* **Sea Change for Marine Omega-3s: Randomized Trials Show Fish Oil Reduces Cardiovascular Events**. Mayo Clinic proceedings 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31627938
ABSTRACT
Recently, 3 large randomized controlled trials (RCTs) have assessed the effects of supplementation with marine omega-3 fatty acids on the occurrence of cardiovascular disease (CVD) events. We reviewed this evidence and considered it in the context of the large and growing body of data on the CV health effects of marine omega-3s. One RCT examining 8179 patients, most with coronary heart disease (CHD), reported that 4 grams/day of a highly purified omega-3 product containing eicosapentaenoic acid (EPA) reduced the risk for major adverse CV events by 25% (P<.001). Two other recent RCTs in primary prevention populations showed that approximately 1 gram/day of purified fish oil containing 840 mg/day of EPA and docosahexaenoic acid (DHA) significantly reduced risks of CHD and CV death, especially in individuals who did not consume fish and seafood frequently. The American Heart Association (AHA) continues to emphasize the importance of marine omega-3s as a nutrient for potentially reducing risks of congestive heart failure, CHD, ischemic stroke, and sudden cardiac death. Marine omega-3s should be used in high doses for patients with CHD on statins who have elevated triglycerides and in primary prevention for individuals who do not consume at least 1.5 fish or seafood meals per week.

[27] *Luirink IK, Wiegman A, Kusters DM et al.* **20-Year Follow-up of Statins in Children with Familial Hypercholesterolemia**. The New England journal of medicine 2019; 381:1547-1556.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31618540

ABSTRACT

BACKGROUND: Familial hypercholesterolemia is characterized by severely elevated low-density lipoprotein (LDL) cholesterol levels and premature cardiovascular disease. The short-term efficacy of statin therapy in children is well established, but longer follow-up studies evaluating changes in the risk of cardiovascular disease are scarce. METHODS: We report a 20-year follow-up study of statin therapy in children. A total of 214 patients with familial hypercholesterolemia (genetically confirmed in 98% of the patients), who were previously participants in a placebo-controlled trial evaluating the 2-year efficacy and safety of pravastatin, were invited for follow-up, together with their 95 unaffected siblings. Participants completed a questionnaire, provided blood samples, and underwent measurements of carotid intima-media thickness. The incidence of cardiovascular disease among the patients with familial hypercholesterolemia was compared with that among their 156 affected parents. RESULTS: Of the original cohort, 184 of 214 patients with familial hypercholesterolemia (86%) and 77 of 95 siblings (81%) were seen in follow-up; among the 214 patients, data on cardiovascular events and on death from cardiovascular causes were available for 203 (95%) and 214 (100%), respectively. The mean LDL cholesterol level in the patients had decreased from 237.3 to 160.7 mg per deciliter (from 6.13 to 4.16 mmol per liter) - a decrease of 32% from the baseline level; treatment goals (LDL cholesterol <100 mg per deciliter [2.59 mmol per liter]) were achieved in 37 patients (20%). Mean progression of carotid intima-media thickness over the entire follow-up period was 0.0056 mm per year in patients with familial hypercholesterolemia and 0.0057 mm per year in siblings (mean difference adjusted for sex, -0.0001 mm per year; 95% confidence interval, -0.0010 to 0.0008). The cumulative incidence of cardiovascular events and of death from cardiovascular causes at 39 years of age was lower among the patients with familial hypercholesterolemia than among their affected parents (1% vs. 26% and 0% vs. 7%, respectively). CONCLUSIONS: In this study, initiation of statin therapy during childhood in patients with familial hypercholesterolemia slowed the progression of carotid intima-media thickness and reduced the risk of cardiovascular disease in adulthood. (Funded by the AMC Foundation.).

[28] *Rohde D, Gaynor E, Large M et al.* **Cognitive impairment and medication adherence post-stroke: A five-year follow-up of the ASPIRE-S cohort**. PloS one 2019; 14:e0223997.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31622438

ABSTRACT

BACKGROUND: Control of vascular risk factors is essential for secondary stroke prevention. However, adherence to secondary prevention medications is often suboptimal, and may be affected by cognitive impairment. Few studies to date have examined associations between cognitive impairment and medication adherence post-stroke, and none have considered whether adherence to secondary prevention medications might affect subsequent cognitive function. The aim of this study was to explore prospective associations between cognitive impairment and medication non-adherence post-stroke. METHODS: A five-year follow-up of

108 stroke survivors from the Action on Secondary Prevention Interventions and Rehabilitation in Stroke (ASPIRE-S) prospective observational cohort study. Cognitive function was assessed using the Montreal Cognitive Assessment at 6 months, and a neuropsychological test battery at 5 years. Adherence to antihypertensive, antithrombotic and lipid-lowering medications was assessed using prescription refill data. RESULTS: The prevalence of cognitive impairment at five years was 35.6%. The prevalence of non-adherence ranged from 15.1% for lipid-lowering agents to 30.2% for antithrombotics. There were no statistically significant associations between medication non-adherence in the first year post-stroke and cognitive impairment at 5 years, nor between cognitive impairment at 6 months and non-adherence at 5 years. Stroke survivors with cognitive impairment were significantly more likely to report receiving help with taking medications [OR (95% CI): 4.84 (1.17, 20.07)]. CONCLUSIONS: This is the first study to explore the potential impact of non-adherence to secondary prevention medications on cognitive impairment in stroke survivors. Findings highlight the role of family members and caregivers in assisting stroke survivors with medication administration, particularly in the context of deficits in cognitive function. Involving family members and caregivers may be a legitimate and cost-effective strategy to improve medication adherence in stroke survivors.

