Literature update week 52 (2019)

[1] *Wu C, Xi C, Tong J et al.* **Design, synthesis, and biological evaluation of novel tetrahydroprotoberberine derivatives (THPBs) as proprotein convertase subtilisin/kexin type 9 (PCSK9) modulators for the treatment of hyperlipidemia**. Acta pharmaceutica Sinica. B 2019; 9:1216-1230.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31867167
ABSTRACT
Proprotein convertase subtilisin/kexin type 9 (PCSK9) modulators may attenuate PCSK9-induced low-density lipoprotein receptor (LDLR) degradation in lysosome and promote the clearance of circulating low-density lipoprotein cholesterol (LDL-C). A novel series of tetrahydroprotoberberine derivatives (THPBs) were designed, synthesized, and evaluated as PCSK9 modulators for the treatment of hyperlipidemia. Among them, eight compounds exhibited excellent activities in downregulating hepatic PCSK9 expression better than berberine in HepG2 cells. In addition, five compounds 15, 18, 22, (R)-22, and (S)-22 showed better performance in the low-density lipoprotein, labeled with 1,1'-dioctadecyl-3,3,3',3'-tetramethyl-indocarbocyanine perchlorate (DiI-LDL) uptake assay, compared with berberine at the same concentration. Compound 22, selected for in vivo evaluation, demonstrated significant reductions of total cholesterol (TC) and LDL-C in hyperlipidemic hamsters with a good pharmacokinetic profile. Further exploring of the lipid-lowering mechanism showed that compound 22 promoted hepatic LDLR expression in a dose-dependent manner in HepG2 cells. Additional results of human ether-a-go-go related gene (hERG) inhibition assay indicated the potential druggability for compound 22, which is a promising lead compound for the development of PCSK9 modulator for the treatment of hyperlipidemia.

[2] *Youn T, Al'Aref SJ, Narula N et al.* **(18)F-NaF PET/CT in Ex Vivo Human Coronary Arteries With Histological Correlation**. Arteriosclerosis, thrombosis, and vascular biology 2019:Atvbaha119312737.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31875701
ABSTRACT
OBJECTIVE: (18)F-NaF PET activity correlates with high-risk plaque. We examined the correlation between (18)F-NaF PET activity and extent of calcification (microcalcification and macrocalcification) in coronary arteries. Approach and Results: Eighteen ex vivo human coronary arteries were imaged with (18)F-NaF PET/CT, and target to background ratios were analyzed from 101 plaques. Histopathologic analysis evaluated for microcalcification and macrocalcification, plaque morphology, and inflammation. Plaques with microcalcification demonstrated higher (18)F-NaF PET activity (n=84; mean target to background ratio+/-SD, 9.0+/-9.7,) than plaques without microcalcification (n=17, 2.9+/-3.8; P<0.0001). Higher (18)F-NaF PET activity was associated with advanced plaques characterized by fibroatheroma (n=54, 10.7+/-10.3) compared with plaques with intimal thickening (n=22, 3.5+/-3.9) or pathological intimal thickening (n=25, 6.1+/-8.4; P=0.004). No significant association was found between (18)F-NaF PET activity and inflammation (P=0.08). CONCLUSIONS: In ex vivo human coronary arteries, higher (18)F-NaF PET activity was associated with microcalcification and advanced plaque morphology. Since microcalcification and fibroatheromas are high-risk plaque features, (18)F-NaF PET/CT may improve risk-stratification.

[3] *Alkhalil M*. **Effects of intensive lipid-lowering therapy on mortality after coronary bypass surgery: A meta-analysis of 7 randomised trials**. Atherosclerosis 2019; 293:75-78.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31865057

ABSTRACT
BACKGROUND AND AIMS: The recent reported analysis from the ODYSSEY OUTCOMES trial showed that patients with previous coronary bypass graft surgery (CABG) had enhanced clinical benefits in response to intensive low-density lipoprotein-cholesterol (LDL-c). Nonetheless, the impact on cardiovascular and all-cause mortality was difficult to ascertain given the relatively small number. METHODS: We conducted a meta-analysis investigating the role of more versus less intensive lipid-lowering treatment, taking into consideration the difference in studies duration when reporting treatment effect. RESULTS: A significant 14% reduction in deaths from any cause [RR 0.86 (95% CI, 0.74 to 0.99)] and 25% reduction in cardiovascular mortality [RR 0.75, (95% CI, 0.65 to 0.86)] were associated with intensive LDL-c reduction in patients post CABG. Importantly, this reduction was apparent in patients who were stable or developed an acute coronary syndrome following CABG. CONCLUSIONS: Patients with previous CABG incurred reduction in all-cause mortality and particularly cardiovascular mortality in response to intensive LDL-c reduction. Patient's clinical presentation following CABG did not modulate the associated benefits with intensive LDL-c reduction. Characterising atherosclerotic disease may help identify other high-risk groups who may benefit maximally from additional lipid-lowering therapies.

[4] *Toth EL, Clarke JD, Csanaky IL, Cherrington NJ*. **Interaction of Oatp1b2 Expression and Nonalcoholic Steatohepatitis on Pravastatin Plasma Clearance**. Biochem Pharmacol 2019:113780.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31881192
ABSTRACT
The downregulation of hepatic uptake transporters, including those of the OATP family, are a well known consequence of nonalcoholic steatohepatitis (NASH). Prior studies have shown that the combination of NASH and Oatp1b2 knockout synergistically reduces the clearance of pravastatin (PRAV) in the methionine and choline deficient (MCD) mouse model of NASH, and the current study therefore aimed to determine the impact of NASH and genetic heterozygosity of Oatp1b2 on PRAV clearance, modeling the overlap between the 24% of the human population who are heterozygous for non-functioning OATP1B1, and the approximately 15% with NASH, potentially placing these people at higher risk of statin-induced myopathy. Therefore, male C57BL/6 wild-type (WT), Oatp1b2+/- (HET), and Oatp1b2-/- (KO) mice were fed either a control (methionine and choline sufficient) or methionine and choline-deficient (MCD) diet to induce NASH. After six weeks of feeding, pravastatin was administered via the carotid artery. Blood and bile samples were collected throughout 90 minutes after PRAV administration. The concentration of PRAV in plasma, bile, liver, kidney, and muscle was determined by liquid chromatography-tandem mass spectrometry. MCD diet did not alter the plasma AUC values of PRAV in either WT or HET mice. However, the MCD diet increased plasma AUC by 4.4-fold in KO mice. MCD diet and nonfunctional Oatp1b2 synergistically increased not only plasma AUC but also the extrahepatic tissue concentration of pravastatin, whereas the partially decreased function of Oatp1b2 and NASH together were insufficient in significantly altering PRAV pharmacokinetics. These data suggest that a single copy of fully functional OATP1B1 in NASH patients may be sufficient to avoid the increase of pravastatin toxicity.

[5] *Costantine MM*. **Pravastatin to ameliorate early-onset pre-eclampsia: promising but not there yet**. BJOG : an international journal of obstetrics and gynaecology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31869519

ABSTRACT

[6] *Parveen K, Siddiqui WA, Arif JM et al.* **Evaluation of vegetables and fish oils for the attenuation of diabetes complications**. Cell Mol Biol (Noisy-le-grand) 2019; 65:38-45.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31880516
ABSTRACT
The present study was accomplished to examine and compare the effect of specific antioxidant-rich oils on hyperglycemia, dyslipidemia, renal function markers and oxidative renal damage in diabetic rats for four weeks. Papaya (P), olive (O), fenugreek (Fe), bitter gourd (B) and fish (Fi) oils were used for this purpose. Streptozotocin (STZ) was injected intraperitoneally in a single dose to induce diabetes. All oils were given orally at a dose of 3g/kg for four weeks in respective group after induction of diabetes. After treatment with oils, blood was collected, and their kidneys were stored. The level of fasting blood glucose (FBG), glycated hemoglobin (HbA1c), total cholesterol (TC), triglycerides (TG), low-density lipoprotein-cholesterol (LDL-C) and very low-density lipoprotein-cholesterol (VLDL-C) increased while amylase and high-density lipoprotein cholesterol (HDL-C) level decreased in the diabetic rats. These changes were augmented by fenugreek, bitter gourd and olive oils treatment. Diabetic rats showed elevated renal function markers in serum, including, serum creatinine (Scr), blood urea nitrogen (BUN) and alkaline phosphatase (ALP), which were restrained significantly by fenugreek and bitter gourd oil treatment. Moreover, fenugreek and bitter gourd oils treatment significantly modulated the level of thiobarbituric reactive substances (TBARS), malonaldehyde (MDA) and catalase (CAT) in the kidney of diabetic rats. The histopathological examination also showed the protective effect of these oils. The study suggests that vegetable oils are effective in reducing hyperglycemia, dyslipidemia and renal damage related to the side effects of diabetes. Thus they may have therapeutic value for preventing diabetes side effects and may be included in oil diet treatment synergically. Thus, our data suggest that oils as potent antidiabetic agent and beneficial in the control of diabetes-related abnormalities such as hyperglycemia, dyslipidemia and renal damage of STZ induced rat model of type 2 diabetes. Our study also supports the suggestion that synergistic possibilities exist concerning the use of these oils in the treatment of diabetes mellitus.

