Literature update week 37 (2018)

[1] *Cahalane RM, Barrett HE, O'Brien JM et al.* **Relating the Mechanical Properties of Atherosclerotic Calcification to Radiographic Density: A Nanoindentation Approach**. Acta biomaterialia 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30218776
ABSTRACT

Calcification is associated with decreased atherosclerotic plaque stability and increased failures rates for endovascular interventions. Computational efforts have sought to elucidate the relationship between calcification and plaque rupture in addition to predicting tissue response during aggressive revascularisation techniques. However, calcified material properties are currently estimated and may not reflect real tissue conditions. The objective of this study is to correlate calcification mechanical properties with three radiographic density groups obtained from corresponding Computed Tomography (CT) images. Seventeen human plaques extracted from carotid (n=10) and peripheral lower limb (n=7) arteries were examined using micro-computed tomography (microCT), simultaneously locating the calcified deposits within their internal structure and quantifying their densities. Three radiographic density groups were defined based on the sample density distribution: (A) 130-299.99 Hounsfield Units (HU), (B) 300-449.99HU and (C) >450HU. Nanoindentation was employed to determine the Elastic Modulus (E) and Hardness (H) values within the three density groups. Results reveal a clear distinction between mechanical properties with respect to radiographic density groups (p<0.0005). No significant differences exist in the density-specific behaviours observed between carotid and peripheral samples. Previously defined calcification classifications indicate an association with specific radiographic density patterns. Scanning Electron Microscopy (SEM) examination revealed that density group A regions consist of both calcified and non-calcified tissues. Further research is required to define the radiographic thresholds which identify varying degrees of tissue calcification. This study demonstrates that the mechanical properties of fully mineralised atherosclerotic calcification emulate that of bone tissues (17-25GPa), affording computational models with accurate material parameters. STATEMENT OF SIGNIFICANCE: Global mechanical characterisation techniques disregard the heterogeneous nature of atherosclerotic lesions. Previous nanoindentation results for carotid calcifications have displayed a wide range. This study evaluates calcification properties with respect to radiographic density obtained from Micro-CT images. This is the first work to characterise calcifications from peripheral lower limb arteries using nanoindentation. Results demonstrate a strong positive correlation between radiographic density and calcification mechanical properties. Characterising calcifications using their density values provides clarity on the variation in published properties for calcified tissues. Furthermore, this study confirms the hypothesis that fully calcified plaque tissue behaviours similar to that of bone. Appropriate material parameters for calcified tissues can now be employed in computational simulations.

[2] *Choi JY, Choi CU, Hwang SY et al.* **Effect of Pitavastatin Compared with Atorvastatin and Rosuvastatin on New-Onset Diabetes Mellitus in Patients With Acute Myocardial Infarction**. The American journal of cardiology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30217375
ABSTRACT

Although statin use in patients with acute myocardial infarction (AMI) is mandatory, it has been suggested to be associated with new-onset diabetes mellitus (NODM). In real world practice, moderate-intensity statin therapy is more commonly used than high-intensity statin therapy. In this study, we investigated the impact of moderate-intensity pitavastatin (2 to 4 mg) compared with moderate-intensity atorvastatin (10 to 20 mg) and rosuvastatin (5 to 10 mg) on the development of NODM during a follow-up period of up to 3years. Between November 2011 and May 2015, 2001 patients with AMI who did not have diabetes mellitus were investigated. The cumulative incidence of NODM was evaluated in all groups. To adjust for potential confounders, multinomial propensity scores were used. Cox proportional hazard models were used to assess the hazard ratio of NODM in the atorvastatin and rosuvastatin groups compared with pitavastatin group. The cumulative incidence of NODM was significantly lower in pitavastatin group compared with the atorvastatin and rosuvastatin groups (3.0% vs 8.4% vs 10.4%, respectively; Log-rank p value=0.001). After weighting the baseline characteristics of the 3 statin groups by multinomial propensity scores, atorvastatin (hazard ratio: 2.615, 95% confidence interval: 1.163 to 5.879) and rosuvastatin (hazard ratio: 3.906, 95% confidence interval: 1.756 to 8.688) were found to be associated with a higher incidence of NODM compared with pitavastatin therapy on multivariable analysis. Moderate-intensity pitavastatin therapy is associated with a lower incidence of NODM in patients with AMI andhas similar clinical outcomes to moderate-intensity atorvastatin and rosuvastatin therapy.

[3] *Buckley LF, Carbone S, Aldemerdash A et al.* **Novel and Emerging Therapeutics for Primary Prevention of Cardiovascular Disease**. The American journal of medicine 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30201240
ABSTRACT

Cardiovascular disease is responsible for 205 deaths per 100,000 persons annually and the leading cause of death worldwide. The public health burden of cardiovascular disease is expected to continue to grow as the prevalence of many cardiovascular risk factors increases. Several novel classes of glucose lowering, lipid lowering and weight loss therapeutics have shown mortality benefits in outcomes trials. However, a large proportion of subjects in those trials had established cardiovascular disease and, as a result, the role of these novel therapeutics in primary cardiovascular prevention is controversial. In this review, we highlight recent advances in the pharmacotherapeutic management of the cardiovascular risk factors of hyperglycemia, dyslipidemia and obesity. We examine key subgroups within recent cardiovascular outcome trials, weigh the risks and benefits of several novel therapeutics and provide practical insight into the use of these agents. Our article concludes with a look towards the future and provides the practitioner and scientist with an early view of emerging therapeutics that may play an important role in primary cardiovascular prevention.

[4] *Memon R, Malek R, Munir KM*. **DOUBLING OF HEMOGLOBIN A1C ON PCSK 9 INHIBITOR THERAPY**. The American journal of medicine 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30201248
ABSTRACT

[5] *Jin JL, Sun D, Cao YX et al.* **Triglyceride glucose and hemoglobin glycation index for predicting outcomes in diabetes patients with new-onset, stable coronary artery disease: a nested case-control study**. Annals of medicine 2018:1-27.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30207490
ABSTRACT
AIM: Previous studies have shown that both triglyceride glucose (TyG) and hemoglobin glycation indexes (HGI) are predictors of cardiovascular risk. However, the prognostic value of TyG index and HGI in patients with type 2 diabetes mellitus (T2DM) and stable coronary artery disease (CAD) is not determined. METHODS: We conducted a nested case-control study among 1282 T2DM patients with stable CAD. Patients were followed up for 3846 person-years. A total of 160 patients with events (12.5%) were identified and matched individually on age, gender, previous use of lipid lowering agents and duration of follow-up with 640 controls. RESULTS: In Kaplan-Meier analysis, the upper tertiles of TyG index and HGI had a significant lower event-free survival (p = 0.002; p = 0.036, respectively). Of the note, both TyG index and HGI were associated with increased risk of MACCEs after adjusting for confounding risk factors [adjusted HR (95% CI): 1.693 (1.238-2.316); 1.215 (1.046-1.411), respectively]. Moreover, adding TyG index to the Cox model increased the C-statistic to 0.638 (95%CI: 0.595-0.683, p = 0.002) while the C-statistic was not statistically improved when HGI was included (p = 0.240). CONCLUSION: Both TyG index and HGI could predict cardiovascular outcomes in T2DM patients with new-onset, stable CAD while TyG index might be better.

[6] *Wang C, Niimi M, Watanabe T et al.* **Treatment of atherosclerosis by traditional Chinese medicine: Questions and quandaries**. Atherosclerosis 2018; 277:136-144.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30212682
ABSTRACT
Atherosclerosis and its complications, such as myocardial infarction and stroke, are the major causes of morbidity and mortality, and development of effective therapies for both prevention and treatment of this disease is critically important. Currently, there are many drugs available for atherosclerotic disease, but the lipid-lowering drugs statins are still the first-choice for treatment of hypercholesterolemia, a major risk factor for atherosclerosis. On the other hand, traditional Chinese medicines, mainly Chinese herbal medicines (CHM), have been widely used in China and in other Asian countries for the treatment of atherosclerotic diseases. Although many CHMs have been reported to be effective for treating atherosclerotic diseases for more than two thousand years, there are still many difficulties for their use, such as lack of scientific evidence assessed by rigorous clinical trials, complicated components and unclear pharmacological mechanisms, which often hamper the widespread use of CHMs in Western countries. Due to these concerns, CHMs are usually considered as complimentary or alternative treatment for atherosclerotic diseases. In this review, we provide an overview of the pathophysiology of atherosclerosis viewed by Western and traditional Chinese medicine, summarize pros and cons on the efficacy of CHMs for atherosclerosis and discuss what is necessary for CHM use to spread to Western societies.

