Literature update week 02 (2020)

[1] *Schafer-Somi S, Budik S*. **The ABCA1 blocking agent probucol decreases capacitation in ejaculated dog spermatozoa**. Acta veterinaria Scandinavica 2020; 62:2.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31907058
ABSTRACT
BACKGROUND: The ATP binding cassette (ABC) transporters participate in the cholesterol and phospholipid transport within and through cell membranes of many cells including spermatozoa. Cholesterol efflux is important for capacitation of spermatozoa. ABCA1 expression has been assessed in canine spermatozoa previously but its role in capacitation still has to be determined. The aim of the study was to test whether inhibition of ABCA1 (1) decreases capacitation in ejaculated and epididymal canine sperm samples and (2) decreases cholesterol efflux in the same samples. Twenty-one ejaculates and sperm from 22 epididymal tails were collected from healthy dogs. Motility was measured by CASA and viability assessed after staining with SYBR-14/PI. Samples from ejaculated sperm and sperm from epididymal tails were aliquoted. One part was incubated with the ABCA1 inhibitor probucol, the other served as a negative control. In all samples, capacitation was evaluated by chlortetracyclin (CTC) assay and cholesterol was measured by cholesterol efflux assay and colorimetric enzymatic assay. RESULTS: In ejaculated sperm, blockade of ABCA1 with 100 microM of probucol/mL of sample resulted in a significantly higher percentage of uncapacitated and acrosome reacted spermatozoa ($P < 0.001$ and $P = 0.031$), capacitation was significantly decreased (35% in probucol samples vs 54.2% in controls, $P < 0.001$). In probucol inhibited sperm samples from epididymal tails, the percentage of capacitated spermatozoa did not differ between groups but the percentage of acrosome reacted spermatozoa increased significantly ($P = 0.014$). The cholesterol measurement revealed significantly lower cholesterol concentration in the probucol group when compared to the controls ($P = 0.035$), however only in ejaculated sperm samples. CONCLUSIONS: CTC assay and cholesterol measurement revealed significant differences between groups; we conclude that inhibition of ABCA1 significantly decreased capacitation and cholesterol efflux in ejaculated canine spermatozoa. The inhibition was not complete but ABCA1 is supposed to contribute to capacitation in canine ejaculated spermatozoa. ABCA1 is probably not important for capacitation of epididymal spermatozoa but might exert other functions during spermatozoa ripening.

[2] *Hilleman DE, Wiggins BS, Bottorff MB*. **Critical Differences Between Dietary Supplement and Prescription Omega-3 Fatty Acids: A Narrative Review**. Adv Ther 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31919792
ABSTRACT
INTRODUCTION: Currently available omega-3 (OM-3) fatty acid products in the US are either nonprescription dietary supplements (e.g., fish oils) or prescription (Rx) medications. As such, we aimed to describe critical therapeutic differences among the OM-3 fatty acids, focusing on differences between fish oil supplements and Rx OM-3s. METHODS: A narrative review of known papers salient to this topic was conducted. RESULTS: Despite the multiple purported clinical benefits, the published evidence for OM-3 dietary supplements is generally insufficient, inconsistent, or negative. Rx OM-3 products are indicated as an adjunct to diet to reduce triglycerides (TG) in adults with severe hypertriglyceridemia (TG >/= 500 mg/dl). Recently, the Rx eicosapentaenoic acid (EPA)-only OM-3, icosapent ethyl, demonstrated cardiovascular (CV) risk reduction among statin-treated patients at high risk of CV disease in a large CV outcomes trial (CVOT), and is now also indicated as an adjunct to maximally tolerated statin therapy to reduce the risk of myocardial infarction, stroke, coronary

revascularization, and unstable angina requiring hospitalization in adult patients with elevated TG (>/= 150 mg/dL) and established CVD or diabetes mellitus and >/= 2 additional risk factors for CVD. In contrast to the rigorous regulatory standards for safety, efficacy, and manufacturing of medications (whether Rx or over the counter), the Food and Drug Administration manages dietary supplements as food. Issues specific to OM-3 dietary supplements include variable content, labeling inconsistencies, and poor product quality/impurity. Given these issues, OM-3 dietary supplements should not be substituted for Rx OM-3 products. The efficacy of the EPA-only Rx OM-3 product in a large CVOT cannot be extrapolated to other OM-3 products. CONCLUSION: Consumers and health care providers need to recognize critical differences between Rx and OM-3 dietary supplements to ensure appropriate use of each OM-3 product.

[3] *Jamilian M, Tabassi Z, Reiner Z et al.* **The effects of omega-3 fatty acids from flaxseed oil on genetic and metabolic profiles in patients with gestational diabetes mellitus: a randomized, double-blind, placebo-controlled trial**. The British journal of nutrition 2020:1-26.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31902378

ABSTRACT

This study was performed to evaluate the effects of omega-3 fatty acids from flaxseed oil on genetic and metabolic profiles in patients with gestational diabetes mellitus (GDM). This randomized, double-blind, placebo-controlled clinical trial was performed in 60 women with GDM. Participants were randomly divided into two groups to intake either 2 x 1,000 mg/day omega-3 fatty acids from flaxseed oil containing 400 mg alpha-linolenic acid in each capsule (n=30) or placebo (n=30) for 6 weeks. Omega-3 fatty acids intake upregulated peroxisome proliferator-activated receptor gamma (P<0.001) and low-density lipoprotein receptor (P=0.004), and downregulated gene expression of interleukin-1 (P=0.002) and tumor necrosis factor alpha (P=0.001) in peripheral blood mononuclear cells of subjects with GDM. In addition, omega-3 fatty acids supplementation reduced fasting plasma glucose (P=0.001), insulin levels (P=0.001) and insulin resistance (P<0.001), and increased insulin sensitivity (P=0.005) when compared with the placebo. Additionally, omega-3 fatty acids supplementation was associated with a decrease in triglycerides (P<0.001), VLDL-cholesterol (P<0.001), total cholesterol (P=0.01) and total-/HDL-cholesterol ratio (P=0.01) when compared with placebo. Omega-3 fatty acids administration was also associated with a significant reduction in high sensitivity C-reactive protein (P=0.006) and malondialdehyde (P<0.001), and an increase in total nitrite (P<0.001) and total glutathione levels (P=0.006) when compared with the placebo. Omega-3 fatty acids supplementation for 6 weeks to women with GDM had beneficial effects on gene expression related to insulin, lipid and inflammation, glycemic control, lipids, inflammatory markers and oxidative stress.This study was registered in the Iranian website (www.irct.ir) for registration of clinical trials (http://www.irct.ir: IRCT20170513033941N42).

[4] *Kotlovskiy MY, Udut EV, Kairov GT et al.* **Effects of Simvastatin on the Metabolism of Fatty Acids in Combined Secondary Prevention of Coronary Heart Disease: Dosage and Gender Differences between the Effects**. Cardiovascular & hematological disorders drug targets 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31916523

ABSTRACT

BACKGROUND: Statins are currently used for secondary prevention of coronary heart disease (CHD), as the lipid-lowering therapy with them is proven safe and effective. OBJECTIVE: The purpose of this

research is to investigate the dose-dependent effect of statins used for secondary prevention of coronary heart disease, as well as mechanisms of quantitative and qualitative changes in lipoproteins, fatty acids, and cholesterol in the blood and tissues of people of both sexes. METHODS: In a clinical trial (n=125, of which 89 patients belong to group 1 and 36 - to group 2) and an experiment on laboratory animals (n = 100), simvastatin reduced the total level of fatty acids in blood plasma, when given in the amount that was within the therapeutic dose range. RESULTS: This effect was achieved through a drug-induced improvement in the capacity of hepatic cells to absorb low-density (LDL) and very-low-density (VLDL) lipoproteins. CONCLUSIONS: Considering the formation of saturated fatty acids, statin performed better in males. With Omega-3 polyunsaturated fatty acids involved, changes in lipoproteins, cholesterol and fatty acids (liver and myocardium) were similar to those caused by small doses of a statin drug. Effects from the combination of bisoprolol and acetylsalicylic acid were completely different from those caused by the use of statin.