[7] *Ma X, Liu S, Li T, Yuan H*. **Intensive statin treatment ameliorate the Th17/Treg functional imbalance in patients with non-ST elevation acute coronary syndrome underwent percutaneous coronary intervention**. Clinical cardiology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31872906
ABSTRACT
BACKGROUND: Inflammation plays important roles in the pathogenesis of acute coronary syndrome (ACS). Statins exert positive effects on the plaque stabilization through anti-inflammation, however, the detailed mechanism is still under investigation. HYPOTHESIS: Studies suggest that the Th17/Treg functional imbalance takes key part in the plaque destabilization and the onset of ACS. We hypothesized that intensive statin therapy could ameliorate the Th17/Treg imbalance in patients with ACS. METHODS: Sixty-six patients with non-ST elevation acute coronary syndrome (NSTE-ACS) were randomized to conventional group and intensive group. Peripheral blood samples were collected on admission and after atorvastatin treatment. The frequencies of circulating Th17 cells and Treg cells, the levels of cytokines associated with Th17 cells (IL-17, IL-6 and IL-23) and associated with Treg cells (IL-10 and TGF-beta1) were measured through flow cytometry and ELISA assay respectively. RESULTS: One

week after therapy, the frequencies of circulating Th17 cells of both the groups decreased and the frequencies of circulating Treg cells increased significantly, compared with the basal levels. Furthermore, the decreased frequencies of circulating Th17 cells and the increased frequencies of circulating Treg cells in the intensive group were significantly higher than those in the conventional group. In consistence, the decreased accumulation of IL-17, IL-6 and IL-23 (cytokines relevant to Th17 cells) and the increased accumulation of IL-10 and TGF-beta1 in peripheral blood were displayed in both groups. The changes are more significant in the intensive group. CONCLUSION: Intensive statins therapy could ameliorate the Th17 and Treg functional imbalance in patients with ACS.

[8] *Kuwabara Y, Yasuno S, Kasahara M et al.* **The association between uric acid levels and renal function of CKD patients with hyperlipidemia: a sub-analysis of the ASUCA trial**. Clinical and experimental nephrology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31875936
ABSTRACT
BACKGROUND: The influence of uric acid (UA) on renal function and the significance of UA-lowering therapy are unclear. The purpose of the sub-analysis of the Assessment of Clinical Usefulness in chronic kidney disease patients with Atorvastatin (ASUCA) trial was to evaluate the influence of serum UA levels on renal function in Japanese chronic kidney disease patients with hyperlipidemia. METHODS: Of 344 participants in the ASUCA trial, 279 participants whose UA levels at both baseline and 24 months were available were included. Based on UA level at baseline or mean UA level during the trial period, they were divided into four groups: < 5.0, 5.0-6.0, 6.0-7.0, or >/= 7.0 mg/dL, irrespective of allocation. Changes in the estimated glomerular filtration rate (eGFR) after 24 months were compared among the groups in relation to baseline or mean UA levels. RESULTS: For baseline UA levels (< 5.0, 5.0-6.0, 6.0-7.0, or >/= 7.0 mg/dL), the change in eGFR after 24 months was - 1.32 +/- 10.3, - 1.74 +/- 8.94, - 2.53 +/- 7.34, and - 3.51 +/- 9.10 mL/min/1.73 m(2), respectively. A negative correlation between changes in eGFR after 24 months and baseline UA level was observed with adjustment for confounding factors. The relationship between changes in eGFR and mean UA levels during trial period showed a similar trend. CONCLUSION: In CKD patients with dyslipidemia, hyperuricemia was an independent risk factor for CKD progression. An ongoing clinical trial (TARGET-UA, UMIN-ID 000,026,741) may reveal the significance of strict UA-lowering therapy in CKD patients.

[9] *Frias JP, Koren MJ, Loizeau V et al.* **The SYDNEY Device Study: A Multicenter, Randomized, Open-Label Usability Study of a 2-mL Alirocumab Autoinjector Device**. Clinical therapeutics 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31879033
ABSTRACT
PURPOSE: The proprotein convertase subtilisin/kexin type 9 inhibitor alirocumab has produced significant reductions in LDL-C at a dose of 300 mg q4w administered as 2 separate 150-mg injections via a 1-mL autoinjector (AI). A recently developed 2-mL device (SYDNEY) permits the administration of a single 300mg dose of alirocumab. METHODS: We assessed the usability and product technical complaints (PTCs) reported by patients using the 2-mL SYDNEY device in unsupervised settings, adverse events, and effects on LDL-C, in a multicenter, randomized, open-label, 16-week study conducted in the United States. For their first dose, 69 patients with hypercholesterolemia despite receiving statin with or without other lipid-lowering therapy randomly received supervised, self-administered alirocumab 300 mg via 1 x 300 mg injection with the SYDNEY device (n = 35) or 2 x 150-mg injections

with the currently approved AI (n = 34). All continuing patients subsequently received unsupervised, self-administered alirocumab 300 mg q4w using the SYDNEY device at weeks 4, 8, and 12. The primary end point was the proportion of SYDNEY device-associated PTCs related to the use of the unsupervised injections. FINDINGS: Baseline characteristics between the study arms varied only in a higher percentage of males being randomized to the study arm using the SYDNEY device (74.3%) compared with the AI arm (44.1%). A single PTC was reported during the unsupervised injections (0.5%; 1 of 196 injections; 95% CI, 0.0%-3.2%). This event was classified as patient related as opposed to device related. No PTCs occurred during supervised injections. Mean LDL-C reductions from baseline at week 4 were 66.2% with SYDNEY and 51.2% with the AI; after adjustment for sex differences between groups, mean LDL-C reductions were 63.5% and 53.9%, respectively. LDL-C reductions persisted for 16 weeks. The most common adverse event was upper respiratory tract infection (3 with SYDNEY and 0 with the AI during weeks 0-4). IMPLICATIONS: The SYDNEY device allowed for a single 2-mL injection of alirocumab 300 mg, providing substantial LDL-C reductions with no new product technical issues or no new safety concerns compared with the currently marketed 1-mL AI device. In conclusion, the 2-mL SYDNEY device provides patients with the possibility of injecting the 300-mg alirocumab dose as a single injection. ClinicalTrials.gov identifier: NCT03415178 (Clin Ther. 2019; XX:XXX-XXX) (c) 2019 Elsevier HS Journals, Inc.