[7] *Elena P, Elena N*. **Are we really what we eat? Nutrition and its role in the onset of rheumatoid arthritis**. Autoimmunity reviews 2018.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30213695
ABSTRACT
Accumulating research evidence suggests that individual dietary factors and dietary patterns might be implicated in the risk of development of rheumatoid arthritis (RA). This narrative review aims to present this evidence and provide nutritional recommendations for reducing RA risk in susceptible individuals. Overall, a 'Western' type diet rich in energy intake, total and saturated fat, an unbalanced ratio of n-3 to n-6 fatty acids, high in refined carbohydrates and sugar and low in fiber and antioxidants might increase the risk of RA both directly through increasing inflammation and indirectly through increasing insulin resistance and obesity, with the latter being a known risk factor for RA. On the contrary, consumption of long-chain omega-3 polyunsaturated fatty acids, derived from fish and fish oil, is associated with a reduced risk of RA probably due to their anti-inflammatory properties. The Mediterranean diet (MD), rich in plant-based foods such as wholegrains, legumes, fruit, vegetables, extra-virgin olive oil and low in red meat consumption, might have the potential to reduce the risk of RA. Based on current research evidence, it is suggested that adherence to the MD enhanced with an increased consumption of fatty fish, reduced consumption of sugar-sweetened drinks and maintenance of a normal body weight, contributes to reducing the risk of RA. Further research on RA susceptibility will allow for more specific dietary recommendations to be made.

[8] *Sara P, Elena P, Carrie R, Elena N*. **The Mediterranean Diet, fish oil supplements and Rheumatoid arthritis outcomes: evidence from clinical trials**. Autoimmunity reviews 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30213690
ABSTRACT
The impact of dietary interventions such as specific types of diet or nutritional supplements in rheumatoid arthritis (RA) has been subject to increased attention in recent years. The recognition of the unmet need to better understand the effects of specific dietary interventions on disease outcomes in RA, along with the growing patient interest on lifestyle interventions beyond pharmacotherapy, have informed the undertaking of this narrative literature review. The benefits of the Mediterranean Diet (MD) have been shown in various studies, although only a limited number of trials focus specifically on RA. Based on the studies reviewed, the MD may provide benefits in reducing pain and swollen and tender joints in RA patients. There is more and better evidence that n-3 polyunsaturated fat (PUFA) supplementation has the potential to reduce inflammation and provide clinical benefit, possibly slowing progression to pharmacotherapy. Yet, many of these studies to date are limited in their methodology; this being partly a reflection of the complexity of the research questions being addressed. Consequently, the conclusions that can be robustly drawn from their results are restricted. With a focus on clinical trials on the MD and fish oil supplementation, this review critically appraises the evidence, discussing the findings of studies in the wider context of impact on RA outcomes, methodological challenges and practical points to consider as part of the routine care of RA patients.

[9] *Afrouzian M, Al-Lahham R, Patrikeeva S et al.* **Role of the Efflux Transporters BCRP and MRP1 in Human Placental Bio-disposition of Pravastatin**. Biochem Pharmacol 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30217571

ABSTRACT
The expression and activity of human placental transporters during pregnancy could be altered by several factors including pathological changes associated with preeclampsia. The aims of this study were to identify the placental efflux transporters involved in the bio-disposition of pravastatin, determine the protein expression of these transporters and their encoding genes as well as the activity of pravastatin uptake in placentas obtained from patients with preeclampsia. ATP-dependent uptake of [3H]-pravastatin by trophoblast tissue apical and basal membrane vesicles exhibited sigmoidal kinetics. The curved shapes of Eadie-Hofstee plots indicate that more than one placental transporter are involved in the uptake of pravastatin. ATP-dependent uptake of [3H]-pravastatin into vesicles expressing MRP1-5, BCRP, and P-gp, as well as the results of inhibition studies suggest that BCRP and MRP1 are the major placental efflux transporters responsible for the in vitro uptake of pravastatin. Compared to placentas from healthy pregnancies, preeclamptic placentas had increased number of syncytial knots with increased expression of BCRP in their apical membrane and increased expression of MRP1 in the cytoplasm of the syncytiotrophoblast and in cytoplasm of syncytial knots. There was a concomitant increase in ABCC1 but not in ABCG2 gene expressions in preeclamptic placentas. ATP-dependent uptake of [3H]-pravastatin by vesicles prepared from apical membranes of preeclamptic placentas was similar to the uptake by vesicles prepared from placentas obtained after uncomplicated pregnancies (13.9 +/- 6.5 vs 14.1 +/- 5.8 pmol.mg protein(-1).min(-1)). The transporter-specific changes in the expression of BCRP and MRP1 in preeclamptic placentas did not affect the efflux activity of transporters localized on the apical membrane of the syncytiotrophoblast.

[10] *Arefieva TI, Filatova AY, Potekhina AV, Shchinova AM*. **Immunotropic Effects and Proposed Mechanism of Action for 3-Hydroxy-3-methylglutaryl-coenzyme A Reductase Inhibitors (Statins)**. Biochemistry. Biokhimiia 2018; 83:874-889.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30208827

ABSTRACT
Inhibitors of HMG-CoA reductase (statins) are the major group of lipid-lowering drugs. Along with hypocholesterolemic activity, statins exhibit anti-inflammatory and immunomodulatory properties that expand their clinical use, particularly, in the treatment of chronic inflammatory and autoimmune disorders. In this review, we critically analyze the data of statin effects on immune cells (e.g., monocytes and T cells) involved in the development of atherosclerosis and other chronic inflammatory diseases. We (i) discuss the properties of statins and routes of cell entry, as well as their major intracellular targets; (ii) evaluate the data on the effects of statins on the subset composition of circulatory monocytes, ability of monocytes to migrate to the site of inflammation (cell motility and expression of adhesion molecules and chemokine receptors), production of cytokines, matrix metalloproteinases, and reactive oxygen species by monocytes/macrophages, and antigen-presenting activity in peripheral blood monocyte-derived dendritic cells; and (iii) summarize the data on the regulation of proliferation and differentiation of various CD4+ T cell subsets (type 1/2/17 helper T cells and regulatory T cells) by statins.

Literature update week 37 (2018)

[11] *Kolber MR, Nickonchuk T, Turgeon R*. **Do PCSK9 inhibitors reduce cardiovascular events?** <u>Canadian family physician Medecin de famille canadien</u> 2018; 64:669.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30209099
ABSTRACT

[12] Jeemon P, Gupta R, Onen C *et al.* Management of Hypertension and Dyslipidemia for Primary Prevention of Cardiovascular Disease. In: Cardiovascular, Respiratory, and Related Disorders. Edited by: rd, Prabhakaran D, Anand S *et al.* Washington (DC): The International Bank for Reconstruction and Development / The World Bank
(c) 2017 International Bank for Reconstruction and Development / The World Bank.; 2017.

[13] *Phinikaridou A, Lacerda S, Lavin B et al.* **Tropoelastin: A novel marker for plaque progression and instability**. <u>Circulation. Cardiovascular imaging</u> 2018; 11.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30214669
ABSTRACT

Background: Elastolysis and ineffective elastogenesis favor the accumulation of tropoelastin, rather than cross-linked elastin, in atherosclerotic plaques. We developed gadolinium-labeled tropoelastin-specific magnetic resonance contrast agents (Gd-TESMAs) for tropoelastin imaging in animal models. Methods and Results: Two peptides, VVGSPSAQDEASPLS and YPDHVQYTHY were selected to target tropoelastin. In vitro binding, relaxivity, and biodistribution experiments enabled characterization of the probes and selecting the best candidate for in vivo MRI. MRI was performed in atherosclerotic apolipoprotein E-deficient (ApoE(-/-)) mice and New Zealand white rabbits with stable and rupture-prone plaques using Gd-TESMA. Additionally, human carotid endarterectomy specimens were imaged ex vivo. The VVGSPSAQDEASPLS-based probe discriminated between tropoelastin and cross-linked elastin (64+/-7% vs 1+/-2%, P=0.001), had high in vitro relaxivity in solution (r1-free=11.7+/-0.6mM(-1)s(-1), r1-bound to tropoelastin = 44+/-1mM(-1)s(-1)) and favorable pharmacokinetics. In vivo mice vascular enhancement (4wks=0.13+/-0.007mm(2), 8wks=0.22+/-0.01mm(2), 12wks=0.33+/-0.01mm(2), P<0.001) and R1 relaxation rate (4wks=0.90+/-0.01 s(-1), 8wks=1.40+/-0.03 s(-1), 12wks=1.87+/-0.04s(-1), P<0.001) increased with atherosclerosis progression after Gd-TESMA injection. Conversely, statin-treated (0.13+/-0.01mm(2), R1 =1.37+/-0.03s(-1)) and control (0.10+/-0.005mm(2), R1 =0.87+/-0.05s(-1)) mice showed less enhancement. Rupture-prone rabbit plaques had higher R1 relaxation rate compared with stale plaques (R1=2.26+/-0.1s(-1)vs R1=1.43+/-0.02s(-1), P=0.001), after administration of Gd-TESMA that allowed detection of rupture-prone plaques with high sensitivity (84.4%) and specificity (92.3%). Increased vascular R1 relaxation rate was observed in carotid endarterectomy plaques after soaking (R1pre= 1.1+/-0.26 s(-1) vs R1post= 3.0+/-0.1s(-1), P=0.01). Ex vivo analyses confirmed the MRI findings and showed uptake of the contrast agent to be specific for tropoelastin. Conclusions: MRI of tropoelastin provides a novel biomarker for atherosclerotic plaque progression and instability.