[5] *Paskova U*. **Lipid profile and risks of cardiovascular diseases in conditions of rheumatoid arthritis**. Ceska a Slovenska farmacie : casopis Ceske farmaceuticke spolecnosti a Slovenske farmaceuticke spolecnosti 2019; 68:219-228.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31906689
ABSTRACT
Cardiovascular diseases (CVD) belong to the leading causes of mortality worldwide. Elevated levels of total cholesterol and LDL cholesterol are associated with increased incidence of CVD in the population. Reversely, reduction of lipoprotein levels in plasma results in a positive impact on CVD prevention. Patients with rheumatoid arthritis (RA), a chronic inflammatory disease, have markedly increased mortality risk due to CVD, despite lower lipoprotein levels in comparison with common population. This is known as the “lipid paradox”. RA itself represents an independent CVD risk factor acting as an inflammatory component. Inflammation, manifested by systemic elevated concentrations of pro-inflammatory cytokines, mainly interleukin 6 (IL-6), interleukin 1β (IL-1β) and the tumour necrosis factor α (TNF-α) in RA, is considered to be the main contributor of atherogenesis via its impact on lipoprotein metabolism and on the biology of the arterial wall. Atherosclerosis, a complex process including a number of mechanisms, is not only regarded as dysregulation of lipid metabolism, but also as a chronic inflammatory disease. This review summarizes the newest findings about the qualitative and quantitative alterations of lipids and lipoproteins affected by low-grade inflammation triggered by RA and their consequences on atherosclerosis.

[6] *Navar AM, Mulder HM, Wojdyla DM, Peterson ED*. **Have the Major Cardiovascular Outcomes Trials Impacted Payer Approval Rates for PCSK9 Inhibitors?** Circulation. Cardiovascular quality and outcomes 2020; 13:e006019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31918581
ABSTRACT

[7] *Becher T, Riascos-Bernal DF, Kramer DJ et al.* **Three-Dimensional Imaging Provides Detailed Atherosclerotic Plaque Morphology and Reveals Angiogenesis after Carotid Artery Ligation**. Circulation research 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31914850
ABSTRACT

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Rationale: Remodeling of the vessel wall and the formation of vascular networks are dynamic processes that occur during mammalian embryonic development and in adulthood. Plaque development and excessive neointima formation are hallmarks of atherosclerosis and vascular injury. As our understanding of these complex processes evolves, there is a need to develop new imaging techniques to study underlying mechanisms. Objective: We used tissue clearing and light-sheet microscopy for three-dimensional (3D) profiling of the vascular response to carotid artery ligation and induction of atherosclerosis in mouse models.Methods and Results: Adipo-Clear and immunolabeling in combination with light-sheet microscopy were applied to image carotid arteries (CAs) and brachiocephalic arteries (BCAs), allowing for 3D reconstruction of vessel architecture. Entire 3D neointima formations with different geometries were observed within the CA and scored by volumetric analysis. Additionally, we identified a CD31-positive adventitial plexus after ligation of the CA that evolved and matured over time. We also used this method to characterize plaque extent and composition in the BCA of ApoE-deficient mice on high-fat diet. The plaques exhibited inter-animal differences in terms of plaque volume, geometry, and ratio of acellular core to plaque volume. A 3D reconstruction of the endothelium overlying the plaque was also generated.Conclusions: We present a novel approach to characterize vascular remodeling in adult mice using Adipo-Clear in combination with light-sheet microscopy. Our method reconstructs 3D neointima formation after arterial injury and allows for volumetric analysis of remodeling, in addition to revealing angiogenesis and maturation of a plexus surrounding the CA. This method generates complete 3D reconstructions of atherosclerotic plaques and uncovers their volume, geometry, acellular component, surface, and spatial position within the BCA. Our approach may be used in a number of mouse models of cardiovascular disease to assess vessel geometry and volume.

[8] *Hwang YC*. **Response: Comparison of the Efficacy of Rosuvastatin Monotherapy 20 mg with Rosuvastatin 5 mg and Ezetimibe 10 mg Combination Therapy on Lipid Parameters in Patients with Type 2 Diabetes Mellitus (Diabetes Metab J 2019;43:582-9)**. Diabetes Metab J 2019; 43:915-916.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31902151
ABSTRACT

[9] *Sohn TS*. **Letter: Comparison of the Efficacy of Rosuvastatin Monotherapy 20 mg with Rosuvastatin 5 mg and Ezetimibe 10 mg Combination Therapy on Lipid Parameters in Patients with Type 2 Diabetes Mellitus (Diabetes Metab J 2019;43:582-9)**. Diabetes Metab J 2019; 43:909-910.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31902148
ABSTRACT

[10] *Burggraaf B, Pouw N, Fernandez Arroyo S et al.* **A Placebo-controlled Proof-of-Concept Study of Alirocumab on Postprandial Lipids and Vascular Elasticity in Insulin-treated patients with Type 2 Diabetes Mellitus**. Diabetes Obes Metab 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31912632
ABSTRACT
AIMS: Type 2 Diabetes Mellitus (T2DM) is associated with an increased risk for cardiovascular disease (CVD) linked to atherogenic dyslipidemia and postprandial hyperlipidemia. Alirocumab, a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor, improves CVD risk by reducing the concentration of low-density lipoprotein-cholesterol (LDL-C). However, effects of PCK9 inhibitors on other aspects of

diabetic dyslipidemia, especially in the postprandial situation, are less clear. MATERIAL AND METHODS: Twelve male patients with T2DM on intensive insulin regimen completed a six week randomized, double-blind, placebo-controlled, proof-of-concept study. Participants received 3 biweekly dosages of subcutaneous alirocumab (150 mg) or placebo. Before and after the intervention, fasting and postprandial triglyceride (TG) plasma levels, apolipoprotein (apo) B48, lipoprotein composition isolated by ultracentrifugation, vascular function and markers of inflammation were evaluated. RESULTS: Alirocumab treatment reduced fasting plasma TG levels (between group median change (-24.7%; p=0.018) and fasting apo B48 serum levels (-35.9%; p=0.039) compared to placebo. Alirocumab reduced the plasma TG area under the curve (AUC) (-26.43%; p=0.006) and apo B48 AUC (-55.7%; p=0.046), as well as plasma TG incremental AUC (-21.4%; p=0.04) and apo B48 incremental AUC (-26.8%; p=0.02). In addition, alirocumab reduced fasting and postprandial TG levels in VLDL and LDL. Alirocumab improved fasting pulse wave velocity, but no changes in postprandial markers of inflammation were observed. CONCLUSIONS: In addition to the well-known LDL-C-reducing effects, 6-weeks alirocumab treatment lowered both fasting and postprandial plasma TG levels by reducing the TG levels in VLDL and LDL and the concentration of intestinal remnants.

[11] *Gencer B, Mach F*. **Potential of Lipoprotein(a)-Lowering Strategies in Treating Coronary Artery Disease**. Drugs 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31916186
ABSTRACT
High levels of lipoprotein(a) [Lp(a)] are considered causal risk factor of cardiovascular disease (CVD), including aortic stenosis. The 2019 ESC/EAC guidelines for the management of dyslipidaemias recommend to measure Lp(a) at least once in each adult person's lifetime to identify those with inherited Lp(a) levels > 180 mg/dL (> 430 nmol/L) who may have a cardiovascular risk similar to heterozygous familial hypercholesterolaemia or in selected patients with a family history of premature CVD and for reclassification in people who are borderline between moderate- and high-risk. Some lipid-lowering agents not specific for Lp(a) have shown to reduce Lp(a) levels (niacin, PCSK9 inhibitors and CETP inhibitors). Prespecified analyses from the FOURIER trial have shown that participants who had reduction in Lp(a) levels with PCSK9 levels had a decreased risk of cardiovascular events. To lower Lp(a), two antisense oligonucleotides are under development targeting apolipoprotein B and apolipoprotein (a). Mipomersen is an oligonucleotide that targets apolipoprotein B, with a potential benefit in reducing Lp(a) by 20-50%. AKCEA-APO(a)-LRX is another antisense oligonucleotide targeting Lp(a) and reducing Lp(a) by 50-80%. A Phase III study with AKCEA-APO(a)-LRX will start in order to evaluate the effect on cardiovascular outcomes.