[10] *Rodrigues AD, Lai Y, Shen H et al.* **Induction of Human Intestinal and Hepatic Organic Anion Transporting Polypeptides; Where is the Evidence for its Relevance in Drug-Drug Interactions?** Drug metabolism and disposition: the biological fate of chemicals 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31879282
ABSTRACT
Organic anion transporting polypeptides (OATPs), expressed in human liver (OATP1B1, OATP1B3, and OATP2B1) and intestine (OATP2B1), govern the pharmacokinetics (PK) of drugs (e.g., statins) and endogenous substrates (e.g., coproporphyrin I, CPI). Their expression is known to be modulated (e.g., disease, age, and environmental factors) and they also present as the loci of clinically relevant polymorphisms and drug interactions involving inhibition. In comparison, relatively few clinical reports describe the induction of OATPs, although the effect of inducers (e.g., rifampicin, RIF; carbamazepine, CBZ) on OATP biomarker plasma levels and statin PK has been reported. Of note, available human tissue (e.g., biopsy) protein and messenger RNA expression profiling data indicate that OATPs in gut and liver are not induced by prototypical inducers such as RIF when compared to cytochrome P450 3A4 (CYP3A4), P-glycoprotein (Pgp), multidrug resistance-associated protein 2 (MRP2), and breast cancer resistance protein (BCRP). Such results are consistent with in vitro human hepatocyte data. Therefore, the observed impact of RIF, and possibly CBZ, on statin PK (> 20% decrease in the area under the plasma concentration versus time curve) cannot be ascribed to OATP induction with certainty. In fact, most statins and CPI have been shown to present variously as substrates of RIF inducible proteins such as CYP3A4, Pgp, MRP2, and BCRP. Interpretation of multi-dose RIF data is further complicated by its auto-induction, which likely leads to decreased inhibition of OATP. In the absence of more conclusive OATP induction data, caution is needed when modeling DDI involving multi-dose inducers such as RIF. SIGNIFICANCE STATEMENT: Presently, there is limited direct clinical evidence supporting the notion that human liver and gut OATPs are inducible by agents like RIF. Such data need to be reconciled and will pose challenges when attempting to incorporate OATP induction into physiologically-based PK models. Although disparate sets of tissue biopsy (atorvastatin and CBZ) and in vitro hepatocyte

(phenobarbital, chenodeoxycholate, and amprenavir) data present OATP messenger RNA induction (>/=2-fold) by agents beyond RIF, the clinical relevance of such data needs to be determined.

[11] *Boden WE, Bhatt DL, Toth PP et al.* **Profound reductions in first and total cardiovascular events with icosapent ethyl in the REDUCE-IT trial: why these results usher in a new era in dyslipidaemia therapeutics**. European heart journal 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31872245
ABSTRACT
The aims of this clinical review are to: (i) highlight the importance of elevated baseline triglycerides (TG) in the setting of well-controlled low-density lipoprotein cholesterol (LDL-C) on statins as a major contributor to residual atherosclerotic cardiovascular disease (ASCVD) risk, particularly among patients with type 2 diabetes mellitus, metabolic syndrome, and obesity whose distinctive lipid phenotype cannot be optimally treated with LDL-C reduction therapy alone; (ii) describe the findings and clinical implications of the landmark REDUCE-IT trial in which ethyl eicosapentaenoic acid significantly improved ASCVD outcomes. While many genetic studies have shown that elevated TG are an independent causal factor for ASCVD, prior placebo-controlled trials using niacin, fibrates, omega-3 fatty acids, and dietary supplement fish oil preparations have failed to demonstrate significant CV event reduction when added to statin therapy. In contrast, the REDUCE-IT trial in 8179 participants showed convincingly that the administration of 4 g daily of icosapent ethyl (an ethyl ester of eicosapentaenoic acid) in patients at high risk for ASCVD with increased levels of baseline TG [median value, 2.44 mmol/L (216.0 mg/dL)] but well-controlled LDL-C [median value, 1.94 mmol/L (75.0 mg/dL)] reduced significantly incident events across both the trial primary endpoint and multiple prespecified secondary endpoints, including cardiovascular death, as well as both subsequent and total primary endpoint and key secondary endpoint events. Icosapent ethyl unequivocally contributed to ASCVD event reduction over and above statin therapy. The REDUCE-IT trial results should alter our approach to managing a growing population of hypertriglyceridaemic patients whose lipid phenotype requires more intensive treatment beyond LDL-C lowering alone.

[12] *Drexel H, Coats AJS, Spoletini I et al.* **ESC Position Paper on statins adherence and implementation of new lipid-lowering medications: barriers to be overcome**. European heart journal. Cardiovascular pharmacotherapy 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31873726
ABSTRACT
Benefits and safety on statins have been well established over 20 years of research. Despite this, the vast majority of patients are not adequately treated and do not achieve the low-density lipoprotein cholesterol target levels. This is mainly due to poor adherence, which is associated with dangerous and sometimes fatal outcomes. To increase adherence and prevent worse outcomes, a combination therapy with lower dosage of statins and new lipid lowering drugs may be used. However, the implementation of new lipid lowering drugs in European countries is still at the beginning. For these reasons, aim of this position paper is to give an up-to-date indication from the European Society of Cardiology in order to discuss the barriers towards statins adherence and new lipid lowering drugs implementation in Europe.

Literature update week 52 (2019)

[13] *Di Taranto MD, Giacobbe C, Fortunato G*. **Familial hypercholesterolemia: A complex genetic disease with variable phenotypes**. European journal of medical genetics 2019:103831.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31883481
ABSTRACT
Familial hypercholesterolemia (FH) is the most frequent genetic disease and is characterized by elevation of LDL-cholesterol that accumulates in tissues leading to premature atherosclerosis and sometime tendon xanthomas. Main causes of FH are pathogenic variants in the genes encoding the LDL receptor (LDLR), its ligand - the apolipoprotein B (APOB) - or Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9). Rarer causes include variants in genes encoding apolipoprotein E (APOE) and the signal-transducing adaptor family member 1 (STAP1). Genetics of FH is extremely complicated by 1. high heterogeneity, 2. presence of variant clusters and 3. phenotypic variability. In fact, a great variability was observed among patients with the same genetic status: an overlap of LDL-cholesterol levels was observed between heterozygous patients (HeFH) and homozygous FH patients, as well as some HeFH showed a normal lipid profile. A correct pathogenicity evaluation is the first step to correctly define the genetic status helping to identify the variants which really cause the FH. Several phenotypic differences were observed among HeFH patients carrying different variant types (null or defective) or variants in different affected genes. Patients with a null variant in LDLR gene showed higher LDL-cholesterol levels and higher risk for coronary artery disease than patients with a defective variant. Pathogenic variants in several lipid-related genes causing different dyslipidemias were found among FH patients acting as both modifying factors (worsening the phenotype) and confounding factors (needing a differential diagnosis to be discriminated from FH). This review aims at depicting the complex genetic basis of FH.

[14] *Shabrina A, Tung TH, Nguyen NTK et al.* **n-3 PUFA and caloric restriction diet alters lipidomic profiles in obese men with metabolic syndrome: a preliminary open study**. European journal of nutrition 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31865423
ABSTRACT
PURPOSE: For people with metabolic syndrome (MetS), altering the macronutrient composition of their diets might ameliorate metabolic abnormalities. The common method of clinical assessment only measures total lipid concentrations but ignores the individual species that contribute to these total concentrations. Thus, to predict the amelioration of MetS following caloric restriction (CR) and the intake of fish oil, we used lipidomics to investigate changes in plasma lipids and identify potential lipid metabolites. METHODS: Lipidomics was performed using ultra-high-performance liquid chromatography-tandem mass spectrometry on plasma samples from a clinical trial conducted over 12 weeks. Subjects were randomized into two groups: CR (n = 12) and CR with fish oil (CRF, n = 9). Anthropometric and clinical parameters were measured and correlated with plasma lipidomics data. RESULTS: Compared with baseline, significant differences were observed in body weight, waist circumference, blood pressure and interleukin-6 in both groups, but triglyceride (TG) levels significantly decreased in only the CRF group (all $p < 0.05$). A total of 138 lipid species were identified. Levels of species containing long-chain polyunsaturated fatty acids were significantly elevated-greater than twofold-following fish oil intake, these included TG (60:9) and phosphatidylcholine (p40:6) (all $q < 0.05$). TG (60:9) tended to correlate negatively with body weight, body mass index, blood pressure, and HbA1c following fish oil intake. CONCLUSION: CR and fish oil can ameliorate MetS features, including

anthropometric parameters, blood pressure, and blood lipid concentrations. The levels of particular lipid species such as TG-containing docosapentaenoic acid were elevated post-intervention and negatively associated with MetS features. TG (60:9) may be proposed as a lipid metabolite to predict amelioration in MetS following the intake of CR and fish oil.