[14] *Cabezas MC, Burggraaf B, Klop B*. **Dyslipidemias in clinical practice**. <u>Clinica chimica acta; international journal of clinical chemistry</u> 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30201369
ABSTRACT

Literature update week 37 (2018)

Most dyslipidemic conditions have been linked to an increased risk of cardiovascular disease. Over the past few years major advances have been made regarding the genetic and metabolic basis of dyslipidemias. Detailed characterization of the genetic basis of familial lipid disorders and knowledge concerning the effects of environmental factors on the expression of dyslipidemias have increased substantially, contributing to a better diagnosis in individual patients. In addition to these developments, therapeutic options to lower cholesterol levels in clinical practice have expanded even further in patients with familial hypercholesterolemia and in subjects with cardiovascular disease. Finally, promising upcoming therapeutic lipid lowering strategies will be reviewed. All these advances will be discussed in relation to current clinical practice with special focus on common lipid disorders including familial dyslipidemias.

[15] *Luthje P, Walker S, Kamolvit W et al.* **Statins influence epithelial expression of the antimicrobial peptide LL-37/hCAP-18 independently of the mevalonate pathway**. Clinical and experimental immunology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30216432
ABSTRACT

Antimicrobial resistance increases among bacterial pathogens and new therapeutic avenues needs to be explored. Boosting innate immune mechanisms could be one attractive alternative in the defense against infectious diseases. The cholesterol-lowering drugs, statins, have been demonstrated to also affect the immune system. Here we investigate the effect of statins on the expression of the human cathelicidin antimicrobial peptide LL-37/hCAP-18 (encoded by the CAMP gene) and explore the underlying mechanisms in four epithelial cell lines of different origin. Simvastatin induced CAMP expression in bladder epithelial cells TERT-NHUCs, intestinal cells HT-29 and keratinocytes HEKa, but not in airway epithelial cells A549. Gene induction in HEKa cells was reversible by mevalonate, while this effect was independent of the cholesterol biosynthesis pathway in TERT-NHUCs. Instead, inhibition of histone deacetylases by simvastatin seems to be involved. For HT-29 cells, both mechanisms may contribute. In addition, simvastatin increased transcription of the vitamin D-activating enzyme CYP27B1, which in turn may activate LL-37/hCAP-18 production. Taken together, simvastatin is able to promote the expression of LL-37/hCAP-18, but cell line-specific differences in efficacy and the involved signaling pathways exist. This article is protected by copyright. All rights reserved.

[16] *Guan XQ, Xue YJ, Wang J et al.* **Low bone mineral density is associated with global coronary atherosclerotic plaque burden in stable angina patients**. Clin Interv Aging 2018; 13:1475-1483.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30197509
ABSTRACT

Background: Accelerated atherosclerosis is considered to be the linking factor between low bone mineral density (BMD) and increased cardiovascular events and mortality, while some coronary angiographic studies do not support this point. In this study, we attempt to provide a distinct comprehensive view of the relationship between BMD and the angiographically determined coronary atherosclerotic burden. Methods: A total of 459 consecutive patients with stable chest pain suspected of coronary artery disease (CAD) underwent both dual-energy X-ray absorptiometry scan and selective coronary angiography. The association between BMD and

global coronary atherosclerotic plaque burden as represented by the multivessel involvement and the modified Gensini score was analyzed. Results: Multivariable analysis revealed that the low BMD at femoral neck and total hip was an independent correlate of multivessel CAD. The T-scores measured at femoral neck and total hip were both negatively and independently associated to the modified Gensini score. These inversely correlated relationships between BMD and CAD were not observed at lumbar spine 1-4. Conclusion: This cross-sectional study elucidated an inverse relationship between hip BMD and the modified Gensini score, and low hip BMD values (T-scores) were significantly and independently associated with increased risk of multivessel coronary disease in patients hospitalized for stable chest pain.

[17] *Shahbaz A, Mahendhar R, Fransawy Alkomos M et al.* **Drug-induced Angioedema: A Rare Side Effect of Rosuvastatin**. Cureus 2018; 10:e2965.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30210953
ABSTRACT

Hydroxymethyl glutaryl coenzyme A reductase inhibitors (statins) are first-line medication for lowering serum cholesterol levels in the prevention of cardiovascular disease. Angioedema is the swelling of mucosa and submucosal tissue. There are no published cases of drug-induced angioedema involving rosuvastatin. We report a case of a 45-year-old female who presented with episodes of self-resolving edema of face, lips, and tongue after being on rosuvastatin. The patient denied any rash during these episodes and mentioned that self-medication with diphenhydramine did not relieve her symptoms. The patient was hemodynamically stable. The complement component 4 (C4), C1 esterase inhibitor, and complement component 1q (C1q) binding assay were within normal range. Therefore, the diagnosis of hereditary angioedema was effectively ruled out. The temporal relation between rosuvastatin and the development of angioedema and prompt resolution of symptoms after the drug discontinued suggest that rosuvastatin was the most probable culprit in the development of angioedema in our patient.

[18] *Ramin-Mangata S, Blanchard V, Lambert G*. **Key aspects of PCSK9 inhibition beyond LDL lowering**. Current opinion in lipidology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30199407
ABSTRACT

PURPOSE OF REVIEW: Our primary objective is to review the most recent findings on the biology of PCSK9 and on two key aspects of PCSK9 inhibition beyond LDL control of great clinical relevance: the regulation of lipoprotein (a) circulating levels by PCSK9 inhibitors and the putative diabetogenic effects of these novel therapies. RECENT FINDINGS: The reality of two distinct extracellular and intracellular pathways by which PCSK9 decreases the abundance of the LDLR at the surface of many cell types, most importantly hepatocytes, has recently been established. In contrast, the exact mechanisms by which PCSK9 inhibitors lower the circulating levels of lipoprotein (a) remain a point of major dispute. Despite strong indications from genetic studies that PCSK9 inhibition should increase diabetes risk, no such effect has been observed in clinical trials, and in-vitro and in-vivo studies do not clarify this issue. SUMMARY: The trafficking pathways by which PCSK9 enhance LDLR degradation via the endolysosomal extracellular route or via the Golgi-lysosomal intracellular route remain to be fully elucidated. The mechanisms by

which PCSK9 inhibitors reduce lipoprotein (a) also merit additional research efforts. The role of PCSK9 on glucose metabolism should likewise be studied in depth.

[19] *Zhu L, Luu T, Emfinger CH et al.* **CETP Inhibition Improves HDL Function but Leads to Fatty Liver and Insulin Resistance in CETP-Expressing Transgenic Mice on a High-Fat Diet**. Diabetes 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30213825
ABSTRACT

In clinical trials inhibition of cholesteryl ester transfer protein (CETP) raises HDL cholesterol levels but doesn't robustly improve cardiovascular outcomes. About 2/3 of trial participants were obese. Lower plasma CETP activity is associated with increased cardiovascular risk in human studies, and protective aspects of CETP have been observed in mice fed a high-fat diet (HFD) with regard to metabolic outcomes. To define if CETP inhibition has different effects depending on the presence of obesity, we performed short-term anacetrapib treatment in chow- and HFD-fed CETP-transgenic mice. Anacetrapib raised HDL cholesterol and improved aspects of HDL functionality including reverse cholesterol transport and HDL's anti-oxidative capacity in HFD-fed mice better than in chow-fed mice. Anacetrapib worsened the anti-inflammatory capacity of HDL in HFD-fed mice. The HDL proteome was markedly different with anacetrapib treatment in HFD-fed vs. chow-fed mice. Despite benefits on HDL, anacetrapib led to liver triglyceride accumulation and insulin resistance in HFD-fed mice. Overall, our results support a physiologic importance of CETP in protecting from fatty liver, and demonstrate a context-selectivity of CETP inhibition that might be important in obese subjects.