[12] *Van Wyngene L, Vanderhaeghen T, Timmermans S et al.* **Hepatic PPARalpha function and lipid metabolic pathways are dysregulated in polymicrobial sepsis**. EMBO molecular medicine 2020:e11319.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31916705
ABSTRACT
Despite intensive research and constant medical progress, sepsis remains one of the most urgent unmet medical needs of today. Most studies have been focused on the inflammatory component of the disease; however, recent advances support the notion that sepsis is accompanied by extensive

metabolic perturbations. During times of limited caloric intake and high energy needs, the liver acts as the central metabolic hub in which PPARalpha is crucial to coordinate the breakdown of fatty acids. The role of hepatic PPARalpha in liver dysfunction during sepsis has hardly been explored. We demonstrate that sepsis leads to a starvation response that is hindered by the rapid decline of hepatic PPARalpha levels, causing excess free fatty acids, leading to lipotoxicity, and glycerol. In addition, treatment of mice with the PPARalpha agonist pemafibrate protects against bacterial sepsis by improving hepatic PPARalpha function, reducing lipotoxicity and tissue damage. Since lipolysis is also increased in sepsis patients and pemafibrate protects after the onset of sepsis, these findings may point toward new therapeutic leads in sepsis.

[13] *Minana G, Nunez J, Bayes-Genis A et al.* **Role of PCSK9 in the course of ejection fraction change after ST-segment elevation myocardial infarction: a pilot study**. ESC heart failure 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31903686
ABSTRACT
AIMS: Proprotein convertase subtilisin/kexin type 9 (PCSK9) has emerged as a therapeutic target for reducing plasma low-density lipoprotein cholesterol. Beyond lipid control, recent findings suggest a deleterious effect of this protein in the pathogenesis of postmyocardial infarction left ventricle remodelling and heart failure-related complications. The aim of this study was to assess the relationship between circulating PCSK9 and 6 month cardiac magnetic resonance imaging-derived left ventricular ejection fraction (LVEF) after a first ST-segment elevation myocardial infarction (STEMI). METHODS AND RESULTS: We prospectively evaluated 40 patients with a first STEMI, LVEF < 50% and treated with primary percutaneous coronary intervention in which PCSK9 was measured 24 h postreperfusion. All patients underwent cardiac magnetic resonance imaging 1 week and 6 months after STEMI. Baseline characteristics were compared across median values of PCSK9. The association between PCSK9 levels and LVEF at 6 months was evaluated by analysis of covariance. The mean age of the sample was 60 +/- 12 years and 33 (82.5%) were male patients. The infarct location was anterior in 27 patients (67.5%), and 9 patients (22.5%) were Killip class >/= II. The mean 1 week and 6 month LVEF were 41 +/- 7% and 48 +/- 10%, respectively. The mean PCSK9 was 1.93 +/- 0.38 U/mL. Testing the association between serum PCSK9 and 6 month LVEF with analysis of covariance revealed an inverse relationship (r = -0.35, P = 0.028). After multivariate adjustment, circulating PCSK9 remained significant and inversely associated with 6 month LVEF (P = 0.002). CONCLUSIONS: In patients with a first STEMI with reduced ejection fraction at index admission and treated with primary percutaneous coronary intervention, circulating PCSK9 was associated with lower LVEF at 6 months.

[14] *Agarwal N, Golwala H*. **Lowering Inflammation Through Lipid Lowering Therapy- Are we there yet?** European heart journal. Quality of care & clinical outcomes 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31913447
ABSTRACT

[15] *Vukovic R, Zeljkovic A, Bufan B et al.* **Hashimoto Thyroiditis and Dyslipidemia in Childhood: A Review**. Frontiers in endocrinology 2019; 10:868.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31920978
ABSTRACT

Hashimoto autoimmune thyroiditis (AIT) is the most common cause of acquired hypothyroidism in the pediatric population. Development of AIT is mediated mainly by cellular immune response directed toward thyroid autoantigens, leading to inflammation and impaired function of thyroid gland. Both thyroid dysfunction and inflammation affect the metabolism of plasma lipoproteins. The alterations in lipid profile worsen with the advancement of hypothyroidism, ranging from discrete changes in euthyroid AIT patients, to atherogenic dyslipidemia in the overt hypothyroidism. In this review, characteristics of dyslipidemia in pediatric AIT patients, and the consequences in respect to the risk for cardiovascular disease (CVD) development are discussed. Additionally, benefit of L-thyroxine treatment on serum lipid profile in pediatric AIT patients is addressed. Finally, potential usefulness of novel lipid biomarkers, such as proprotein convertase subtilisin/kexin type 9 (PCSK9), non-cholesterol sterols, low-density lipoprotein particle size and number, and high-density lipoprotein structure and functionality in AIT patients is also covered. Further longitudinal studies are needed in order to elucidate the long-term cardiovascular outcomes of dyslipidemia in pediatric patients with Hashimoto AIT.

[16] *Shinozaki N, Murakami T, Ohno Y et al.* **Effect of high-dose strong statin for preventing periprocedural ischemic complications of carotid artery stenting**. Heart Vessels 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31925501
ABSTRACT
Statin therapy has been shown to induce carotid atherosclerotic plaque regression and reduce the periprocedural ischemic complications of carotid artery stenting (CAS). This study assessed the safety and usefulness of pretreatment using a high-dose strong statin (HDSS) to reduce the periprocedural ischemic complications of CAS. We analyzed 117 carotid lesions treated by CAS that were evaluated with magnetic resonance imaging (MRI) within 48 h after the procedure. For 67 lesions, an HDSS (rosuvastatin 20 mg or atorvastatin 40 mg daily) were prescribed from at least 14 days before CAS to at least 14 days after procedure (HDSS group). Clinical and angiographic data, as well as in-hospital outcomes, of the HDSS group were retrospectively compared with 50 lesions with conventional treatment without an HDSS (non-HDSS group). There were no significant differences in the baseline clinical and procedural characteristics between the two groups. There was no side effect related to the HDSS. Stroke rates were similar between the two groups (3.0% in HDSS group vs 8.0% in non-HDSS group, p = 0.22). All were minor strokes. Compared to the non-HDSS group, the HDSS group had a lower frequency of new lesions on diffusion-weighted imaging (DWI) with MRI (25.4% vs 44.0%, p = 0.0345). New ipsilateral DWI-positive rate in the HDSS group was significantly lower than in the non-HDSS group (16.4% vs 34.0%, p = 0.0275). Nonipsilateral (contralateral or posterior circulation) DWI-positive rates were similar between the two groups (13.4% vs 20.0%, p = 0.34). Pretreatment with an HDSS might reduce the periprocedural ischemic complications of CAS.

[17] *D'Ardes D, Santilli F, Guagnano MT et al.* **From Endothelium to Lipids, Through microRNAs and PCSK9: A Fascinating Travel Across Atherosclerosis**. High blood pressure & cardiovascular prevention : the official journal of the Italian Society of Hypertension 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31925708
ABSTRACT
Lipids and endothelium are pivotal players on the scene of atherosclerosis and their interaction is crucial for the establishment of the pathological processes. The endothelium is not only the border of the arterial wall: it plays a key role in regulating circulating fatty acids and lipoproteins and vice versa it

is regulated by these lipidic molecules thereby promoting atherosclerosis. Inflammation is another important element in the relationship between lipids and endothelium. Recently, proprotein convertase subtilisin/kexin type 9 (PCSK9) has been recognized as a fundamental regulator of LDL-C and anti-PCSK9 monoclonal antibodies have been approved for therapeutic use in hypercholesterolemia, with the promise to subvert the natural history of the disease. Moreover, growing experimental and clinical evidence is enlarging our understanding of the mechanisms through which this protein may facilitate the genesis of atherosclerosis, independently of its impact on lipid metabolism. In addition, environmental stimuli may affect the post-transcriptional regulation of genes through micro-RNAs, which in turn play a key role in orchestrating the crosstalk between endothelium and cholesterol. Advances in experimental research, with development of high throughput techniques, have led, over the last century, to a tremendous progress in the understanding and fine tuning of the molecular mechanisms leading to atherosclerosis. Identification of pivotal keystone molecules bridging lipid metabolism, endothelial dysfunction and atherogenesis will provide the mechanistic substrate to test valuable targets for prediction, prevention and treatment of atherosclerosis-related disease.