[15] *Rout A, Sukhi A, Chaudhary R et al.* **Investigational drugs in phase II clinical trials for acute coronary syndromes**. Expert opinion on investigational drugs 2020; 29:33-47.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31869253
ABSTRACT
Introduction: Despite current guideline-based, secondary prevention strategies in patients with the acute coronary syndrome, the residual ischemic risk is still at an unacceptable rate, and there is a concomitant high bleeding event rate. These observations mandate investigations of novel treatment strategies to meet the unmet need to improve outcomes in patients with ACS.Areas covered: In this review, the author(s) focus on new agents with ongoing or recently completed phase II trials for the treatment of ACS. We searched MEDLINE and clinicaltrials.org for Phase II trials in ACS patients, and important original investigations are reviewed.Expert opinion: Some of the novel drugs evaluated in the Phase II trials hold promise for future therapies such as AZD5718, anakinra, tocilizumab, CSL112, MEDI 6102, inclisiran, PZ128, selatogrel, and RVX-208. Their efficacy and safety should be evaluated in large scale Phase III trials. The higher cost of the drug will be a major limitation for wide-spread use of novel agents in general practice in future.

[16] *Mayyas F, Alsaheb A, Alzoubi KH*. **The role of fish oil in attenuating cardiac oxidative stress, inflammation and fibrosis in rat model of thyrotoxicosis**. Heliyon 2019; 5:e02976.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31872133
ABSTRACT
Hyperthyroidism is associated with cardiovascular complications. Fish oil reduces risk of cardiovascular diseases. This study aims to evaluate the impact of fish oil on myocardial oxidative stress, inflammation and fibrosis in rat model of thyrotoxicosis. Rats were randomized into four groups; control rats, fish oil treated rats (FO, 100mg omega-3/100g body weight/day), hyperthyroid rats (Hyper, i.p levothyroxine 3 mg/kg/day), and hyperthyroid rats treated with fish oil (Hyper + FO) for 8 weeks. Changes in oxidants/antioxidants, inflammatory and fibrotic markers were measured. Thyrotoxicosis increased serum endothelin-1, thiobarbituric acid reactive substances (TBARS) and reduced activities of cardiac catalase and super oxide dismutase (SOD). Cardiac fibrosis paralleled with a decrease of matrix metalloproteinase -2 (MMP2) levels were observed in Hyper group. Use of FO increased activities of SOD and catalase, increased TBARS levels, and attenuated cardiac fibrosis by normalizing MMP-2 levels. Use of FO may attenuate cardiac oxidative stress and fibrosis in hyperthyroid states.

[17] *Scolaro B, Andrade LFS, Castro IA*. **Cardiovascular Disease Prevention: The Earlier the Better? A Review of Plant Sterol Metabolism and Implications of Childhood Supplementation**. International journal of molecular sciences 2019; 21.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31878116
ABSTRACT
Atherosclerosis is the underlying cause of major cardiovascular events. The development of atherosclerotic plaques begins early in life, indicating that dietary interventions in childhood might be

more effective at preventing cardiovascular disease (CVD) than treating established CVD in adulthood. Although plant sterols are considered safe and consistently effective in lowering plasma cholesterol, the health effects of early-life supplementation are unclear. Studies suggest there is an age-dependent effect on plant sterol metabolism: at a younger age, plant sterol absorption might be increased, while esterification and elimination might be decreased. Worryingly, the introduction of low-cholesterol diets in childhood may unintentionally favor a higher intake of plant sterols. Although CVD prevention should start as early as possible, more studies are needed to better elucidate the long-term effects of plant sterol accumulation and its implication on child development.

[18] *Wu D, Zhou Y, Pan Y et al.* **Vaccine Against PCSK9 Improved Renal Fibrosis by Regulating Fatty Acid beta-Oxidation**. Journal of the American Heart Association 2020; 9:e014358.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31870234
ABSTRACT
Background Defects in the renal fatty acid beta-oxidation pathway have been implicated in the development of renal fibrosis. Our group has developed a therapeutic vaccine targeting PCSK9 (proprotein convertase subtilisin/kexin type 9), named PCSK9Qbeta-003. In this study, we investigated the potential effectiveness of the PCSK9Qbeta-003 vaccine on hypercholesterolemia with renal fibrosis. Methods and Results The low-density lipoprotein receptor(+/-) male mice fed with a high-cholesterol (1%) Western diet were randomly assigned into 4 groups: the sham group (or the control group), the phosphate-buffered saline group, the Qbeta virus-like particles group and the PCSK9Qbeta-003 vaccine group. Mice of the PCSK9Qbeta-003 group were injected with the PCSK9Qbeta-003 vaccine (100 mug/time) every 2 or 4 weeks. The mice were administered with either unilateral ureteral obstruction for 2 weeks or N-nitro-l-arginine methyl ester (50 mg/kg per day) for 6 weeks to establish a renal fibrosis model. Compared with the other 3 groups, the PCSK9Qbeta-003 vaccine obviously decreased total cholesterol and low-density lipoprotein cholesterol in low-density lipoprotein receptor(+/-) mice with hypercholesterolemia. Compared with the phosphate-buffered saline and Qbeta virus-like particles groups, the PCSK9Qbeta-003 vaccine improved hepatic steatosis and renal function. Histology analysis showed that the PCSK9Qbeta-003 vaccine significantly ameliorated renal lipid accumulation and renal fibrosis. Moreover, the PCSK9Qbeta-003 vaccine obviously upregulated the expression of low-density lipoprotein receptor, very-low-density lipoprotein receptor, sterol-regulatory element binding protein 2, and fatty acid beta-oxidation-related factors, and ameliorated renal fibrosis-related molecules both in the unilateral ureteral obstruction and N-nitro-l-arginine methyl ester models. Conclusions This study suggested that the PCSK9Qbeta-003 vaccine improved renal lipid accumulation and renal fibrosis by regulating fatty acid beta-oxidation, which may provide a promising method for treating hypercholesterolemia with renal fibrosis.

[19] *Xie C, Zhu M, Hu Y, Wang K*. **Effect of intensive and standard lipid-lowering therapy on the progression of stroke in patients with coronary artery syndromes: a meta-analysis of randomized controlled trials**. Journal of cardiovascular pharmacology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31876797
ABSTRACT
This meta-analysis demonstrated the effect of intensive vs. standard statins on the risk of stroke in patients with coronary artery syndromes (CAS). PubMed, Embase, the Cochrane library, and clinicaltrials.gov were searched, and the retrieved studies were undertaken for randomized controlled

trials (RCTs) throughout September 2018. Study designed as randomized controlled trials (RCTs) and recruited at least 1,000 CAS patients followed up greater than 1 year were eligible for this study. The summary relative risk with the 95% confidence interval was employed as an effect estimate and calculated using the random-effects model. Five RCTs comprising a total of 39,612 coronary syndrome patients with reported 1,236 stroke events were included in this meta-analysis. The summary result indicated a 14% reduction in the risk of stroke in CAS patients receiving intensive statin therapy as compared to standard statin therapy. The significant differences mainly occurred in mean age >/=60 years (P=0.007), percentage of males >/=80% (P=0.011), percentage diabetes mellitus (DM)>/=15% (P=0.018), percentage hypertension >/=50% (P=0.030), percentage of current smokers<30% (P=0.011), percentage of prior myocardial infarction >/=50% (P=0.011), percentage of peripheral arterial disease >/=10% (P=0.030), patients with stable CAS (P=0.011), patients using atorvastatin (P=0.015), follow-up duration >/=3 years (P=0.011), and study with moderate quality (P=0.013). Intensive statin therapy should be considered for CAS patients at high risk of stroke events. Further large-scale RCT should be conducted to verify the results of stratified analysis in this study.