[20] *Shaw LJ, Min JK, Nasir K et al.* **Sex differences in calcified plaque and long-term cardiovascular mortality: observations from the CAC Consortium**. European heart journal 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30212857
ABSTRACT

Aims: Pathologic evidence supports unique sex-specific mechanisms as precursors for acute cardiovascular (CV) events. Current evidence on long-term CV risk among women when compared with men based on measures of coronary artery calcium (CAC) remains incomplete. Methods and results: A total of 63 215 asymptomatic women and men were enrolled in the multicentre, CAC Consortium with median follow-up of 12.6 years. Pooled cohort equation (PCE) risk scores and risk factor data were collected with the Agatston score and other CAC measures (number of lesions and vessels, lesion size, volume, and plaque density). Cox proportional hazard models were employed to estimate CV mortality (n = 919). Sex interactions were calculated. Women and men had average PCE risk scores of 5.8% and 9.1% (P < 0.001). Within CAC subgroups, women had fewer calcified lesions (P < 0.0001) and vessels (P = 0.017), greater lesion size (P < 0.0001), and higher plaque density (P = 0.013) when compared with men. For women and men without CAC, long-term CV mortality was similar (P = 0.67), whereas detectable CAC was associated with 1.3-higher hazard for CV death among women when compared with men (P < 0001). Cardiovascular mortality was higher among women with more extensive, numerous, or larger CAC lesions. The relative hazard for cardiovascular disease (CVD) mortality for women and men was 8.2 vs. 5.1 for multivessel CAC, 8.6 vs. 5.9 for >/=5 CAC

lesions, and 8.5 vs. 4.4 for a lesion size >/=15 mm3, respectively. Additional explorations revealed that women with larger sized and more numerous CAC lesions had 2.2-fold higher CVD mortality (P < 0.0001) as compared to men. Moreover, CAC density was not predictive of CV mortality in women (P = 0.51) but was for men (P < 0.001), when controlling for CAC volume and cardiac risk factors. Conclusion: Our overall findings support that measures beyond the Agatston score provide important clues to sex differences in atherosclerotic plaque and may further refine risk detection and focus preventive strategies of care.

[21] *Poh KK, Ambegaonkar B, Baxter CA et al.* **Low-density lipoprotein cholesterol target attainment in patients with stable or acute coronary heart disease in the Asia-Pacific region: results from the Dyslipidemia International Study II**. European journal of preventive cardiology 2018:2047487318798927.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30198749
ABSTRACT
Background As mortality due to cardiovascular disease increases throughout the world, accurate data on risk factors such as hyperlipidemia are required. This is lacking in the Asia-Pacific region. Design The observational Dyslipidemia International Study (DYSIS) II was established to quantify the extent of hyperlipidemia in adults with acute and stable coronary heart disease globally. Methods Patients with stable coronary heart disease or hospitalised with an acute coronary syndrome were enrolled across nine Asia-Pacific countries from July 2013 to October 2014. Lipid-lowering therapy and low-density lipoprotein cholesterol target attainment (<70 mg/dL) were assessed. The acute coronary syndrome cohort was followed up 4 months post-discharge. Results Of the 4592 patients enrolled, 2794 had stable coronary heart disease and 1798 were admitted with an acute coronary syndrome. In the coronary heart disease cohort, the mean low-density lipoprotein cholesterol level was 86.9 mg/dL, with 91.7% using lipid-lowering therapy and 31% achieving low-density lipoprotein cholesterol of less than 70 mg/dL. In the acute coronary syndrome cohort at admission, the corresponding values were 103.2 mg/dL, 63.4% and 23.0%, respectively. Target attainment was significantly higher in lipid-lowering therapy-treated than non-treated patients in each cohort (32.6% vs. 12.9% and 31.1% vs. 9.0%, respectively). Mean atorvastatin-equivalent dosages were low (20 +/- 15 and 22 +/- 18 mg/day, respectively), with little use of non-statin adjuvants (13.0% and 6.8%, respectively). Low-density lipoprotein cholesterol target attainment had improved by follow-up for the acute coronary syndrome patients, but remained low (41.7%). Conclusions Many patients in Asia at very high risk of recurrent cardiovascular events had a low-density lipoprotein cholesterol level above the recommended target. Although lipid-lowering therapy was common, it was not used to its full potential.

[22] *Wu Z, Xia Z, Wu B et al.* **Lipid profiling in serum from apolipoprotein E-knock out mice fed with different diets and its application to the study of the regulatory effect on lipid metabolism**. Food & function 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30207361
ABSTRACT
Atherosclerosis is a chronic disease associated with oxidative stress and inflammatory activation and is the main underlying trigger for cardiovascular disease. There are many

cardiovascular health products in the market; in order to evaluate the effect of these products, in this paper, a novel lipid profiling platform was established using the shot-gun mass spectrum method for the analysis of free fatty acid and phospholipids, and the high performance liquid chromatography coupled with mass spectroscopy method for the analysis of lipid mediators and triacylglycerol, respectively, in serum from male apolipoprotein E-knock out mice after different diet interventions. Changes in the four lipids above, and pathways and regulation of lipid metabolism in mice from different groups were further investigated. The result showed that all cardiovascular health products showed some certain potential to alleviate atherogenesis and ameliorate inflammation; among them, lemon apple cider vinegar drink and seal oil could significantly decrease triacylglycerol in mouse serum. The establishment of this lipidome profiling platform helps to better understand the metabolism regulation and intervention mechanism of different cardiovascular health products in chronic diseases, such as atherogenesis. This platform could be applied to other cardiovascular health products and provide reliable lipid profiling data for their potential effect.

[23] *Ungar L, Sanders D, Becerra B, Barseghian A*. **Percutaneous Coronary Intervention in Familial Hypercholesterolemia Is Understudied**. Frontiers in cardiovascular medicine 2018; 5:116.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30214904
ABSTRACT

Familial hypercholesterolemia (FH) is a common heritable condition in which mutations of genes governing cholesterol metabolism result in elevated LDL levels and accelerated atherosclerosis. The treatment of FH focuses on lipid lowering drugs to decrease patients' cholesterol levels and reduce their risk of cardiovascular events. Even with optimal medical therapy, some FH patients will develop coronary atherosclerosis, suffer myocardial infarction, and require revascularization. Yet, the revascularization of FH patients has not been widely studied. Here we review FH, identify unanswered questions in the interventional management of FH patients, and explore barriers and opportunities for answering these questions. Further research is needed in this neglected but important topic in interventional cardiology.

[24] *Cheng KH, Lin JR, Anderson CS et al.* **Lipid Paradox in Statin-Naive Acute Ischemic Stroke But Not Hemorrhagic Stroke**. Frontiers in neurology 2018; 9:541.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30210423
ABSTRACT

Background: Low lipid level is associated with better cardiovascular outcome. However, lipid paradox indicating low lipid level having worse outcomes could be seen under acute injury in some diseases. The present study was designed to clarify the prognostic significance of acute-phase lipid levels within 1 day after admission for stroke on mortality in first-ever statin-naive acute ischemic stroke (IS) and hemorrhagic stroke (HS). Methods: This observational study was conducted using the data collected from Stroke Registry In Chang-Gung Healthcare System (SRICHS) between 2009 and 2012. Patients with recurrent stroke, onset of symptoms >1 day, and history of the use of lipid-lowering agents prior to index stroke were excluded. Stroke was classified into IS and hypertension-related HS. The primary outcomes were 30-day and 1-year mortality identified by linkage to national death registry for date and cause of death. Receiver

operating characteristic (ROC) curve analysis and multivariate Cox proportional hazard models were used to examine the association of lipid profiles on admission with mortality. Results: Among the 18,268 admitted stroke patients, 3,746 IS and 465 HS patients were eligible for analysis. In IS, total cholesterol (TC) <163.5 mg/dL, triglyceride (TG) <94.5 mg/dL, low-density lipoprotein (LDL) <100 mg/dL, non-high-density lipoprotein cholesterol (non-HDL-C) <130.5 mg/dL, and TC/HDL ratio <4.06 had significantly higher risk for 30-day/1-year mortality with hazard ratio (HR) of 2.05/1.37, 1.65/1.31, 1.68/1.38, 1.80/1.41, and 1.58/1.38, respectively, compared with high TC, TG, LDL, non-HDL-C, and TC/HDL ratio (p < 0.01 in all cases). In HS, lipid profiles were not associated with mortality, except HDL for 30-day mortality (p = 0.025) and high uric acid (UA) concentrations for 30-day and 1-year mortality (p = 0.002 and 0.012, respectively). High fasting glucose and high National Institute of Health Stroke Scale (NIHSS) score at admission were associated with higher 30-day and 1-year mortality in both IS and HS and low blood pressure only in IS (p < 0.05). Synergic effects on mortality were found when low lipids were incorporated with high fasting glucose, low blood pressure, and high NIHSS score in IS (p < 0.05). Conclusions: Lipid paradox showing low acute-phase lipid levels with high mortality could be seen in statin-naive acute IS but not in HS. The mortality in IS was increased when low lipids were incorporated with high fasting glucose, low blood pressure, and high NIHSS score.