[18] *Kim YU, Kee P, Danila D, Teng BB*. **A Critical Role of PCSK9 in Mediating IL-17-Producing T Cell Responses in Hyperlipidemia**. Immune network 2019; 19:e41.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31921471
ABSTRACT
We previously demonstrated that atherogenic Ldlr (-/-) Apobec1 (-/-) (LDb) double knockout mice lacking both low-density lipoprotein receptor (LDLR) and apolipoprotein B mRNA-editing catalytic polypeptide-1 (Apobec1) had increased serum IL-17 levels, with T cell programming shifted towards Th17 cells. In this study, we assessed the role of proprotein convertase subtilisin/kexin type 9 (PCSK9) in T cell programming and atherogenesis. We deleted the Pcsk9 gene from LDb mice to generate Ldlr (-/-) Apobec1 (-/-) Pcsk9 (-/-) (LTp) triple knockout mice. Atherosclerosis in the aortic sinus and aorta were quantitated. Lymphoid cells were analyzed by flow cytometry, ELISA and real-time PCR. Despite of dyslipidemia, LTp mice developed barely detectable atherosclerotic lesions. The IL-17, was very low in plasma and barely detectable in the aortic sinus in the LTp mice. In the spleen, the number of CD4(+)CD8(-) cells and splenocytes were much lower in the LDb mice than LTp mice, whereas, the IL-17-producing cells of gammadeltaTCR(+) T cells and effector memory CD4(+) T cells (CD44(hi)CD4(+)) in the spleen were significantly higher in the LDb mice than in the LTp mice. The Rorc mRNA expression levels were elevated in LDb mice compared to LTp mice. When re-stimulated with an anti-CD3 Ab, CD44(hi)CD4(+) T cells from LDb mice secreted more IL-17 than those from LTp mice. T cells from LDb mice (with PCSK9) produce more IL-17 at basal and stimulated conditions when compared with LTp mice (without PCSK9). Despite the dyslipidemic profile and the lack of LDLR, atherogenesis is markedly reduced in LTp mice. These results suggest that PCSK9 is associated with changes in T cell programming that contributes to the development of atherosclerosis.

[19] *Bettadahalli S, Acharya P, Talahalli R*. **Evidence on n-3 Fatty Acids and Oleic Acid Role in Retinal Inflammation and Microvascular Integrity: Insight from a Hyperlipidemic Rat Model**. Inflammation 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31903511
ABSTRACT

Loss of retinal function due to manifestation of chronic inflammation and oxidative stress in hyperglycemia is well addressed. However, the effect of hyperlipidemia on retinal inflammation and microvascular integrity, and the modulatory effects of oxidation-stable oleic acid and long-chain n-3 fatty acids have never been addressed. The objective of this investigation was to assess the retinoprotective effect of oxidation stable oleic acid and oxidation-susceptible EPA + DHA on retinal inflammation and microvascular integrity, under hyperlipidemic conditions. Male Wistar rats were fed with control (7.0% lard), high-fat (35.0% lard), high-fat with fish oil (17.5% fish oil + 17.5% lard), high-fat with olive oil (17.5% olive oil + 17.5% lard), and high-fat with fish oil and olive oil (11.66% fish oil + 11.66% of olive oil + 11.66% of lard) diet for 90 days. Systemic and retinal inflammation, as measured by eicosanoids and cytokines, retinal expression of NF-kB, capillary degeneration, and pericyte loss, were assessed. Hyperlipidemia significantly ($p < 0.05$) increased the markers of inflammation (PGE2, LTB4, LTC4, IL-1beta, MCP-1, and TNF-alpha) in serum and retina. Besides, the retinal NF-kB-p65 expression, capillary degeneration, and pericyte loss were significantly ($p < 0.05$) increased under hyperlipidemic conditions. Dietary incorporation of oleic acid and EPA + DHA significantly ($p < 0.05$) suppressed hyperlipidemia-induced effects in the retina. In conclusion, hyperlipidemia causes retinal aberrations by compromising the balance in the inflammatory response and microvascular integrity. Dietary incorporation of oleic acid and long-chain n-3 fatty acids prevents hyperlipidemia-induced aberrations in the retina.

[20] *Carrero A, Berenguer J, Hontanon V et al.* **Effects of eradication of HCV on cardiovascular risk and preclinical atherosclerosis in HIV/HCV-coinfected patients**. Journal of acquired immune deficiency syndromes (1999) 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31913996
ABSTRACT
BACKGROUND: To assess the effects of eradication of HCV on cardiovascular risk and preclinical atherosclerosis in HIV/HCV-coinfected patients. SETTING: Prospective cohort study METHODS:: We assessed serum lipids, 10-year Framingham cardiovascular risk (CVR) scores, pulse wave velocity (PWV), carotid intima-media thickness (cIMT), and biomarkers of inflammation and endothelial dysfunction (BMKs) at baseline and 96 weeks (wk) after initiation of anti-HCV therapy (Rx) in HIV/HCV-coinfected patients. RESULTS: A total of 237 patients were included. Anti-HCV therapy comprised pegylated interferon and ribavirin (PR) plus 1 direct-acting antiviral (DAA) in 55.2%, PR in 33.8%, and all-oral DAA in 11.0%. A total of 147 (62.0%) patients achieved sustained viral response (SVR). Median increases in low-density lipoprotein cholesterol (LDL-C) in patients with and without SVR were 14 mg/dl and 0 mg/dl (P=.024), respectively. Increases in CVR categories were found in 26.9% of patients with SVR (P=.005 vs. baseline) and 8.1% of patients without SVR (P=.433). This resulted in a significant interaction between SVR and CVR over time (P<0.001). No significant effect of SVR was observed for PWV (P=0.446), cIMT (P=0.320), and BMKs of inflammation and endothelial dysfunction. CONCLUSIONS: In coinfected patients, eradication of HCV had no effect on markers of preclinical atherosclerosis and BMKs of inflammation and endothelial dysfunction; but was associated with a clinically relevant rise in serum LDL-C. Evaluation of CVR should be an integral part of care following the cure of chronic hepatitis C in patients with HIV.

[21] *Webel A, Davey CH, Schexnayder J et al.* **The Impact of Perceived Cardiovascular Risk on Cardiovascular Disease Prevention Behaviors in People With and Without HIV Infection**. Journal of acquired immune deficiency syndromes (1999) 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31914003
ABSTRACT
BACKGROUND: People living with HIV (PLHIV) are at elevated risk of developing atherosclerotic cardiovascular disease (ASCVD). PLHIV do not engage in recommended levels of ASCVD prevention behaviors, perhaps due to a reduced perception of risk for ASCVD. We examined how HIV status influences knowledge, beliefs, and perception of risk for ASCVD and ASCVD prevention behaviors. METHODS AND RESULTS: We conducted a mixed-methods study of 191 PLHIV and demographically similar HIV-uninfected adults. Participants completed self-reported surveys on CVD risk perceptions, adherence to CVD medication (aspirin, antihypertensives, lipid lowering medication), and three dietary intake interviews. All wore an accelerometer to measure physical activity. A subset of PLHIV (n=38) also completed qualitative focus groups to further examine the influence of HIV on knowledge, perception of risk for ASCVD, and behavior. PARTICIPANTS: were approximately 54 (+/-10) years, mostly male (n=111; 58%), and African American (n=151, 83%) with an average 10-year risk of an ASCVD event of 10.4 (+/-8.2)%. PLHIV were less likely to engage in physical activity (44% vs 65%, p<0.05), and HIV status was associated with 43 fewer minutes of physical activity per week (p=0.004). Adherence to ASCVD medications was better among PLHIV (p<0.001). Diet composition was similar between groups (p>0.05). HIV status did not influence ASCVD risk perceptions (p> 0.05) and modestly influenced physical activity and smoking. CONCLUSIONS: While perceptions of ASCVD risk modestly influence some behaviors, additional barriers and insufficient cues to action result in suboptimal physical activity, dietary intake, and smoking rates. However, PLHIV have high adherence to ASCVD medications, which can be harnessed to reduce their high burden of ASCVD.