[20] *Cao J, Nomura SO, Steffen BT et al.* **Apolipoprotein B discordance with low-density lipoprotein cholesterol and non-high-density lipoprotein cholesterol in relation to coronary artery calcification in the Multi-Ethnic Study of Atherosclerosis (MESA)**. Journal of clinical lipidology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31882375
ABSTRACT
BACKGROUND: Discordant levels of apolipoprotein B (apo B) relative to low-density lipoprotein cholesterol (LDL-C) or non-high-density lipoprotein cholesterol (non-HDL-C) may be associated with subclinical atherosclerotic cardiovascular disease (ASCVD). OBJECTIVE: The present study investigated whether discordance between apo B and LDL-C or non-HDL-C levels was associated with subclinical ASCVD measured by coronary artery calcium (CAC). METHODS: This study was conducted in a subpopulation of the Multi-Ethnic Study of Atherosclerosis (MESA) cohort, aged 45 to 84 years, free of ASCVD, and not taking lipid-lowering medications at the baseline (2000-2002) (prevalence analytic N = 4623; incidence analytic N = 2216; progression analytic N = 3947). Apo B discordance relative to LDL-C and non-HDL-C was defined using residuals and percentile rankings (>5/10/15 percentile). Associations with prevalent and incident CAC (CAC > 0 vs CAC = 0) were assessed using prevalence ratio/relative risk regression and CAC progression (absolute increase/year) using multinomial logistic regression. RESULTS: Higher apo B levels were associated with CAC prevalence, incidence, and progression. Apo B discordance relative to LDL-C or non-HDL-C was inconsistently associated with CAC prevalence and progression. Discordantly high apo B relative to LDL-C and non-HDL-C was associated with CAC progression. Associations for apo B discordance with non-HDL-C remained after further adjustment for metabolic syndrome components. CONCLUSION: Apo B was associated with CAC among adults aged >/=45 years not taking statins, but provided only modest additional predictive value of apo B for CAC prevalence, incidence, or progression beyond LDL-C or non-HDL-C. Apo B discordance may still be important for ASCVD risk assessment and further research is needed to confirm findings.

[21] *Dyrbus K, Gasior M, Penson P et al.* **Inclisiran-New hope in the management of lipid disorders?** Journal of clinical lipidology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31879073
ABSTRACT

Literature update week 52 (2019)

Drugs reducing plasma concentrations of apolipoprotein B-containing lipoproteins have been demonstrated to reduce the risk of cardiovascular disease (CVD) in both primary and secondary prevention. Despite the demonstrated efficacy of statins and ezetimibe on low-density lipoprotein (LDL) concentration and long-term CVD risk, a large number of patients do not achieve their therapeutic goals. The introduction of monoclonal antibodies against proprotein convertase subtilisin/kexin type 9 (PCSK9) protein was a milestone in the treatment of lipid disorders, as their administration leads to unprecedentedly low LDL cholesterol concentrations. Inclisiran represents an entirely new mechanism of PSCK9 protein inhibition in hepatocytes, targeting the messenger RNA for PCSK9. Its administration is necessary only every 3 to 6 months, which is an essential advantage over statin and monoclonal antibody therapy. The infrequent administration regimen can increase the number of patients who maintain their therapeutic goals, especially in patients struggling to comply with daily or biweekly pharmacotherapy. Preclinical studies and Phase I and Phase II clinical trials of inclisiran have demonstrated its tolerability and efficacy in promoting long-term reduction of both PCSK9 protein and LDL cholesterol. The efficacy and safety of inclisiran will continue to be assessed in ongoing and forthcoming trials on larger patient groups. If the results of these trials reflect previously published data, they will add further evidence that inclisiran might be a revolutionary new tool in the pharmacologic management of plasma lipids. This review summarizes the currently available literature data on inclisiran with respect to its mechanism of action, effectiveness, and safety as a lipid-lowering drug for CVD prevention.

[22] *Han Y, Chen J, Chopra VK et al.* **ODYSSEY EAST: Alirocumab efficacy and safety vs ezetimibe in high cardiovascular risk patients with hypercholesterolemia and on maximally tolerated statin in China, India, and Thailand**. Journal of clinical lipidology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31882376
ABSTRACT
BACKGROUND: The proprotein convertase subtilisin/kexin type 9 inhibitor alirocumab significantly reduces low-density lipoprotein cholesterol (LDL-C). OBJECTIVE: This study (ODYSSEY EAST) assessed the efficacy and safety of alirocumab vs ezetimibe in high cardiovascular risk patients from Asia. METHODS: Patients (n = 615) from China, India, and Thailand with hypercholesterolemia at high cardiovascular risk on maximally tolerated statin were randomized (2:1) to alirocumab (75 mg every 2 weeks [Q2W]; with dose increase to 150 mg Q2W at week 12 if week 8 LDL-C was >1.81 mmol/L [>70 mg/dL]) or ezetimibe (10 mg daily) for 24 weeks. The primary efficacy endpoint was percentage change in calculated LDL-C from baseline to week 24. Safety was assessed throughout. RESULTS: Baseline data were similar in both groups. LDL-C levels were reduced from baseline to week 24 by 56.0% and 20.3% in the alirocumab and ezetimibe groups, respectively (P < .0001 vs ezetimibe). Overall, 18.8% of alirocumab-treated patients received a dose increase to 150 mg Q2W. At week 24, 85.1% of alirocumab-treated and 40.5% of ezetimibe-treated patients reached LDL-C <1.81 mmol/L (<70 mg/dL, P < .0001 vs ezetimibe). Treatment-emergent adverse events occurred in 68.5% of alirocumab-treated and 63.1% of ezetimibe-treated patients, with upper respiratory tract infection the most common (alirocumab: 13.3%; ezetimibe: 14.1%). Injection-site reactions occurred more frequently in alirocumab-treated patients (2.7%) than in ezetimibe-treated patients (1.0%). CONCLUSIONS: Alirocumab significantly reduced LDL-C vs ezetimibe in high cardiovascular risk patients from Asia and was generally well tolerated. These findings are consistent with previous ODYSSEY studies.

[23] *van Dijk PR, Abdulle AE, Bulthuis MLC et al.* **The Systemic Redox Status Is Maintained in Non-Smoking Type 2 Diabetic Subjects Without Cardiovascular Disease: Association with Elevated Triglycerides and Large VLDL**. Journal of clinical medicine 2019; 9.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31878321
ABSTRACT
Decreased circulating levels of free thiols (R-SH, sulfhydryl groups) reflect enhanced oxidative stress, which plays an important role in the pathogenesis of cardiometabolic diseases. Since hyperglycemia causes oxidative stress, we questioned whether plasma free thiols are altered in patients with type 2 diabetes mellitus (T2DM) without cardiovascular disease or renal function impairment. We also determined their relationship with elevated triglycerides and very low density lipoproteins (VLDL), a central feature of diabetic dyslipidemia. Fasting plasma free thiols (colorimetric method), lipoproteins, VLDL (nuclear magnetic resonance spectrometry), free fatty acids (FFA), phospholipid transfer protein (PLTP) activity and adiponectin were measured in 79 adult non-smoking T2DM subjects (HbA1c 51 +/- 8 mmol/mol, no use of insulin or lipid lowering drugs), and in 89 non-smoking subjects without T2DM. Plasma free thiols were univariately correlated with glucose ($r = 0.196$, $p < 0.05$), but were not decreased in T2DM subjects versus non-diabetic subjects ($p = 0.31$). Free thiols were higher in subjects with (663 +/- 84 micromol/L) versus subjects without elevated triglycerides (619 +/- 91 micromol/L; $p = 0.002$). Age- and sex-adjusted multivariable linear regression analysis demonstrated that plasma triglycerides were positively and independently associated with free thiols (beta = 0.215, $p = 0.004$), FFA (beta = 0.168, $p = 0.029$) and PLTP activity (beta = 0.228, $p = 0.002$), inversely with adiponectin (beta = -0.308, $p < 0.001$) but not with glucose (beta = 0.052, $p = 0.51$). Notably, the positive association of free thiols with (elevated) triglycerides appeared to be particularly evident in men. Additionally, large VLDL were independently associated with free thiols (beta = 0.188, $p = 0.029$). In conclusion, circulating free thiols are not decreased in this cohort of non-smoking and generally well-controlled T2DM subjects. Paradoxically, higher triglycerides and more large VLDL particles are likely associated with higher plasma levels of thiols, reflecting lower systemic oxidative stress.