[25] *Ruggio A, Pedicino D, Flego D et al.* **Correlation between CD4(+)CD28(null) T lymphocytes, regulatory T cells and plaque rupture: An Optical Coherence Tomography study in Acute Coronary Syndromes**. International journal of cardiology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30217424
ABSTRACT

BACKGROUND: A sizeable proportion of patients with Acute Coronary Syndromes (ACS) shows a unique adaptive immune system profile, associated to a worse outcome, characterized by higher CD4(+)CD28(null) T-cells, lower regulatory T-cells (Treg) and increased CD4(+)CD28(null)/Treg ratio. We sought to investigate the correlation between CD4(+)CD28(null) T-cells, Treg, CD4(+)CD28(null)/Treg ratio and plaque phenotype as assessed by Optical Coherence Tomography (OCT). METHODS: Peripheral blood mononuclear cells (PBMC) were collected from 30 Non-ST Elevation Myocardial Infarction (NSTEMI) patients, sub-grouped according to OCT analysis of culprit lesions into two cohorts: Ruptured Fibrous Cap (NSTEMI-RFC, n=12) and Intact Fibrous Cap (NSTEMI-IFC, n=18). Stable Angina patients (SA, n=18) were used as controls. We examined the frequency of CD4(+)CD28(null) and Treg (defined as CD4(+)CD25(high)CD127(low)Foxp3(+) T-cells) by flow-cytometry. RESULTS: CD4(+)CD28(null) frequency (median, range) was significantly higher in NSTEMI-RFC patients (17.3%, 12.5-33.8) as compared with NSTEMI-IFC (3.8%, 0.3-14.1) and SA (3%, 0.6-17.7) (P<0.001 for all comparisons). We also found a higher CD4(+)CD28(null)/Treg ratio in NSTEMI-RFC patients (6.6%, 3.7-13.9) than in NSTEMI-IFC (1.6%, 0.3-5.2) and SA (1.2%, 0.3-8.7) (P<0.001 for all comparisons). Finally, there was an inverse correlation between CD4(+)CD28(null)/Treg ratio and cap-thickness (R=-0.44; P=0.002). CONCLUSION: Patients with NSTEMI presenting with RFC as culprit lesion at OCT evaluation have a specific perturbation of adaptive immunity, mostly involving CD4(+)CD28(null) T- cells and Tregs, as compared with patients with IFC and

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SA. This specific imbalance of T-cells might play a key role in fibrous cap thinning, predisposing atherosclerotic plaque to rupture.

[26] *Tanaka S, Ueno T, Tsunemi A et al.* **Lipoprotein Lipase Deficiency Arising in Type V Dyslipidemia**. Intern Med 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30210108
ABSTRACT

A 40-year-old Japanese man presented with child-onset hypertriglyceridemia recently complicated by diabetes mellitus. The patient's diabetes mellitus was maintained, but he had persistent insulin resistance. The patient also had persistent severe hypertriglyceridemia (1,224-4,104 mg/dL), despite the administration of bezafibrate and ezetimibe. Type V dyslipidemia was revealed by agarose gel electrophoresis and the refrigerator test, and a significantly reduced post-heparin lipoprotein lipase mass of 26 ng/mL was confirmed. Genetic testing confirmed two heterozygous LPL variants, p.Tyr88X and p.Gly215Glu in trans; thus, the patient was diagnosed with lipoprotein lipase deficiency. Lipoprotein lipase deficiency typically arises in type I dyslipidemia, but is latent in type V dyslipidemia.

[27] *Pentz R, Kaun C, Thaler B et al.* **Cardioprotective cytokine interleukin-33 is up-regulated by statins in human cardiac tissue**. Journal of cellular and molecular medicine 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30216659
ABSTRACT

Interleukin (IL)-33 is a member of the IL-1 family and is able to act cardioprotective. The aim of this study was to investigate the regulation of IL-33 by 3-hydroxy-3-methylglutaryl-coenzyme-A (HMG-CoA) reductase inhibitors (statins) and bisphosphonates (BPs) in human cardiac tissue. The lipophilic fluvastatin, simvastatin, atorvastatin, and lovastatin as well as the nitrogenous BPs alendronate and ibandronate, but not hydrophilic pravastatin increased IL-33 mRNA and intracellular IL-33 protein levels in both human adult cardiac myocytes (HACM) and fibroblasts (HACF). Additionally, fluvastatin reduced soluble ST2 secretion from HACM. IL-33 was also up-regulated by the general inhibitor of prenylation perillic acid, a RhoA kinase inhibitor Y-27632, and by latrunculin B, but statin-induced IL-33 expression was inhibited by mevalonate, geranylgeranyl pyrophosphate (GGPP) and RhoA activator U-46619. The IL-33 promoter was 2.3-fold more accessible in statin-treated HACM compared to untreated cells (P = 0.037). In explanted hearts of statin-treated patients IL-33 protein was up-regulated as compared with the hearts of non-statin-treated patients (P = 0.048). As IL-33 was previously shown to exert cardioprotective effects, one could speculate that such up-regulation of IL-33 expression in human cardiac cells, which might happen mainly through protein geranylgeranylation, could be a novel mechanism contributing to known cardioprotective effects of statins and BPs.

[28] *Chopra S, Ridley L, Murphy WR et al.* **Quantitative Analysis of Polycyclic Aromatic Hydrocarbons at Part Per Billion Levels in Fish Oil by Headspace Solid-Phase Microextraction and Gas Chromatography-Mass Spectrometry (HS-SPME-GC-MS)**. Journal of chromatographic science 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30215681
ABSTRACT

Headspace solid-phase microextraction (HS-SPME) was used in combination with gas chromatography-mass spectrometry (GC-MS) for the analysis of polycyclic aromatic hydrocarbons (PAH) at part per billion levels in fish oil samples collected from menhaden fish. The method was initially developed using fish oil from capsules spiked with a standard PAH mixture. The final HS-SPME-GC-MS method presented a linear range from 3 to 1,500 ng/g, with precision for most analytes <10% relative standard deviation. The limits of detection varied from 1 to 7 ng/g depending on the analyte. Real sample analysis was done on menhaden fish oil extracted from fish collected off the coasts of New Jersey and Louisiana. Naphthalene, fluorene, fluoranthene, pyrene, anthracene were detected at low levels of 70-180 ng/g in the real samples. The concentrations of PAHs detected in the real samples were well below established levels of concern for PAHs in finfish.

[29] *Anantharamaiah GM, Garber DW, Goldberg D et al.* **Novel Fatty Acyl ApoE Mimetic Peptides Have Increased Potency To Reduce Plasma Cholesterol In Mice And Macaques**. Journal of lipid research 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30201630
ABSTRACT

Ac-hE18A-NH2 is a dual-domain apoE mimetic peptide that possesses the putative receptor binding domain from apoE (LRKLRKRLLR, denoted hE, residues 141 to 150) covalently attached to lipid-associating peptide 18A. Like apoE, Ac-hE18A-NH2 reduces plasma cholesterol in animal models and exhibits anti-inflammatory properties independent of its cholesterol-reducing effect. Ac-hE18A-NH2 has already undergone phase I clinical trials as a lipid-lowering agent. To explore the therapeutic potential more, we designed and synthesized new analogs by linking a-aminohexanoic acid, octanoic acid, or myristic acid to LRRLRRRLLR-18A-NH2 ([R]hE18A-NH2) and examined the cholesterol-lowering potency in animals. The modified peptides effectively reduced plasma cholesterol in apoE-null mice fed standard chow or a Western diet; the myristyl analog was the most effective. A single administration of the myristyl analog reduced plasma total and LDL cholesterol in a dose-dependent manner in hypercholesterolemic cynomolgus macaques for up to 1 week despite continuation of a cholesterol-supplemented diet. The myristyl peptide (7.4 mg/kg) reduced total and LDL cholesterol at 24 hours by 64% and 74%, respectively; plasma HDL levels were modestly reduced and returned to baseline by the seventh day. These new analogs should exhibit enhanced potency at lower doses than Ac-hE18A-NH2, which may make them attractive therapeutic candidates for clinical trials.

[30] *Tort O, Escriba T, Egana-Gorrono L et al.* **Cholesterol efflux responds to viral load and CD4 counts in HIV+ patients and is dampened in HIV-exposed**. Journal of lipid research 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30213800
ABSTRACT

BACKGROUND: Cholesterol efflux (CE) capacity has been inversely associated with atherosclerosis and may provide an insight on inflammation occurring in HIV-individuals. We address this, by studying CE in HIV-patients at different stages of HIV-disease progression. METHODS: In this cross-sectional study CE from ApoB-depleted plasma, lipids levels, viral load (VL), CD4+/CD8+T-cell, high-sensitive-C-reactive protein (hsCRP) and lipoprotein(a) were evaluated in untreated HIV-patients (UHIV; n=43), elite controllers (EC; n=8), HIV-exposed

seronegative (HESN; n=32) and healthy control (HC; n=14). RESULTS: Among UHIV, those with CD4+<500cells/mm3 presented the significant lowest CE, HDL-C and ApoAI levels. EC showed similar HDL-C, ApoAI and CE compared to HC. Among UHIV, CE positively correlated with CD4+T-cell counts (Beta:1.05; 95%CI: 1.02;1.07) and for VL higher than 3.8 log, CE was inversely associated with VL (Beta:0.70; 95%CI: 0.51;0.95). Remarkably, HESN presented higher CE (0.78+-0.14) than UHIV (0.65+-0.17; p=0.0005), but lower than HC (0.90+-0.13; p=0.009). hsCRP levels were highest in the UHIV group (0.45+-0.49). CONCLUSIONS: CE was sensitive to HIV-disease progression. Low CE in HIV-patients was associated with lower CD4+T-cell, higher VL and hsCRP. CE was also lower in HESN compared with HC. Our results suggest immune status secondary to HIV progression and exposure influence plasma HDL-CE capacity.