[22] *Weingartner O, Sijbrands EJG, Lutjohann D*. **Optimizing Clinical Cardiovascular Outcomes by a Personalized Approach to Add Ezetimibe to a Statin**. Journal of the American College of Cardiology 2020; 75:128.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31918825
ABSTRACT

[23] *Wang WT, Hsu PF, Lin CC et al.* **Hemoglobin A1C Levels are Independently Associated with the Risk of Coronary Atherosclerotic Plaques in Patients without Diabetes: A Cross-Sectional Study**. Journal of atherosclerosis and thrombosis 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31902804
ABSTRACT
AIM: Coronary atherosclerotic plaques can be detected in asymptomatic subjects and are related to low-density lipoprotein cholesterol (LDL) levels in patients with coronary artery disease. However, researchers have not yet determined the associations between various plaque characteristics and other lipid parameters, such as HDL-C and TG levels, in low-risk populations. METHODS: One thousand sixty-four non-diabetic subjects (age, 57.86+/-9.73 years; 752 males) who underwent coronary computed tomography angiography (CCTA) were enrolled and the severity and patterns of atherosclerotic plaques were analyzed. RESULTS: Statin use was reported by 25% of the study population, and subjects with greater coronary plaque involvement (segment involvement score, SIS)

were older and had a higher body mass index (BMI), blood pressure, unfavorable lipid profiles and comorbidities. After adjusting for comorbidities, only age (beta=0.085, p0.001), the male gender (beta=1.384, p0.001), BMI (beta=0.055, p=0.019) and HbA1C levels (beta=0.894, p0.001) were independent factors predicting the greater coronary plaque involvement in non-diabetic subjects. In the analysis of significantly different (50%) stenosis plaque patterns, age (OR: 1.082, 95% CI: 10.47-1.118) and a former smoking status (OR: 2.061, 95% CI: 1.013-4.193) were independently associated with calcified plaques. For partial calcified (mixed type) plaques, only age (OR: 1.085, 95% CI: 1.052-1.119), the male gender (OR: 7.082, 95% CI: 2.638-19.018), HbA1C levels (OR: 2.074, 95% CI: 1.036-4.151), and current smoking status (OR: 1.848, 95% CI: 1.089-3.138) were independently associated with the risk of the presence of significant stenosis in mixed plaques. CONCLUSIONS: A higher HbA1c levels is independently associated with the presence and severity of coronary artery atherosclerosis in non-diabetic subjects, even when LDL-C levels are tightly controlled.

[24] *Wang X, He Y, Wang T et al.* **Lipid-Lowering Therapy and Low-Density Lipoprotein Cholesterol (LDL-C) Goal Achievement in High-Cardiovascular-Risk Patients in Fuzhou, China**. Journal of cardiovascular pharmacology and therapeutics 2020:1074248419899298.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31918567
ABSTRACT
PURPOSE: This study aims to analyze the treatment patterns and goal attainment of low-density lipoprotein cholesterol (LDL-C) among patients with atherosclerotic cardiovascular disease (ASCVD) and diabetes mellitus (DM) in the real-world setting in Fuzhou, China. METHODS: Patients aged >/=20 years with a valid LDL-C measurement (index date) in 2016 were selected from National Healthcare Big Data in Fuzhou, China. Patients were stratified into mutually exclusive cardiovascular risk categories: ASCVD (including recent acute coronary syndrome [ACS], chronic coronary heart disease [CHD], stroke, and peripheral arterial disease [PAD]), and DM alone (without ASCVD). Lipid-modifying medication and LDL-C attainment at the index date were assessed. RESULTS: A total of 21 989 patients met the inclusion criteria, including 17 320 (78.8%) with ASCVD and 4669 (21.2%) with DM alone; 47.7% of patients received current statin therapy in the overall cohort (53.5% in ASCVD, 26.5% for DM); 20.5% ASCVD population achieved LDL-C target with the highest in patients with recent ACS (33.8%), followed by chronic CHD (21.2%), PAD (20.9%), and ischemic stroke (17.3%); 49.0% of patients with DM achieved LDL-C target. Higher LDL-C attainment was observed in high-intensity statin and a combination of statin and nonstatin groups. Atorvastatin was the most commonly used statin with the highest LDL-C attainment, followed by rosuvastatin. CONCLUSION: Compared with previous studies in China, our study found a relatively low statin use and LDL-C target attainment, but higher than similar studies in Europe. Guidelines should be well complied and more prescription of high-intensity statin or statin and nonstatin combination should be advocated.

[25] *Taskinen MR, Bjornson E, Andersson L et al.* **Impact of proprotein convertase subtilisin/kexin type 9 inhibition with evolocumab on the postprandial responses of triglyceride-rich lipoproteins in type II diabetic subjects**. Journal of clinical lipidology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31917184
ABSTRACT
BACKGROUND: Monoclonal antibodies to proprotein convertase subtilisin/kexin type 9 (PCSK9) significantly lower the levels of low-density lipoprotein and very-low-density lipoproteins (VLDL), but

their effect on postprandial lipoprotein metabolism in dyslipidemic subjects is unclear. OBJECTIVE: This study aimed to investigate the effects of evolocumab on postprandial lipid responses, ectopic fat depots, whole-body cholesterol synthesis, hepatic lipogenesis, and fat oxidation in patients with type II diabetes. METHODS: The trial was a single-phase, nonrandomized study of 12-week treatment with evolocumab 140 mg subcutaneously every 2 weeks in 15 patients with type II diabetes on background statin therapy. Cardiometabolic responses to a high-fat mixed meal were assessed before and at the end of the intervention period. RESULTS: Evolocumab treatment reduced significantly postprandial rises in plasma total triglyceride (by 21%; P < .0001) and VLDL1 triglyceride (by 15%; P = .018), but the increase in chylomicron triglyceride after the meal was not significantly perturbed (P = .053). There were reduced postprandial responses in plasma total apolipoprotein C-III (by 14%; P < .0001) and apolipoprotein B-48 concentration (by 17%; P = .0046) and in "remnant-like particles" cholesterol (by 29%; P < .0001) on the PCSK9 inhibitor. Treatment reduced the steady-state (ie, fasting and postprandial) concentrations of VLDL2 cholesterol by 50% (P < .0001) and VLDL2 triglyceride by 29% (P < .0001), in addition to the 78% reduction of low-density lipoprotein cholesterol (P < .001). The changes in apolipoprotein C-III associated significantly with reduction in postprandial responses of remnant-like particles cholesterol and triglyceride-rich lipoprotein cholesterol. Evolocumab therapy did not influence liver fat accumulation, hepatic de novo lipogenesis, or fasting beta-hydroxybutyrate but did increase total body cholesterol synthesis (P < .01). CONCLUSION: Evolocumab treatment improved postprandial responses of triglyceride-rich lipoproteins and measures of cholesterol-enriched remnant particles in type II diabetic subjects. These results indicate that postprandial phenomena need to be taken into account in assessing the full range of actions of PCSK9 inhibitors in dyslipidemic individuals.

[26] *Sallam HS, Tuvdendorj DR, Jialal I et al.* **Therapeutic lifestyle change intervention improved metabolic syndrome criteria and is complementary to amlodipine/atorvastatin**. Journal of diabetes and its complications 2019:107480.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31902653
ABSTRACT
AIMS: To examine whether addition of amlodipine (5mg)/atorvastatin (10mg) A/A to Therapeutic Lifestyle change intervention (TLC) would beneficially modulate Metabolic Syndrome (MetS) and oxidized low-density lipoprotein (Ox-LDL) levels. METHODS: Patients with MetS (n=53) were randomized to TLC+placebo or TLC+A/A for 12months. Anthropometric measurements, blood pressure (BP), lipid profile, plasma Ox-LDL, and area under the curve of free fatty acid (AUCFFA) during oral glucose tolerance test, a marker of adipose tissue health, were assessed before and after the intervention. RESULTS: Twenty-six patients completed the study with an overall improvement of MetS (p=0.02). TLC+placebo was beneficial in reversing MetS comparable to TLC+A/A (54% vs. 39%; p=0.08). Both treatments decreased systolic BP (p</=0.01). TLC+A/A also decreased diastolic BP and triglyceride levels. The changes in Ox-LDL levels directly correlated with changes in weight in the TLC-placebo group (r=0.64; p=0.04). AUCFFA determined the loss of fat mass (r=0.472, p=0.03). CONCLUSIONS: 1) Addition of A/A has the advantage of improving the lipid profile and BP; but TLC alone was comparable to TLC+A/A in improving MetS; 2) weight change determines the TLC-associated change in Ox-LDL levels; and 3) AT metabolic health is a significant predictor of TLC-associated loss of body fat mass.