[24] *Kusznir Vitturi B, Jose Gagliardi R*. **The role of statins in cardioembolic stroke**. Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31874811
ABSTRACT
BACKGROUND: Statin therapy has become one of the most important advances in stroke secondary prevention. Nevertheless, statin therapy in patients with cardioembolic stroke has not been supported by clinical evidence yet. This study aimed to investigate the effect of statins on the neurological outcomes after a cardioembolic stroke. METHODS: We conducted a prospective cohort study including consecutive patients with cardioembolic stroke. Subjects were classified into non-statin, simvastatin 20 mg, simvastatin 40 mg, and high-potency statin groups. After 2 years, the functional outcome, stroke recurrence, major cardiovascular events, and mortality were assessed. RESULTS: Among the 91 patients included in our cohort, there were 18 (19.8%) patients without statins, 30 (33.0%) with simvastatin 20 mg, 38 (41.7%) with simvastatin 40 mg and 5 (5.5%) with high-potency statins. Using simvastatin 40 mg was associated with a significantly lower incidence of stroke recurrence lower. Patients with simvastatin 40 mg and high-potency statins presented the best functional recovery throughout the follow-up ($p < 0.01$). CONCLUSIONS: The use of statins in patients with cardioembolic

stroke may be beneficial in some cases, preventing stroke recurrence and improving functional outcomes.

[25] *Pomozova TP, Lykov YV, Komarova IS et al.* **[Clinical and laboratory features of primary acute myocardial infarction in patients with obstructive and non-obstructive coronary atherosclerosis]**. Kardiologiia 2019; 59:41-51.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31876461

ABSTRACT

According to the literature, 40-60% of patients with acute myocardial infarction (AMI) have obstructive multivessel coronary artery disease (CA) and 8.8% of patients have non-obstructive CA lesions. And it is around these two groups of patients that there are active discussions and disputes regarding the choice of optimal treatment tactics and further prognosis. The aim of the study was to study clinical and laboratory features of development and course of primary AMI in patients with multi-and single-vessel obstructive lesion of the CA compared with patients with non-obstructive CA lesions. Methods. The study has included patients hospitalized "through the ambulance channel" in the Department of cardiac intensive care of municipal clinical hospital named after S. S. Yudin Moscow with a diagnosis "primary acute myocardial infarction", ACS with and without ST segment elevation, unstable angina in 2015-2016. The diagnosis of acute myocardial infarction (AMI) was established at the hospital stage according to the criteria of the "Third universal definition of myocardial infarction" in 2012. The study included 1240 patients who underwent coronary angiography (CAG) no later than 12 hours from the time of admission. The first group (comparison group) consisted of patients with AMI and the first detected multivessel obstructive atherosclerotic lesion of CA (664 patients), the second (interest group) consisted of patients with AMI and non-obstructive atherosclerotic lesion of CA (96 patients) meeting the MINOCA criteria. The third group consisted of patients with single-vessel obstructive lesion and complete acute occlusion of the CA (272 patients). Patients with hemodynamically significant lesions of the left CA trunk were not included in the study. The clinical and laboratory features of the course of acute primary myocardial infarction in patients with obstructive and non-obstructive coronary atherosclerosis were studied. The generally accepted statistical processing methods were used. A year after discharge from the hospital, 727 patients (468 patients from the 1st group, 78 from the 2nd group, 181 from the 3rd group) were interviewed by means of a structured telephone survey about the course of the disease (collection of medical history). The median follow-up was 12 months. (interquartile range 11-13 months). The endpoints were: re-hospitalization for any reason, re-coronary event, death. The received answers are entered into questionnaires and statistically processed. Results and conclusions. In patients with AMI and non-obstructive atherosclerotic CA lesion, pain behind the sternum is observed one and a half times less often (54.2%) than in patients with obstructive CA lesion (MOAPCA 86.1%, OAPCA 89.7%) and the cardiac co duction system is almost three times more likely to be affected (30% versus 8.4% and 12%). Only 12.5% of patients in this group had an abnormal Q wave (Q - myocardial infarction) on the ECG, therefore, a smaller volume of myocardial damage and a lower level of troponin than in patients of groups 1 and 3. During the first year after the development of AMI, patients with obstructive coronary atherosclerosis did not experience repeated coronary events, there were no indications for conducting CAG, PCI or CABG, in contrast to patients with obstructive lesion of CA. For multivascular obstruction (group 1), PCI was performed in 9.6% of patients and 3.8% of CABG. PCI was performed in group 3 with obstructive single-vessel lesion of CA in 7.7% of patients. In patients with AMI and obstructive single-vessel

atherosclerotic lesion of CA (group 3), two and a half times less often (9.1%) myocardial reperfusion injury is observed, while in patients with multivascular obstructive CA defeat, this syndrome was observed in 21.3%.

[26] *Irwin JC, Fenning AS, Vella RK*. **Statins with different lipophilic indices exert distinct effects on skeletal, cardiac and vascular smooth muscle**. Life sciences 2019; 242:117225.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31881229
ABSTRACT
AIMS: Data concerning the influence of statin lipophilicity on the myotoxic and pleiotropic effects of statins is conflicting, and mechanistic head-to-head comparison studies evaluating this parameter are limited. In order to address the disparity, this mechanistic investigation aimed to assess the effects of two short-acting statins with different lipophilic indices on skeletal, cardiac and vascular smooth muscle physiology. MATERIALS AND METHODS: Young female Wistar rats were randomised to simvastatin (80 mg kg(-)(1) day(-)(1)), pravastatin (160 mg kg(-)(1) day(-)(1)) or control treatment groups. Changes in functional muscle performance were assessed, as well as mRNA levels of genes relating to atrophy, hypertrophy, mitochondrial function and/or oxidative stress. KEY FINDINGS: There were no significant differences in the mRNA profiles of isolated skeletal muscles amongst the treatment groups. In terms of skeleletal muscle performance, simvastatin reduced functionality but treatment with pravastatin significantly improved force production. Rodents given simvastatin demonstrated comparable myocardial integrity to the control group. Conversely, pravastatin reduced left ventricular action potential duration, diastolic stiffness and Mhc-beta expression. Pravastatin improved endothelium-dependent relaxation, particularly in muscular arteries, but this effect was absent in the simvastatin-treated rats. The responsiveness of isolated blood vessels to noradrenaline also differed between the statin groups. The findings of this study support that the effects of statins on skeletal, cardiac and vascular smooth muscle vary with their lipophilic indices. SIGNIFICANCE: The results of this work have important implications for elucidating the mechanisms responsible for the myotoxic and pleiotropic effects of statins.

[27] *Liu X, Zhang W, Zhao M et al.* **Effect of atorvastatin treatment on circulating adiponectin: a meta-analysis of randomized controlled trials**. Lipids in health and disease 2019; 18:228.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31870381
ABSTRACT
BACKGROUND: Influences of atorvastatin on atherosclerosis and glycemic metabolism may be related to its potential impact on circulating adiponectin, an adipocyte that exerts anti-inflammatory, ant-atherosclerotic, and anti-oxidative effects. However, results of previous randomized controlled trials (RCTs) were not consistent. We performed a meta-analysis of RCTs to systematic evaluate the influence of atorvastatin on circulating adiponectin. METHODS: Relevant studies were identified via search of electronic databases of PubMed, Embase, and Cochrane's Library. A random-effect model was applied to pool the results via incorporating the potential heterogeneity. Predefined meta-regression and subgroup analyses were used to evaluate the influences of study characteristics on the outcome. RESULTS: Fourteen datasets from ten RCTs including 931 patients were included. Pooled results showed that atorvastatin did not significantly affect circulating adiponectin as compared with controls (weighed mean difference = - 0.27 mug/mL, 95% confidence interval: - 0.89 to 0.35 mug/mL, p = 0.39). Results of univariate meta-regression analyses showed that study characteristics including

number of patients, mean age, proportion of male patients, body mass index, dose of atorvastatin, or treatment duration did not significantly affect the outcome (p all > 0.05). Moreover, subgroup analyses showed that atorvastatin did not significantly affect circulating adiponectin in studies stratified according to these study characteristics (p all > 0.05). CONCLUSIONS: Atorvastatin treatment does not significantly affect circulating adiponectin. Influences of atorvastatin on atherosclerosis and glycemic metabolism are not likely to be mediated by modulation of circulating adiponectin.