[29] *Aranow C, Cush J, Bolster MB et al.* **A double-blind, placebo-controlled, phase II, randomized study of lovastatin therapy in the treatment of mildly active rheumatoid arthritis**. Rheumatology (Oxford, England) 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31628482
ABSTRACT
OBJECTIVES: 3-hydroxy-3-methylglutaryl coenzyme-A (HMG Co-A) reductase inhibitors (statins) are standard treatment for hyperlipidaemia. In addition to lipid-lowering abilities, statins exhibit multiple anti-inflammatory effects. The objectives of this study were to determine whether treatment of patients with RA with lovastatin decreased CRP or reduced disease activity. METHODS: We conducted a randomized double-blind placebo-controlled 12 week trial of lovastatin vs placebo in 64 RA patients with mild clinical disease activity but an elevated CRP. The primary efficacy end point was the reduction in mean log CRP. Secondary end points included disease activity, RF and anti-CCP antibody titres. Mechanistic end points included levels of serum cytokines. Safety was assessed; hepatic and muscle toxicities were of particular interest. RESULTS: Baseline features were similar between groups. No significant difference in mean log CRP reduction between the two groups was observed, and disease activity did not change from baseline in either treatment group. Mechanistic analyses did not reveal significant changes in any biomarkers. A post hoc analysis of subjects not using biologic therapy demonstrated a significantly greater proportion achieving 20% reduction in CRP from baseline in the lovastatin group compared with placebo (P-value = 0.007). No difference was observed in subjects receiving biologics. Lovastatin was well tolerated with no serious safety concerns. CONCLUSION: This study showed no anti-inflammatory or clinical effects on RA disease activity after 12 weeks of treatment with lovastatin. Lovastatin had a modest effect on CRP in subjects not using biologics, suggesting statins may be anti-inflammatory in selected patients. TRIAL REGISTRATION: ClinicalTrials.gov, http://clinicaltrials.gov, NCT00302952.

[30] *Alqarni A, Mitchell TW, McGorry PD et al.* **Supplementation with the omega-3 long chain polyunsaturated fatty acids: Changes in the concentrations of omega-3 index, fatty acids and molecular phospholipids of people at ultra high risk of developing psychosis**. Schizophrenia research 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31606244
ABSTRACT
Omega-3 long chain polyunsaturated fatty acids (n-3 LCPUFA) are necessary for optimum mental health, with recent studies showing low n-3 LCPUFA in people at ultra-high risk (UHR) of developing psychosis. Furthermore, people at UHR of psychosis had increased erythrocyte sphingomyelin (SM) and reduced phosphatidylethanolamine (PE) concentrations as well as 27 erythrocyte phospholipid species that differed when compared to erythrocytes from age matched people not at UHR of psychosis. The aim of this analysis was to evaluate the effect of n-3 supplementation on the different erythrocyte lipid species (including SM and PE concentrations) in people at UHR of psychosis. Participants were randomly assigned to fish oil (containing 840mg EPA and 560mg DHA per day) or placebo (paraffin oil) for 6months. Fasted blood samples were taken at baseline and post intervention. Mass spectrometry was used to analyse the molecular phospholipids and fatty acid composition of erythrocytes for both groups. The n-3 index was significantly increased from 3.0% to 4.12% after 6months of receiving n-3 capsules. Fish oil capsules increased the phospholipid molecular species containing n-3 LCPUFA, and concomitant decreases in n-6 LCPUFA species. SM species did not show any significant changes in n-3 LCPUFA group however, three SM species (SM 16:0, SM 18:0, SM 18:1) significantly increased after 6months of supplementation with placebo. N-3 supplementation for 6months led to higher n-3 incorporation into erythrocytes, at the expense of n-6 PUFA across all phospholipid classes analyzed and may have prevented the increase in SM seen in the placebo group.

[31] Singh G, Correa R. Fibrate Medications. In: StatPearls. Treasure Island (FL): StatPearls Publishing
StatPearls Publishing LLC.; 2019.
[32] *Cho S, Kang TS*. **Multi-vessel intractable coronary spasm development in a patient with aborted sudden cardiac death: a case study with intravascular ultrasound findings**. Yeungnam University journal of medicine 2018; 35:121-126.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31620582
ABSTRACT
Coronary spasm generally occurs in patients with minimal atherosclerotic plaque lesion, and it has a rather favorable prognosis. However, in some cases, coronary spasm may induce myocardial infarction and even sudden cardiac death (SCD). Here, we report a case in which multi-vessel intractable coronary vasospasm suddenly occurred in a diffuse atherosclerotic lesion after percutaneous coronary intervention (PCI) in a patient with aborted SCD. We identified the characteristics of the spasm portion in intravascular ultrasound (IVUS) images and conducted percutaneous cardiopulmonary bypass support-PCI with stenting as treatment. Intima and media thickening and a large attenuated plaque burden with rupture were identified in IVUS images at the obstructive spasm portion.

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