[27] *Vlad CE, Foia L, Popescu R et al.* **Apolipoproteins A and B and PCSK9: Nontraditional Cardiovascular Risk Factors in Chronic Kidney Disease and in End-Stage Renal Disease**. Journal of diabetes research 2019; 2019:6906278.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31915710
ABSTRACT
Purpose: Nontraditional cardiovascular risk factors as apolipoprotein A (ApoA), apolipoprotein B (ApoB), and the proprotein convertase subtilisin/kexin type 9 (PCSK9) increase the prevalence of cardiovascular mortality in chronic kidney disease (CKD) or in end-stage renal disease (ESRD) through quantitative alterations. This review is aimed at establishing the biomarker (ApoA, ApoB, and PCSK9) level variations in uremic patients, to identify the studies showing the association between these biomarkers and the development of cardiovascular events and to depict the therapeutic options to reduce cardiovascular risk in CKD and ESRD patients. Methods: We searched the electronic database of PubMed, Scopus, EBSCO, and Cochrane CENTRAL for studies evaluating apolipoproteins and PCSK9 in CKD and ESRD. Randomized controlled trials, observational studies (including case-control, prospective or retrospective cohort), and reviews/meta-analysis were included if reference was made to those keys and cardiovascular outcomes in CKD/ESRD. Results: 18 studies met inclusion criteria. Serum ApoA-I has been significantly associated with the development of new cardiovascular event and with cardiovascular mortality in ESRD patients. ApoA-IV level was independently associated with maximum carotid intima-media thickness (cIMT) and was a predictor for sudden cardiac death. The ApoB/ApoA-I ratio represents a strong predictor for coronary artery calcifications, cardiovascular mortality, and myocardial infarction in CKD/ESRD. Plasma levels of PCSK9 were not associated with cardiovascular events in CKD patients. Conclusions: Although the "dyslipidemic status" in CKD/ESRD is not clearly depicted, due to different research findings, ApoA-I, ApoA-IV, and ApoB/ApoA-I ratio could be predictors of cardiovascular risk. Serum PCSK9 levels were not associated with the cardiovascular events in patients with CKD/ESRD. Probably in the future, the treatment of dyslipidemia in CKD/ESRD will be aimed at discovering new effective therapies on the action of these biomarkers.

[28] *Zhou D, Li J, Liu D et al.* **Irregular surface of carotid atherosclerotic plaque is associated with ischemic stroke: a magnetic resonance imaging study**. Journal of geriatric cardiology : JGC 2019; 16:872-879.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31911791
ABSTRACT
Objective: To determine the association between the irregularity of carotid plaque surface using multidimensional magnetic resonance imaging (MRI) of ipsilateral acute cerebral infarction (ACI) cases. Methods: Patients with recent cerebrovascular symptoms (stroke or transient ischemic attack < 2 weeks) and atherosclerotic plaque in at least one carotid artery were diagnosed by B-mode ultrasound imaging (intima-media thickness >/= 1.5 mm) and recruited for the present study. Irregular surface was defined when plaque surface was uneven with high and low fluctuation or plaque with surface ulceration. The irregularity of carotid plaque surface was determined on axial or oblique images alone (single-dimension) and on both axial images and oblique images (multidimensions), separately. Univariate and multivariate logistic regression analyses were performed to calculate the odds ratio (OR) and the corresponding 95% CI of the irregular plaque surface in discriminating the presence of ipsilateral ACI. Results: A total of 217 included subjects (mean age: 60.7 +/- 10.2 years, 149 men) were recruited and 89 (41.0%), 88 (40.6%) and 118 (54.4%) of them exhibited irregular plaque surface on

axial, oblique and multidimensional MR images, respectively. The OR of irregularity of the plaque surface was determined by multidimensional MRI to be 5.88 (95% CI: 3.16-10.96, P < 0.001) in discriminating the presence of ipsilateral ACI. Following adjustment for clinical confounding factors, this association remained statistically significant (OR = 5.65, 95% CI: 2.53-12.60, P < 0.001). The analysis included further adjustment for the presence of lipid-rich necrotic core, intraplaque hemorrhage and stenosis and the results included that this association also remained statistically significant (OR = 6.08, 95% CI: 2.52-14.68, P < 0.001). Conclusions: The irregular plaque surface was determined by multidimensional MRI as an independent indicator for ipsilateral acute cerebral infarction.

[29] *Tindall AM, Kris-Etherton PM, Petersen KS*. **Replacing Saturated Fats with Unsaturated Fats from Walnuts or Vegetable Oils Lowers Atherogenic Lipoprotein Classes Without Increasing Lipoprotein(a)**. The Journal of nutrition 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31909809
ABSTRACT
BACKGROUND: Walnuts have established lipid-/lipoprotein-lowering properties; however, their effect on lipoprotein subclasses has not been investigated. Furthermore, the mechanisms by which walnuts improve lipid/lipoprotein concentrations are incompletely understood. OBJECTIVES: We aimed to examine, as exploratory outcomes of this trial, the effect of replacing SFAs with unsaturated fats from walnuts or vegetable oils on lipoprotein subclasses, cholesterol efflux, and proprotein convertase subtilisin/kexin type 9 (PCSK9). METHODS: A randomized, crossover, controlled-feeding study was conducted in individuals at risk of cardiovascular disease (CVD) (n = 34; 62% men; mean +/- SD age 44 +/- 10 y; BMI: 30.1 +/- 4.9 kg/m2). After a 2-wk run-in diet (12% SFAs, 7% PUFAs, 12% MUFAs), subjects consumed the following diets, in randomized order, for 6 wk: 1) walnut diet (WD) [57-99 g/d walnuts, 7% SFAs, 16% PUFAs [2.7% alpha-linolenic acid (ALA)], 9% MUFAs]; 2) walnut fatty acid-matched diet [7% SFAs, 16% PUFAs (2.6% ALA), 9% MUFAs]; and 3) oleic acid replaces ALA diet (ORAD) [7% SFAs, 14% PUFAs (0.4% ALA); 12% MUFAs] (all percentages listed are of total kilocalories). Serum collected after the run-in (baseline) and each diet period was analyzed for lipoprotein classes and subclasses (vertical auto profile), cholesterol efflux, and PCSK9. Linear mixed models were used for data analysis. RESULTS: Compared with the ORAD, total cholesterol (mean +/- SEM -8.9+/- 2.3 mg/dL; -5.1%; P < 0.001), non-HDL cholesterol (-7.4 +/- 2.0 mg/dL; -5.4%; P = 0.001), and LDL cholesterol (-6.9 +/- 1.9 mg/dL; -6.5%; P = 0.001) were lower after the WD; no other pairwise differences existed. There were no between-diet differences for HDL-cholesterol or LDL-cholesterol subclasses. Lipoprotein(a) [Lp(a)], cholesterol efflux, and PCSK9 were unchanged after the diets. CONCLUSIONS: In individuals at risk of CVD, replacement of SFAs with unsaturated fats from walnuts or vegetable oils improved lipid/lipoprotein classes, including LDL-cholesterol, non-HDL cholesterol, and total cholesterol, without an increase in Lp(a). These improvements were not explained by changes in cholesterol efflux capacity or PCSK9. This trial was registered at clinicaltrials.gov as NCT01235832.

[30] *Velez DE, Mestre-Cordero VE, Hermann R et al.* **Rosuvastatin protects isolated hearts against ischemia-reperfusion injury: role of Akt-GSK-3beta, metabolic environment, and mitochondrial permeability transition pore**. Journal of physiology and biochemistry 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31916218
ABSTRACT

The cardioprotective activity of rosuvastatin (R) is yet to be known. The objective of this study was to research whether R perfusion before global ischemia can mitigate myocardial ischemia-reperfusion damage, considering the metabolic condition in which these effects occur, and to contemplate potential mitochondrial benefits. Protein kinase B (Akt)/glycogen synthase kinase-3beta (GSK-3beta) and mitochondrial permeability transition pore (MPTP) are key elements in myocardial injury produced by ischemia-reperfusion. Isolated rat hearts were subjected to 25-min ischemia and 1-h reperfusion in the presence or absence of R, with or without Wortmannin (W), a phosphatidylinositol 3-kinase (PI3K)/Akt inhibitor. Akt and GSK-3beta were measured by Western blot analysis; lactate, glycogen, and G6PDH were determined; and Ca(2+)-induced MPTP opening was evaluated using a spectrophotometric method. Contractility was assessed by left ventricular developed pressure (LVDP), and rate-pressure product (RPP), peak rate of contraction and peak rate of relaxation (+/- dP/dt), and left ventricular end-diastolic pressure (LVEDP) were determined. Tissue samples were extracted to evaluate mitochondrial damage by electron microscopy and to assess infarct size. Statistical analysis employed ANOVA (n = 6/per group). Myocardial infarct size was significantly reduced by R, which also improved cardiac function. MPTP opening was delayed to 300 muM CaCl2, while use of W resulted in MPTP opening at 200 muM CaCl2. Electron microscopy showed better mitochondrial preservation with R, which reduced lactic acid production, increased glycogen consumption and G6PDH activity, as well as phosphorylation of Akt and GSK-3beta. R before ischemia is cardioprotective against ischemic and reperfusion damage, activating Akt and regulating GSK-3beta negatively and attenuating the MPTP opening.