[28] *Wang C, Niimi M, Kitajima S et al.* **Sex hormones affect endothelial lipase-mediated lipid metabolism and atherosclerosis**. Lipids in health and disease 2019; 18:226.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31870448
ABSTRACT
BACKGROUND: Endothelial lipase (EL) plays an important role in lipoprotein metabolism and atherosclerosis. To study the functional roles of EL, we recently generated transgenic (Tg) rabbits and reported that increased hepatic expression of EL in male Tg rabbits significantly reduced diet-induced hypercholesterolemia compared with non-Tg controls. This gender difference suggests that sex hormones may mediate EL functions thereby influencing lipoprotein metabolism. To examine this hypothesis, we compared the effects of orchiectomy and ovariectomy on plasma lipids and diet-induced atherosclerosis in both Tg and non-Tg rabbits. METHODS: Male rabbits were under orchiectomy whereas female rabbits were under ovariectomy. We compared plasma lipids, lipoproteins, and apolipoproteins of rabbits before and after surgery in each group fed either a chow diet or cholesterol-rich diet. RESULTS: On a chow diet, both male and female Tg rabbits showed lower plasma lipids than non-Tg counterparts and this lipid-lowering effect of EL was not affected by either orchiectomy in male or ovariectomy in female Tg rabbits. On a cholesterol diet; however, male Tg rabbits but not female Tg rabbits showed significant resistance to diet-induced hypercholesterolemia and atherosclerosis. The EL-mediated atheroprotective effect was eliminated after orchiectomy in male Tg rabbits. Female Tg rabbits showed similar levels of total cholesterol and lesion size of atherosclerosis compared with non-Tg rabbits and ovariectomy did not affect diet-induced hypercholesterolemia or atherosclerosis. CONCLUSION: These results suggest that increased EL protects against diet-induced hypercholesterolemia and atherosclerosis. The beneficial effect of EL was dependent upon the presence of androgenic hormones.

[29] *Jia Z, An L, Lu Y et al.* **Oxidized Low Density Lipoprotein-Induced Atherogenic Response of Human Umbilical Vascular Endothelial Cells (HUVECs) was Protected by Atorvastatin by Regulating miR-26a-5p/Phosphatase and Tensin Homolog (PTEN)**. Medical science monitor : international medical journal of experimental and clinical research 2019; 25:9836-9843.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31865360
ABSTRACT
BACKGROUND Atherosclerosis is a chronic and multifactorial disease, and it is the main reason of coronary heart disease, cerebral infarction, and peripheral vascular disease, which leads to the formation of lesions in arterial blood vessels. Our study aimed to explore the protective effect and its underlying mechanism of atorvastatin (ATV) on oxidized low-density lipoprotein (ox-LDL)-induced atherosclerosis. MATERIAL AND METHODS Human umbilical vascular endothelial cells (HUVECs) were cultured and pretreated with ox-LDL to establish an in vitro atherosclerotic cell model. Cell Counting Kit-8 (CCK-8) assay, TUNEL staining, and Transwell assay were used to detect the cell activity,

apoptosis, and migration in HUVECs. Quantitative real-time polymerase chain reaction (qRT-PCR) and western blot were applied to measure the mRNA and protein expressions of adhesion-related genes in HUVECs. RESULTS Pretreated with 100 mg/L ox-LDL resulted in a 57.23% decrease of cell viability and 81.09% increase of apoptotic injury in HUVECs compare to the control. Meanwhile, ox-LDL pretreatment increased the cell migration and the expression of miR-26a-5p in HUVECs. ATV treatment could effectively reverse the cellular damage induced by ox-LDL, decrease the release of adhesion-related molecules, and downregulate the expression of miR-26a-5p by 44.79% in HUVECs. Moreover, phosphatase and tensin homolog (PTEN) was demonstrated to be the target gene of miR-26a-5p. CONCLUSIONS Our results highlight that ATV protects against ox-LDL-induced downregulation of cell viability, upregulation of cell apoptosis, migration, as well as the release of adhesion-related molecules in HUVECs through the miR-26a-5p/PTEN axis. This study provides new insights into the underlying mechanism of ATV therapeutic potential in atherosclerosis, and also provides a new strategy for the treatment of atherosclerosis.

[30] *Wang W, Zhang K, Zhang H et al.* **Underlying Genes Involved in Atherosclerotic Macrophages: Insights from Microarray Data Mining**. Medical science monitor : international medical journal of experimental and clinical research 2019; 25:9949-9962.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31875420
ABSTRACT
BACKGROUND In an atherosclerotic artery wall, monocyte-derived macrophages are the principal mediators that respond to pathogens and inflammation. The present study aimed to investigate potential genetic changes in gene expression between normal tissue-resident macrophages and atherosclerotic macrophages in the human body. MATERIAL AND METHODS The expression profile data of GSE7074 acquired from the Gene Expression Omnibus (GEO) database, which includes the transcriptome of 4 types of macrophages, was downloaded. Di ff erentially expressed genes (DEGs) were identified using R software, then we performed functional enrichment, proteinprotein interaction (PPI) network construction, key node and module analysis, and prediction of microRNAs (miRNAs)/transcription factors (TFs) targeting genes. RESULTS After data processing, 236 DEGs were identified, including 21 upregulated genes and 215 downregulated genes. The DEG set was enriched in 22 significant Gene Ontology (GO) terms and 25 Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways, and the PPI network constructed with these DEGs comprised 6 key nodes with degrees >/=8. Key nodes in the PPI network and simultaneously involved in the prime modules, including rhodopsin (RHO), coagulation factor V (F5), and bestrophin-1 (BEST1), are promising for the prediction of atherosclerotic plaque formation. Furthermore, in the miRNA/TF-target network, hsa-miR-3177-5p might be involved in the pathogenesis of -atherosclerosis via regulating BEST1, and the transcription factor early growth response-1 (EGR1) was found to be a potential promoter in atherogenesis. CONCLUSIONS The identified key hub genes, predicted miRNAs/TFs, and underlying molecular mechanisms may be involved in atherogenesis, thus potentially contributing to the treatment and diagnosis of patients with atherosclerotic disease.

[31] *Heo SJ, Kim JS, Kwon SH, Kim JS*. **Lipid keratopathy and septal abscess: Case report**. Medicine (Baltimore) 2019; 98:e17802.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31876702
ABSTRACT

RATIONALE: Epistaxis is a common otorhinolaryngological emergency, but septal abscess has not been reported before as a complication of epistaxis. PATIENT CONCERNS: We report a case of a 51-year-old man complaining of nasal obstruction and facial numbness for 3 weeks. He had a history of epistaxis, and had been treated with electrocauterization of the left nasal septum at a local clinic 1 month earlier. DIAGNOSES: On nasal endoscopy, swelling of the septum was noticed; computed tomography (CT) was performed, and revealed a septal abscess. INTERVENTIONS: The patient was treated with incision and drainage under local anesthesia. A left vertical hemitransfixion incision was made and 4 mL of purulent material was drained. There was no quadrangular septal cartilage. OUTCOMES: On the 5th postoperative day, the patient complained of blurred vision in his right eye. Visual acuity of the left eye was 0.5, but acuity of the right eye was finger count at 50 cm. Examination of the right eye revealed a whitish fan-shaped corneal opacity on the medial side with neovascularization, diagnostic of lipid keratopathy. CONCLUSION: Electrocautery of epistaxis should be performed carefully during hemostasis, and there should be careful follow-up after the procedure to detect the occurrence of septal hematoma or septal abscess. These conditions should be treated as early as possible to avoid further serious complications. Since lipid keratopathy is difficult to treat once it occurs, care should be taken to avoid a septal abscess.