[31] *Maki KC, Hasse W, Dicklin MR et al.* **Corn Oil Lowers Plasma Cholesterol Compared with Coconut Oil in Adults with Above-Desirable Levels of Cholesterol in a Randomized Crossover Trial**. The Journal of nutrition 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30204921
ABSTRACT

Background: Few trials have examined the effects of coconut oil consumption in comparison with polyunsaturated fatty acid-rich oils such as corn oil. Objective: This trial assessed the effects of consuming foods made with corn oil compared with coconut oil on lipids, glucose homeostasis, and inflammation. Methods: This was a preliminary randomized crossover study of men (n = 12) and women (n = 13) with a mean age of 45.2 y, mean body mass index (in kg/m2) of 27.7, fasting LDL cholesterol >/=115 mg/dL and <190 mg/dL, and triglycerides (TGs) </=375 mg/dL. Subjects consumed muffins and rolls providing 4 tablespoons (approximately 54 g) per day of corn oil or coconut oil as part of their habitual diets for 4 wk, with a 3-wk washout between conditions. Fasting plasma lipids and high-sensitivity C-reactive protein (hs-CRP) and glucose metabolism were assessed via an intravenous glucose tolerance test at baseline and 15 and 29 d of treatment. Responses were compared between treatments by ANCOVA. Results: Median baseline concentrations of LDL cholesterol, non-HDL cholesterol, total cholesterol (total-C), HDL cholesterol, total-C:HDL cholesterol, and TGs were 123, 144, 188, 46.0, 4.21, and 92.5 mg/dL, respectively. Changes from baseline for corn oil and coconut oil conditions, respectively, were: LDL cholesterol (primary outcome; -2.7% compared with +4.6%), non-HDL cholesterol (-3.0% compared with +5.8%), total-C (-0.5% compared with +7.1%), HDL cholesterol (+5.4% compared with +6.5%), total-C:HDL cholesterol (-4.3% compared with -3.3%), and TGs (-2.1% compared with +6.0%). Non-HDL cholesterol responses were significantly different between corn and coconut oil conditions (P = 0.034); differences between conditions in total-C and LDL cholesterol approached significance (both P = 0.06). Responses for hs-CRP and carbohydrate homeostasis parameters did not differ significantly between diet conditions. Conclusions: When incorporated into the habitual diet, consumption of foods providing approximately 54 g of corn oil/d produced a more favorable plasma lipid profile than did coconut oil in adults with elevated cholesterol. This trial was registered at clinicaltrials.gov as NCT03202654.

[32] *Tanaka H, Inuzuka K, Iida Y et al.* **Proprotein Convertase Subtilisin/Kexin Type 9 Is Associated with Degenerating Adipocytes in Abdominal Aortic Aneurysm**. Journal of oleo science 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30210081
ABSTRACT
Abdominal aortic aneurysm (AAA) is a common disease among the elderly. Recently, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors have been indicated as useful therapeutic tools for the treatment of cardiovascular diseases. The aim of this study was to elucidate the role of PCSK9 in the pathogenesis of AAA. We used fluorescence immunohistochemistry to assess the expression of PCSK9 in aortic tissues resected from 24 patients with AAA. Histological examination showed that PCSK9 expression in the adventitia region of the aneurysms was decreased in AAA samples. In the same region, the expression of CD36 increased. We hypothesized that CD36 expression might upregulate the transport of fatty acids into cells such as the adipocytes, and subsequently cause degradation of the adventitia in the aortic wall, contributing to AAA development.

[33] *Chang TI, Lee UK, Zeidler MR et al.* **Severity of Obstructive Sleep Apnea Is Positively Associated With the Presence of Carotid Artery Atheromas**. Journal of oral and maxillofacial surgery : official journal of the American Association of Oral and Maxillofacial Surgeons 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30213534
ABSTRACT
PURPOSE: Hypoxemia and hypertension caused by obstructive sleep apnea (OSA) often result in atherosclerosis of the carotid and coronary vessels and heightened risk of stroke and myocardial infarction (MI). Therefore, this study investigated whether severity of OSA, based on the apnea-hypopnea index (AHI), is associated with the presence of calcified carotid artery (atherosclerotic) plaque (CCAP) seen on panoramic images (PIs). MATERIALS AND METHODS: Using a cross-sectional study design, the electronic medical records and PIs of all male patients referred from the sleep medicine service to the dental service from 2010 through 2016 were reviewed. The predictor variable was the patients' OSA intensity level as defined by the American Academy of Sleep Medicine based on the AHI score. The outcome variable was the presence of CCAP on the PI. Other variables of interest, that is, demographic and atherogenic risk factors (age, body mass index, diabetes, hypertension, and hyperlipidemia), were included in a multivariate analysis to assess the association of OSA with CCAP. RESULTS: The study sample consisted of 108 men (mean age, 54.7 +/- 13.5 yr). Approximately one third (n = 33; 30.6%) presented with CCAP and this group was significantly older with greater odds of co-diagnosis of diabetes (P < .05). Patients with more "severe" OSA showed significantly greater odds of having CCAP on their PIs compared with those with "milder" OSA (odds ratio = 1.035; 95% confidence interval, 1.008-1.062; P = .010) when adjusted for confounders. CONCLUSION: There is a strong association between severity of OSA and the presence of CCAP visible on PI. These atherosclerotic plaques are "risk factors" for stroke and "risk indicators" for future MI; therefore, clinicians providing corrective airway surgery for these patients and noting concomitant CCAP on PI should refer these patients for a thorough cerebrovascular and cardiovascular workup.

[34] *Arian A, Mortazavi Moghadam SG, Kazemi T et al.* **Trial of Atorvastatin on Serum Interleukin-6, Total Antioxidant Capacity, C-Reactive Protein, and Alpha-1 Antitrypsin in Patients with Chronic Obstructive Pulmonary Disease**. Journal of research in pharmacy practice 2018; 7:141-146.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30211239
ABSTRACT

Objective: The present study was designed to investigate the effects of atorvastatin on serum high-sensitivity C-reactive protein (hs-CRP), interleukin-6 (IL-6), total antioxidant capacity (TAC), and alpha-1 antitrypsin (AAT) in patients with chronic obstructive pulmonary disease (COPD). Methods: A clinical trial study conducted on 42 cases of COPD (Vali-Asr Hospital, Birjand, East of Iran, years 2014-16). Patients were randomly assigned to 21 controls and 21 cases who treated with atorvastatin (40 mg/day for 6 months). Inhaled corticosteroid and long-acting beta-agonist were administrated in both groups. The trial was registered at the Iranian Registry of Clinical Trials (registration number: IRCT2016042527594N1). TAC was measured by ferric reducing/antioxidant power assay. An enzyme-linked immunosorbent assay was used to determine IL-6, AAT, and hs-CRP. Spearman's rho test and Wilcoxon, Mann-Whitney, paired, and independent t-tests were used for data analysis in SPSS 23. $P < 0.05$ was considered significant. Findings: A number of patients completed the study were 16 in atorvastatin and 18 in control group. Mean increments (mumol/L) of TAC (mean +/- standard deviation [SD]) were 12.81 +/- 605.25 (P = 0.68) in atorvastatin and 160.26 +/- 280.54 (P = 0.14) in control group. Mean decrements of IL-6, CRP, and AAT (mean +/- SD) were 1.41 +/- 5.51 (P = 0.71), 0.98 +/- 5.68 (P = 0.72), and 10.94 +/- 46.83 (P = 0.21) in atorvastatin and 0.91 +/- 11.70 (P = 0.75), 3.23 +/- 7.00 (P = 0.19), and 18.77 +/- 55.90 (P = 0.21) in control group. Conclusion: Atorvastatin did not succeed in maintaining TAC and CRP reduction. However, less reduction in AAT and more reduction in IL-6 in the atorvastatin group would be likely a beneficial effect in COPD.