[31] *Jarrett MJ, Yao Q, Venardos N et al.* **Simvastatin down-regulates osteogenic response in cultured human aortic valve interstitial cells**. The Journal of thoracic and cardiovascular surgery 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31924353

ABSTRACT

BACKGROUND: Aortic valve interstitial cells have been implicated in the pathogenesis of aortic stenosis. In response to proinflammatory stimuli, aortic valve interstitial cells undergo an osteogenic phenotypic change. The purpose of this study was to determine whether the anti-inflammatory effects of statins prevent osteogenic activity in cultured aortic valve interstitial cells. METHODS: Human aortic valve interstitial cells were isolated from hearts explanted for cardiac transplantation. To test whether simvastatin down-regulates TLR4-induced osteogenic response, aortic valve interstitial cells were treated with simvastatin with and without TLR4 agonist lipopolysaccharide (LPS), and osteogenic markers were measured. Simvastatin's influence on in vitro calcium deposition was assessed by alizarin red staining. Knockdown of postreceptor signaling proteins (MyD88 and TRIF) was performed to determine which of 2 TLR4-associated pathways mediates the osteogenic response. Expression levels of TLR4-induced nuclear factor kappa light chain enhancer of activated B cells (NF-kappaB) and TLR4 expression were assessed after treatment with simvastatin. Statistical testing was done by analysis of variance ($P < .05$). RESULTS: Simvastatin decreased LPS-induced ALP and Runx2 expression and inhibited in vitro calcium deposition in aortic valve interstitial cells. Knockdown of MyD88 and TRIF attenuated the osteogenic response. Simvastatin attenuated TLR4-dependent NF-kappaB signaling and down-regulated TLR4 levels. CONCLUSIONS: Simvastatin prevented TLR4-induced osteogenic phenotypic changes in isolated aortic valve interstitial cells via down-regulation of TLR4 and inhibition of NF-kappaB signaling. These data offer mechanistic insight into a possible therapeutic role for simvastatin in the prevention of aortic stenosis.

[32] *Tada H, Okada H, Nomura A et al.* **Beneficial effect of ezetimibe-atorvastatin combination therapy in patients with a mutation in ABCG5 or ABCG8 gene**. Lipids in health and disease 2020; 19:3.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31901240
ABSTRACT
BACKGROUND: Use of ezetimibe on top of statin therapy has been shown to be effective to reduce LDL cholesterol level in hypercholesterolemic patients. However, little is known regarding the individual variety of the effectiveness of ezetimibe. We hypothesized that hypercholesterolemic patients with a mutation in ABCG5 or ABCG8 gene exhibit better response to ezetimibe than those without, based on the fact that ezetimibe is hyper-effective for in patients with sitosterolemia caused by ABCG5 or ABCG8 genetic mutations. METHODS: Electronical medical record were reviewed in a total of 321 hypercholesterolemic patients (baseline LDL cholesterol = 192 +/- 46 mg/dl) prescribed ezetimibe 10 mg daily on top of atorvastatin 10 mg daily who had undergone genetic analysis of ABCG5 or ABCG8 gene in our institute since 2006 to 2017. Pathogenicity of the variants were determined using standard variant filtering schema, including minor allele frequency, in silico annotation tools. Patients were divided into 2 groups based on the presence of ABCG5 or ABCG8 mutation. We compared the percent reduction of LDL cholesterol as well as the achieved LDL cholesterol levels between these 2 groups. RESULTS: We found 26 (8%) individuals who exhibit deleterious mutations in ABCG5 or ABCG8 gene. Baseline characteristics under the atorvastatin 10 mg therapy were comparable in age, gender, and LDL cholesterol level between 2 groups. Under these conditions, percent reduction of LDL cholesterol in mutation positive group was significantly larger than that of mutation negative group (28 +/- 16% vs. 39 +/- 21%, $p < 0.05$). As a result, the achieved LDL cholesterol level in mutation positive group was significantly lower than that of mutation negative group (87 +/- 29 mg/dl vs. 72 +/- 26% mg/dl, $p < 0.05$). CONCLUSION: These results suggest that ezetimibe-atorvastatin combination therapy might be more beneficial in hypercholesterolemic patients with a mutation in ABCG5 or ABCG8 gene.

[33] *Zijlstra LE, Trompet S, Mooijaart SP et al.* **Renal Impairment, Cardiovascular Disease, and the Short-Term Efficacy and Safety of PCSK9 Targeted by Inclisiran**. Mayo Clinic proceedings 2020; 95:12-14.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31902406
ABSTRACT

[34] *Angoulvant D, Pathak A*. **[Monoclonal antibodies in cardiovascular diseases and metabolic disorders today]**. Medecine sciences : M/S 2019; 35:1014-1016.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31903910
ABSTRACT
The use of monoclonal antibodies in cardiovascular diseases and metabolic disorders is still in its infancy. Recent development of anti-PCSK9 monoclonal antibodies for the treatment of dyslipidemia and of patients in secondary prevention is a breakthrough in the field. Anti- PCSK9 antibodies significantly improved LDL cholesterol reduction in patients with familial hypercholesterolemia. These antibodies have also demonstrated a significant reduction of clinical events in patients with previously established atherosclerotic disease such as myocardial infarction, ischemia stroke or peripheral artery disease. Other targets are under investigation such as inflammatory cells and cytokines to reduce atherosclerosis or myocardial lesions following myocardial infarction.

[35] *Tseng CH, Chung WJ, Li CY et al.* **Statins reduce new-onset atrial fibrillation after acute myocardial infarction: A nationwide study**. Medicine (Baltimore) 2020; 99:e18517.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31914024
ABSTRACT
Atrial fibrillation (AF) is an important complication of acute myocardial infarction (AMI). The association between AF and serum lipid profile is unclear and statin use for lowering the incidence of new-onset AF remains controversial. The objective of this study was to investigate whether statins confer a beneficial effect on AF after AMI.Data available in the Taiwan National Health Insurance Research Database on 32886 AMI patients between 2008 and 2011 were retrospectively analyzed. Total 27553 (83.8%) had complete 1-yr follow-up data. Cardiovascular outcomes were analyzed based on the baseline characteristics and AF type (existing, new-onset, or non-AF). AF groups had significantly higher incidence of heart failure (HF), stroke, all-cause death, and major adverse cardiac and cerebrovascular event (MACCE) after index AMI (all P < .05). In contrast, myocardial re-infarction (re-MI) was not significantly different among the three groups (P = .95). Statin use tended to be associated with lower risk of new-onset AF after AMI (HR: 0.935; 95% confidence interval (CI): 0.877-0.998; P = .0427).Existing AF and new-onset AF subgroups had similar cardiovascular outcomes after AMI and were both inferior to the non-AF group. Statin tended to reduce new-onset AF after AMI.