[32] *Khetarpal SA, Wang M, Khera AV*. **Volanesorsen, Familial Chylomicronemia Syndrome, and Thrombocytopenia**. The New England journal of medicine 2019; 381:2582-2584.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31881147
ABSTRACT

[33] *Witztum JL, Geary RS, O'Dea L*. **Volanesorsen, Familial Chylomicronemia Syndrome, and Thrombocytopenia. Reply**. The New England journal of medicine 2019; 381:2584.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31881148
ABSTRACT

[34] *Bravo M, Raurell I, Hide D et al.* **Restoration of liver sinusoidal cell phenotypes by statins improves portal hypertension and histology in rats with NASH**. Scientific reports 2019; 9:20183.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31882668
ABSTRACT
Non-alcoholic steatohepatitis (NASH) is a common chronic liver disorder in developed countries, with the associated clinical complications driven by portal hypertension (PH). PH may precede fibrosis development, probably due to endothelial dysfunction at early stages of the disease. Our aim was to characterize liver sinusoidal endothelial cell (LSEC) dedifferentiation/capillarization and its contribution to PH in NASH, together with assessing statins capability to revert endothelial function improving early NASH stages. Sprague-Dawley rats were fed with high fat glucose-fructose diet (HFGFD), or control diet (CD) for 8 weeks and then treated with simvastatin (sim) (10 mg.kg(-1).day(-1)), atorvastatin (ato) (10 mg.kg(-1).day(-1)) or vehicle during 2 weeks. Biochemical, histological and hemodynamic determinations were carried out. Sinusoidal endothelial dysfunction was assessed in individualized sorted LSEC and hepatic stellate cells (HSC) from animal groups and in whole liver samples. HFGFD rats showed full NASH features without fibrosis but with significantly increased portal pressure compared with CD rats (10.47 +/- 0.37 mmHg vs 8.30 +/- 0.22 mmHg; $p < 0.001$). Moreover, HFGFD rats showed a higher percentage of capillarized (CD32b(-)/CD11b(-)) LSEC (8% vs 1%, $p = 0.005$) showing a contractile

phenotype associated to HSC activation. Statin treatments caused a significant portal pressure reduction (sim: 9.29 +/- 0.25 mmHg, p < 0.01; ato: 8.85 +/- 0.30 mmHg, p < 0.001), NASH histology reversion, along with significant recovery of LSEC differentiation and a regression of HSC activation to a more quiescent phenotype. In an early NASH model without fibrosis with PH, LSEC transition to capillarization and HSC activation are reverted by statin treatment inducing portal pressure decrease and NASH features improvement.

[35] *Rabacal W, Schweitzer F, Rayens E et al.* **Statin treatment prevents the development of pulmonary arterial hypertension in a nonhuman primate model of HIV-associated PAH**. Scientific reports 2019; 9:19832.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31882598
ABSTRACT
Pulmonary arterial hypertension (PAH) is a life-threatening disease characterized by pulmonary vascular remodeling, elevated pulmonary arterial pressure, and right heart failure. Human immunodeficiency virus (HIV)-infected individuals have a higher incidence of PAH than the non-HIV infected population and evidence suggests a role for systemic and pulmonary inflammation in the pathogenesis of HIV-associated PAH. Due to their pleiotropic effects, including immune-modulatory and anti-inflammatory effects, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) have been considered for the treatment of PAH, with conflicting results. The effects of statins on HIV-associated PAH have not been specifically evaluated. We have developed a non-human primate (NHP) model of HIV-associated PAH that closely mimics HIV-PAH using simian immunodeficiency virus (SIV)-infected rhesus macaques (Macaca mulatta). We determined that treatment of healthy macaques with atorvastatin prior to and throughout SIV infection prevented the development of SIV-associated PAH. Additionally, SIV-infected macaques that initiated atorvastatin treatment during the early chronic disease stage had reduced incidence of PAH compared to untreated animals. Statin treatment reduced inflammatory mediators TGF-beta, MIP-1alpha, and TNF-alpha and the numbers of CD14(dim)CD16(+) non-classical monocytes, and CD14(+)CCR7(-)CD163(-)CD206(+) alveolar macrophages previously shown to be associated with SIV-PAH. These results support the concept that statins reduce inflammatory processes that contribute to PAH and may provide a safe and effective prophylactic strategy for the prevention of PAH in HIV-infected individuals.

[36] Sidhu G, Sapra A. Pravastatin. In: StatPearls. Treasure Island (FL): StatPearls Publishing StatPearls Publishing LLC.; 2019.
[37] *Haley MJ, White CS, Roberts D et al.* **Stroke Induces Prolonged Changes in Lipid Metabolism, the Liver and Body Composition in Mice**. Translational stroke research 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31865538
ABSTRACT
During recovery, stroke patients are at risk of developing long-term complications that impact quality of life, including changes in body weight and composition, depression and anxiety, as well as an increased risk of subsequent vascular events. The aetiologies and time-course of these post-stroke complications have not been extensively studied and are poorly understood. Therefore, we assessed long-term changes in body composition, metabolic markers and behaviour after middle cerebral artery occlusion in mice. These outcomes were also studied in the context of obesity, a common stroke co-morbidity proposed to protect against post-stroke weight loss in patients. We found that stroke

induced long-term changes in body composition, characterised by a sustained loss of fat mass with a recovery of lean weight loss. These global changes in response to stroke were accompanied by an altered lipid profile (increased plasma free fatty acids and triglycerides) and increased adipokine release at 60 days. After stroke, the liver also showed histological changes indicative of liver damage and a decrease in plasma alanine aminotransferase (ALT) was observed. Stroke induced depression and anxiety-like behaviours in mice, illustrated by deficits in exploration, nest building and burrowing behaviours. When initial infarct volumes were matched between mice with and without comorbid obesity, these outcomes were not drastically altered. Overall, we found that stroke induced long-term changes in depressive/anxiety-like behaviours, and changes in plasma lipids, adipokines and the liver that may impact negatively on future vascular health.

[38] *Wong ND, Toth PP, Amsterdam EA*. **Most important advances in preventive cardiology during this past decade: Viewpoint from the American Society for Preventive Cardiology**. Trends in cardiovascular medicine 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31882264
ABSTRACT
The rapidly expanding field of preventive cardiology has brought with it several major advances in the past decade. Changes in guidelines for cholesterol mangement focusing on the identification of "statin eligible groups" and removal of actual low-density lipoprotein cholesterol (LDL-C) targets, in particular, as well as lower targets for blood pressure in updated hypertension guidelines, have made a major impact on healthcare. The availability of the sodium glucose transport protein-2 (SGLT2) inhibitors and glucagon-like peptide -1 receptor antagonists (GLP1-RA) for managing diabetes have shifted our focus in diabetes care beyond glucose lowering to addressing cardiovascular risk reduction. While many prior trials of fish oil therapy have failed to show benefit, the recent Reduction of Cardiovascular Events With EPA - Intervention Trial (REDUCE-IT) testing the efficacy of icosapent ethyl has shown dramatic benefit in further addressing residual atherosclerotic cardiovascular disease (ASCVD) risk beyond statin therapy not only in those with known ASCVD, but also in diabetic patients with multiple risk factors. The past decade also ushered in confirmation of the inflammation hypothesis of atherosclerosis with the Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS) using canakinumab, despite the fact the therapy was not approved by the Food and Drug Administration (FDA) for cardiovascular risk reduction. Also, to improve our understanding of heart disease in women, the emergence of novel concepts of ischemia or myocardial infarction in those with normal or nonobstructive atherosclerotic disease has been a major advance. Moreover, the past decade brought the emergence of proprotein convertase subtilisin/kexin type 9 (PCSK9) monoclonal antibody therapy and the cardiovascular risk reduction benefits seen in the Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) and Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab (ODYSSEY OUTCOMES) trials, providing further evidence-based therapy for additional reduction of ASCVD risk beyond statin therapy. The PCSK9 monoclonal antibodies have facilitated the attainment of LDL-C levels never previously thought possible. Finally with the mRNA interference therapy inclisiran in development, we may soon have a "vaccine-like" approach for addressing dyslipidemia and atherosclerosis.