[35] *Cai G, Yu L, Huang Z et al.* **Serum PCSK9 levels, but not PCSK9 polymorphisms, are associated with CAD risk and lipid profiles in southern Chinese Han population**. Lipids in health and disease 2018; 17:213.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30205809
ABSTRACT

BACKGROUND: Genetic and environment factors affect the occurrence and development of coronary artery disease (CAD). Proprotein convertase subtilisin/kexin type 9 (PCSK9), has been investigated extensively in the field of lipid metabolism and CAD. We performed this case-control study to investigate the relationship between serum PCSK9 levels and PCSK9 polymorphisms and lipid levels and CAD risk in a southern Chinese population. METHODS: A hospital-based case-control study with 1, 096 subjects, including 626 CAD patients and 470 controls, were conducted. Genotyping of PCSK9 polymorphisms was performed using polymerase chain reaction-ligase detection reaction (PCR-LDR) method. RESULTS: The frequencies of the AA, AG and GG genotypes of PCSK9 E670G polymorphism were 90.58, 9.27, and 0.16% in the CAD patients, compared with 88.72, 10.85 and 0.43% in the controls, respectively. No R46L variant was detected in this population. There were no significant differences in genotype and allele frequencies of PCSK9E670G polymorphism between the CAD group and the controls. Serum lipid levels were not significantly different in carriers with the G

allele and those with the AA genotype. The median (QR) of PCSK9 concentration was 1205.00 ng/l (577.28-1694.13 ng/l) in cases and 565.87 ng/l (357.17-967.50 ng/l) in controls, respectively. Compared with controls, CAD patients had significantly higher PCSK9 levels (z = 4.559, P < 0.001). After adjusting for age, gender, essential hypertension, diabetic mellitus, smoking and lipid profiles, PCSK9 levels remain significantly associated with increased CAD susceptibility (OR = 1.002, 95% CI = 1.001-1.002, P < 0.001). The correlation analyses showed that serum PCSK9 levels were positively associated with triglyceride (TG), Apo B and atherogenic index of plasma (AIP) levels in controls. No significant association between the PCSK9 E670G polymorphism and serum PCSK9 levels was observed in the CAD group and the controls. CONCLUSIONS: The present study shows that serum PCSK9 levels, but not PCSK9 polymorphisms, are associated with CAD risk in Southern Chinese Han population, and that serum PCSK9 levels are positively associated with AIP.

[36] *Jones DE, Hegade VS*. **Bezafibrate in Primary Biliary Cholangitis**. The New England journal of medicine 2018; 379:984.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30207645
ABSTRACT

[37] *Duivenvoorden R, Senders ML, van Leent MMT et al.* **Nanoimmunotherapy to treat ischaemic heart disease**. Nature reviews. Cardiology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30209355
ABSTRACT
Atherosclerosis is a chronic disease of the large arteries and the underlying cause of myocardial infarction and stroke. Atherosclerosis is driven by cholesterol accumulation and subsequent inflammation in the vessel wall. Despite the clinical successes of lipid-lowering treatments, atherosclerosis remains one of the major threats to human health worldwide. Over the past 20 years, insights into cardiovascular immunopathology have provided a plethora of new potential therapeutic targets to reduce the risk of atherosclerosis and have shifted the therapeutic focus from lipids to inflammation. In 2017, the CANTOS trial demonstrated for the first time the beneficial effects of targeting inflammation to treat cardiovascular disease by showing that IL-1beta inhibition can reduce the recurrence rate of cardiovascular events in a large cohort of patients. At the same time, preclinical studies have highlighted nanotechnology approaches that facilitate the specific targeting of innate immune cells, which could potentially generate more effective immunomodulatory treatments to induce disease regression and prevent the recurrence of cardiovascular events. The clinical translation of such nanoimmunotherapies and their application to treat patients with ischaemic heart disease are challenges that lie ahead.

[38] *Jiang X, Suenaga J, Pu H et al.* **Post-stroke administration of omega-3 polyunsaturated fatty acids promotes neurovascular restoration after ischemic stroke in mice: Efficacy declines with aging**. Neurobiology of disease 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30218758
ABSTRACT
Post-stroke treatment with omega-3 polyunsaturated fatty acids (n-3 PUFAs) may be a promising therapy in young animals but this has not been tested in aged subjects, a population

at most risk of ischemic stroke. Herein we examined the therapeutic efficacy of n-3 PUFAs after distal middle cerebral artery occlusion (dMCAO) in young (10-12weeks old) and aged (18months old) mice. Post-ischemic mice were randomly assigned to 4 groups that received: 1) regular food with low content of n-3 PUFAs, 2) intraperitoneal docosahexaenoic acid (DHA, a major component of n-3 PUFAs) injections, 3) Fish oil (FO, containing high concentration of n-3 PUFAs) dietary supplement, or 4) combined treatment with DHA and FO dietary supplement. Long-term neurorestoration induced by n-3 PUFA post-stroke administration and its underlying mechanism(s) were analyzed up to 35days after dMCAO. Aged mice showed more severe neurological deficits than young mice after dMCAO with histological lesions extended to the striatum. Notably, post-stroke treatment with combined DHA injections and FO dietary supplementation was more effective in reducing brain injury and improving sensorimotor function in aged mice than either treatment alone, albeit to a lesser extent than in the young mice. Unlike the improvement in spatial cognitive function observed in young mice, the combined treatment regimen failed to improve cognitive function in aged mice. The reduction in stroke-induced neurological deficits with n-3 PUFA post-treatment was associated with enhanced angiogenesis, oligodendrogenesis, neuron survival and white matter restoration. Together, these results indicate that the neurological benefits of n-3 PUFA administration after stroke extend to older animals and are associated with improved neuronal survival and brain remodeling, therefore suggesting that post-stroke administration of n-3 PUFAs is a viable clinically relevant treatment option against stroke.

[39] *Busnelli M, Manzini S, Sirtori CR et al.* **Effects of Vegetable Proteins on Hypercholesterolemia and Gut Microbiota Modulation**. Nutrients 2018; 10.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30200592
ABSTRACT

Risk assessment tools, i.e., validated risk prediction algorithms, to estimate the patient's 10-year risk of developing cardiovascular disease (CVD) should be used to identify high-risk people for primary prevention. Current evidence confirms that appropriate monitoring and control of risk factors either reduces the likelihood of CVD or slows down its progression. It is thus crucial that all health professionals make appropriate use of all the available intervention strategies to control risk factors: from dietary improvement and adequate physical activity to the use of functional foods, food supplements, and drugs. The gut microbiota, which encompasses 1 x 10(14) resident microorganisms, has been recently recognized as a contributing factor in the development of human disease. This review examines the effect of both some vegetable food components belong to the "protein food group" and the underexploited protein-rich hempseed on cholesterolemia and gut microbiota composition.

[40] *Henao Agudelo JS, Baia LC, Ormanji MS et al.* **Fish Oil Supplementation Reduces Inflammation but Does Not Restore Renal Function and Klotho Expression in an Adenine-Induced CKD Model**. Nutrients 2018; 10.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30208590
ABSTRACT
BACKGROUND: Chronic kidney disease and inflammation promote loss of Klotho expression. Given the well-established anti-inflammatory effects of omega-3 fatty acids, we aimed to

investigate the effect of fish oil supplementation in a model of CKD. METHODS: Male C57BL/6 mice received supplementation with an adenine-enriched diet (AD, n = 5) or standard diet (CTL, n = 5) for 10 days. Two other experimental groups were kept under the adenine diet for 10 days. Following adenine withdrawal on the 11th day, the animals returned to a standard diet supplemented with fish oil (Post AD-Fish oil, n = 9) or not (Post AD-CTL, n = 9) for an additional period of 7 days. RESULTS: Adenine mice exhibited significantly higher mean serum urea, creatinine, and renal expression of the pro-inflammatory markers Interleukin-6 (IL-6), C-X-C motif chemokine 10 (CXCL10), and Interleukin-1beta (IL-1beta), in addition to prominent renal fibrosis and reduced renal Klotho gene expression compared to the control. Post AD-Fish oil animals demonstrated a significant reduction of IL-6, C-X-C motif chemokine 9 (CXCL9), and IL-1beta compared to Post AD-CTL animals. However, serum creatinine, renal fibrosis, and Klotho were not significantly different in the fish oil-treated group. Furthermore, renal histomorphological changes such as tubular dilatation and interstitial infiltration persisted despite treatment. CONCLUSIONS: Fish oil supplementation reduced renal pro-inflammatory markers but was not able to restore renal function nor Klotho expression in an adenine-induced CKD model.

[41] *Trautwein EA, Vermeer MA, Hiemstra H, Ras RT*. **LDL-Cholesterol Lowering of Plant Sterols and Stanols-Which Factors Influence Their Efficacy?** <u>Nutrients</u> 2018; 10.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30205492
ABSTRACT
The LDL-cholesterol (LDL-C) lowering effect of plant sterols/stanols (PSS) is summarized in several meta-analyses showing a dose-response relationship with intakes of 1.5 to 3 g/day lowering LDL-C by 7.5% to 12%. This review summarizes evidence for the impact of various factors potentially influencing the LDL-C-lowering efficacy of PSS. PSS are efficacious in all food formats and in food supplements. Some factors related to food format, e.g., solid vs. liquid foods, seem to impact efficacy, while there is no difference between free PSS and esters. Compared to multiple daily intakes, once-a-day intake of PSS, especially in the morning with light breakfast, leads to a sub-optimal LDL-C lowering. However, intake frequency seems influenced by intake occasion, i.e., with or without a meal, and time of day. Meal intake is a critical factor for an optimal LDL-C lowering efficacy of PSS. While age has no impact, gender is suggested to influence the LDL-C lowering effect of PSS with greater reductions reported for men than women; but overall evidence is inconclusive and larger studies show no gender by treatment interaction. In conclusion, PSS are efficacious in all foods and food supplements; for optimal efficacy they should be consumed with a (main) meal and twice daily.

[42] *Liu M, Liu G, Wang M*. **Comparison and analysis of the therapeutic effect of different statins in the treatment of atherosclerosis**. <u>Pak J Pharm Sci</u> 2018; 31:1737-1742.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30203772
ABSTRACT
Studies have confirmed that lipid-lowering drugs can effectively control the morbidity and mortality of cardiovascular and cerebrovascular diseases and statins are the most widely used. The aim of this study is to investigate the effect and mechanism of different statins on atherosclerotic patients. The patients were randomly divided into 4 groups according to the

digital method, and the patients were treated with conventional therapy, simvastatin treatment, pravastatin treatment, atorvastatin treatment. It is concluded that statins are safe, effective and reliable for the treatment of atherosclerosis, and worthy of clinical promotion. The results also showed that after 6 months of taking statins, the levels of NO and NOS increased, the thickness of carotid intima-media became thinner and the plaque score decreased. This study provides a basis for elucidating the role of statins in the body.

[43] *Song L, Zou G, Wang X*. **Effect of doxycycline and atorvastatin on improving exercise tolerance in patients with angina pectoris**. Pak J Pharm Sci 2018; 31:1731-1735.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30203771
ABSTRACT

The therapeutic effect of statins on the stabilization of atherosclerotic plaques has been affirmed. In recent years, the inhibition of matrix metalloproteinases (MMPS) of tetracycline drug doxycycline has attracted more and more attention. In this paper, we observed the effect of atorvastatin and doxycycline on exercise tolerance in patients with stable angina pectoris. The results showed that there was no significant difference in the clinical efficacy of the two groups and the effect on the exercise tolerance (P<0.05). There were 4 cases of mild gastrointestinal reaction in the doxycycline group and no other serious adverse reactions. The total effective rate of treatment in the doxycycline group was 93.3%. Doxycycline treatment significantly reduced the frequency of angina pectoris and the incidence of cardiovascular events, and the treatment effect was better. To sum up, we think doxycycline is a safe, cheap, therapeutic drug to stabilize plaque.

[44] *Zou G, Song L, Chang L, Wang H*. **Comparison and analysis of statins drug use in the treatment of diastolic dysfunction in patients**. Pak J Pharm Sci 2018; 31:1725-1730.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30203770
ABSTRACT

Statins have multiple anti lipid effects, such as anti-inflammatory, anti-oxidation and anti arteriosclerosis, which are beneficial to improve cardiac function. Statins can effectively improve left ventricular remodeling and protect ventricular diastolic function. In this study, the effects of statin therapy on diastolic function and BNP level and exercise tolerance after exercise were observed by statins in patients with diastolic dysfunction. The results showed that after atorvastatin treatment, the exercise BNP decreased in the treatment group, which was significantly different from that before treatment and in the control group (P<0.05). This study demonstrated that atorvastatin was used to treat patients with diastolic dysfunction and exercise hypertension by lowering blood pressure and reducing exercise SBP, anti-inflammatory and improving vascular endothelial function.

[45] *Alvarado FL, Calabuig-Navarro V, Haghiac M et al.* **Maternal obesity is not associated with placental lipid accumulation in women with high omega-3 fatty acid levels**. Placenta 2018; 69:96-101.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30213493
ABSTRACT

INTRODUCTION: Placentas of obese women have higher lipid content compared to lean women. We have previously shown that supplementation of overweight and obese women with omega-3 fatty acids decreases placental esterification pathways and total lipid content in a mid-western population (Ohio). We hypothesized that placental lipid accumulation and inflammation would be similar between lean and obese women living in a region of high omega-3 intake, such as Hawaii. METHODS: Fifty-five healthy, normal glucose tolerant women from Honolulu Hawaii, dichotomized based on pre-pregnancy BMI into lean (BMI <25kg/m(2), n=29) and obese (BMI >30kg/m(2), n=26), were recruited at scheduled term cesarean delivery. Maternal plasma DHA levels were analyzed by mass spectrometry. Expression of key genes involved in fatty acid oxidation and esterification were measured in placental tissue using qPCR. Total lipids were extracted from placental tissue via the Folch method. TNF-alpha concentration was measured by enzyme-linked immunosorbent assay in placental lysates. RESULTS: DHA levels were higher in lean women compared to obese women (P=0.02). However, DHA levels in obese women in Hawaii were eight times higher compared to obese Ohioan women (P=<0.0001). Placental lipid content and expression of key genes involved in fatty acid oxidation and esterification were similar (P>0.05) between lean and obese women in Hawaii. Furthermore, TNF-alpha placental lysates were not different between lean and obese women. CONCLUSIONS: Though obese women in Hawaii have lower DHA levels compared to their lean counterparts, these levels remain over eight times as high as obese Ohioan women. These relatively high plasma omega-3 levels in obese women in Hawaii may suppress placental lipid esterification/storage and inflammation to the same levels of lean women, as seen previously in vitro.

[46] *Baum SJ, Brown AS*. **Familial Hypercholesterolemia: Although Identification Advances, Appreciation and Treatment Lag**. Reviews in cardiovascular medicine 2018; 19:S25-s30.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30207555
ABSTRACT
Familial hypercholesterolemia is one of the most common autosomal dominant inherited genetic disorders, yet it is frequently undiagnosed, leading to a markedly increased risk for cardiovascular events. Understanding the pathophysiology of the disease as well as the importance of cascade screening is critical to appropriate treatment of patients. Though the mainstay of therapy for heterozygous familial hypercholesterolemia remains statins, many patients require additional therapy including ezetimibe and/or proprotein convertase subtilisin/kexin type 9 (PCSK9) antibodies to achieve adequate low-density lipoprotein cholesterol (LDL-C) lowering. Access to PCSK9 inhibitors remains a significant clinical problem.

[47] *Baum SJ, Lepor NE, Robinson JG*. **Access to PCSK9 Inhibitors**. Reviews in cardiovascular medicine 2018; 19:S47-s50.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30207557
ABSTRACT

[48] *Robinson JG, Watson KE*. **Identifying Patients for Nonstatin Therapy**. Reviews in cardiovascular medicine 2018; 19:S1-s8.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30207552

Literature update week 37 (2018)

ABSTRACT
Statins are first-line therapy for reducing atherosclerotic cardiovascular disease (ASCVD) risk. Some patients remain at high ASCVD risk despite maximizing statin therapy. Ezetimibe and proprotein convertase subtilisin/kexin type 9 (PCSK9) monoclonal antibodies (mAbs) have been shown to reduce ASCVD events in randomized trials and may be of benefit in selected high-risk patients with cardiovascular disease (CVD) or familial hypercholesterolemia (FH). Number-needed-to-treat (NNT) to prevent one ASCVD event can help identify groups of patients who may gain a net benefit from added nonstatin therapy. Patient groups with NNTs <25 (in whom PCSK9 mAbs may approach cost effectiveness with discounting) include extremely high-risk patients (those with CVD with FH, polyvascular disease, or recurrent ASCVD events) with lowdensity lipoprotein cholesterol (LDL-C) levels >/=70 mg/dL, very high-risk patients (those with CVD with diabetes [and no polyvascular disease], chronic kidney disease, or acute coronary syndromes, or CVD or FH with poorly controlled risk factors) with LDL-C levels >/=100 mg/dL, and high-risk patients (those with CVD or FH with well-controlled risk factors) with LDL-C >/=130 mg/dL. Ezetimibe, which is generic in the United States, is reasonable for patient groups with NNTs <30, the level considered reasonable by most patients. This includes extremely high-risk patients with LDL-C levels >/=130 mg/dL, or very high-risk patients with LDL-C >/=190 mg/dL. All guidelines recommend statin therapy for the prevention of ASCVD.

[49] *Roth EM, Davidson MH*. **PCSK9 Inhibitors: Mechanism of Action, Efficacy, and Safety**. Reviews in cardiovascular medicine 2018; 19:S31-s46.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30207556

ABSTRACT
Low-density lipoprotein (LDL) receptors on the surface of liver hepatocytes are the primary way that humans regulate serum LDL cholesterol levels. Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a proteolytic enzyme that indirectly regulates serum LDL cholesterol (LDL-C) by causing the destruction of LDL receptors. Less LDL receptors result in increased LDL-C in the bloodstream but inhibiting or binding the circulating PCSK9 results in increased LDL receptors with the resultant decrease in serum LDL-C. Two PCSK9 inhibitors are currently approved for use: alirocumab and evolocumab. Both are fully human monoclonal antibodies that bind free PCSK9. Herein we discuss the mechanism of action, efficacy, and safety of PCSK9 inhibitors. clinical problem.

[50] *Tang R, Shi J, Li X et al.* **Corrigendum to "Effects of Atorvastatin on Surgical Treatments of Chronic Subdural Hematoma" [World Neurosurgery 117 (2018) e425-e429]**. World neurosurgery 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30213465
ABSTRACT