[36] *Hoffmeister T, Kaiser J, Ludtke S et al.* **Interactions between atorvastatin and the farnesoid X receptor impair insulinotropic effects of bile acids and modulate diabetogenic risk**. Molecular pharmacology 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31911428
ABSTRACT
Bile acids such as chenodeoxycholic acid (CDC) acutely enhance insulin secretion via the farnesoid X receptor (FXR). Statins, which are frequently prescribed for type 2 diabetic patients suffering from dyslipidemia, are known for their diabetogenic risk and are reported to interact with the FXR. Our study investigates whether this interaction is relevant for beta cell signaling and plays a role for negative effects of statins on glycemic control. Experiments were performed with islets and islet cells from C57BL/6N wildtype and FXR knock-out mice. Culturing islets with atorvastatin (15 microM) for 24 h decreased glucose-stimulated insulin secretion by approximately 30 % without affecting ATP synthesis. Prolonged exposure for 7 d lowered the concentration necessary for impairment of insulin release to 150 nM. After 24-h culture with atorvastatin, the ability of CDC (500 nM) to elevate [Ca2+]c was diminished and the potentiating effect on insulin secretion was completely lost. Mevalonate largely reduced the negative effect of atorvastatin. Nuclear activity of FXR was reduced by atorvastatin in a mouse FXR reporter assay. The atorvastatin-induced decrease in insulin release was also present in FXR-KO mice. Though not a prerequisite, FXR seems to influence the degree of damage caused by atorvastatin in dependence of its interaction with CDC: Preparations responding to CDC with an increase in insulin secretion under control conditions were less impaired by atorvastatin than preparations that were non-responsive to CDC. Extended stimulation of FXR by the synthetic agonist GW4064, which is suggested to induce translocation of FXR from the cytosol into the nucleus, increased the inhibitory effect of atorvastatin. In conclusion, atorvastatin inhibits insulin release and prevents positive effects of bile acids on beta cell function. Both interactions may contribute to progression of type 2 diabetes mellitus. SIGNIFICANCE STATEMENT: This study shows that the

diabetogenic risk of statins is coupled to the activity of FXR-dependent signaling pathways in beta cells. On the one hand, statins abolish the insulinotropic effects of bile acids and on the other hand, FXR determines the level of impairment of islet function by the statin.

[37] *Provenzano M, Coppolino G, Faga T et al.* **Epidemiology of cardiovascular risk in chronic kidney disease patients: the real silent killer**. Reviews in cardiovascular medicine 2019; 20:209-220.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31912712
ABSTRACT
Chronic kidney disease is a growing public health problem, as its prevalence and incidence have almost doubled over the last three decades. Chronic kidney disease is defined as the presence of an estimated glomerular filtration rate < 60 ml/min/1.73 m(2) and/or proteinuria >/= 0.150 g/24 h. It has been demonstrated that both proteinuria and reduction in estimated glomerular filtration rate can predict the development of fatal and non-fatal cardiovascular events, regardless of traditional cardiovascular risk factors, namely blood pressure, smoking habit, cholesterol, age, gender. This relationship is found in the general population, high-risk cohorts and in patients referred to Nephrologists (tertiary care). The accuracy by which proteinuria or estimated glomerular filtration rate can predict these events, exceeds that obtained by the combination of all the other traditional risk factors. These important findings have led to chronic kidney disease being considered as a cardiovascular risk equivalent. Although this needs further investigation, a great effort has been made to reduce the cardiovascular risk in chronic kidney disease patients. Indeed, many clinical trials have been carried-out testing the effect of antihypertensive, proteinuria-lowering, lipid-lowering and hypoglycemic agents on cardiovascular risk protection. All these trials reduced, but did not eliminate, the overall cardiovascular risk. Future studies should be undertaken to identify high cardiovascular risk patients and novel therapeutic targets for cardiovascular protection in chronic kidney disease patients.

[38] *Murata K, Murata N, Chu B et al.* **Characterization of Carotid Atherosclerotic Plaques Using 3-Dimensional MERGE Magnetic Resonance Imaging and Correlation With Stroke Risk Factors**. Stroke 2020:Strokeaha119027779.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31902332
ABSTRACT
Background and Purpose- High-resolution magnetic resonance imaging is capable of characterizing carotid atherosclerotic plaque morphology and composition. Most reported carotid plaque imaging techniques are 2-dimensional (2D) based with limited longitudinal coverage of approximately 30 mm, which may be insufficient for complete visualization of extracranial carotid atheroma. A 3D black-blood imaging technique, motion-sensitized driven equilibrium prepared rapid gradient echo technique (3D-MERGE) can provide larger coverage. We sought to use 3D-MERGE to investigate carotid atherosclerosis plaque distribution and to analyze their correlation with clinical information and stroke risk factors. Methods- From 5 hospitals in China, 97 subjects suspected of recent stroke or transient ischemic attack were imaged with 3D-MERGE within 2 weeks of symptoms using 3T magnetic resonance imaging. Images were analyzed by 2 reviewers. Plaque length was calculated and categorized as plaques within, partially outside, or completely outside of typical 2D magnetic resonance imaging coverage. Associations between plaque features and clinical information, stroke risk factors were assessed. Results- Ninety-seven subjects with 194 carotid arteries (70 men and 27 women, mean age 60 years) were analyzed. Of the 136 plaques identified, 68 (50%) were within, 46

(33.8%) were partially outside, and 22 (16.2%) were completely outside of 2D magnetic resonance imaging coverage. Total plaque length was significantly positively associated with male sex (P<0.001), hypertension (P=0.011), and history of smoking (P<0.001). Hypertensive subjects were more likely to have at least one plaque completely outside the 2D magnetic resonance imaging coverage than nonhypertensive subjects (P=0.007). Conclusions- The 3D-MERGE allows for the identification of substantially more carotid plaques than 2D black-blood techniques. The extent and distribution of plaque, identified by the larger coverage afforded by 3D-MERGE, were found to correlate significantly with male sex and risk factors that are common among patients with stroke, including hypertension and history of cigarette smoking.

[39] *Catala-Lopez F, Aleixandre-Benavent R, Caulley L et al.* **Global mapping of randomised trials related articles published in high-impact-factor medical journals: a cross-sectional analysis**. Trials 2020; 21:34.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31910857
ABSTRACT
BACKGROUND: Randomised controlled trials (RCTs) provide the most reliable information to inform clinical practice and patient care. We aimed to map global clinical research publication activity through RCT-related articles in high-impact-factor medical journals over the past five decades. METHODS: We conducted a cross-sectional analysis of articles published in the highest ranked medical journals with an impact factor > 10 (according to Journal Citation Reports published in 2017). We searched PubMed/MEDLINE (from inception to December 31, 2017) for all RCT-related articles (e.g. primary RCTs, secondary analyses and methodology papers) published in high-impact-factor medical journals. For each included article, raw metadata were abstracted from the Web of Science. A process of standardization was conducted to unify the different terms and grammatical variants and to remove typographical, transcription and/or indexing errors. Descriptive analyses were conducted (including the number of articles, citations, most prolific authors, countries, journals, funding sources and keywords). Network analyses of collaborations between countries and co-words are presented. RESULTS: We included 39,305 articles (for the period 1965-2017) published in forty journals. The Lancet (n = 3593; 9.1%), the Journal of Clinical Oncology (n = 3343; 8.5%) and The New England Journal of Medicine (n = 3275 articles; 8.3%) published the largest number of RCTs. A total of 154 countries were involved in the production of articles. The global productivity ranking was led by the United States (n = 18,393 articles), followed by the United Kingdom (n = 8028 articles), Canada (n = 4548 articles) and Germany (n = 4415 articles). Seventeen authors who had published 100 or more articles were identified; the most prolific authors were affiliated with Duke University (United States), Harvard University (United States) and McMaster University (Canada). The main funding institutions were the National Institutes of Health (United States), Hoffmann-La Roche (Switzerland), Pfizer (United States), Merck Sharp & Dohme (United States) and Novartis (Switzerland). The 100 most cited RCTs were published in nine journals, led by The New England Journal of Medicine (n = 78 articles), The Lancet (n = 9 articles) and JAMA (n = 7 articles). These landmark contributions focused on novel methodological approaches (e.g. the "Bland-Altman method") and trials on the management of chronic conditions (e.g. diabetes control, hormone replacement therapy in postmenopausal women, multiple therapies for diverse cancers, cardiovascular therapies such as lipid-lowering statins, antihypertensive medications, and antiplatelet and antithrombotic therapy). CONCLUSIONS: Our analysis identified authors, countries, funding institutions, landmark contributions and high-impact-factor medical journals publishing RCTs.

Literature update week 02 (2020)

Over the last 50 years, publication production in leading medical journals has increased, with Western countries leading in research but with low- and middle-income countries showing very limited representation.

[40] *Vrablik M*. **Current and future trends in the treatment of dyslipidemias**. Vnitr Lek 2019; 65:643-650.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31906686
ABSTRACT
Lipid-lowering treatment is a part of prevention and treatment of vascular diseases caused by atherosclerosis. We need new strategies for modifying plasma lipoprotein levels in the light of new findings that reduce target lipid levels further lower, as well as the growing population of patients for whom existing treatments cannot be offered. The spectrum of existing drugs (new statins) is widening, pharmacological treatments (recombinant lipoproteins-bound statins), improved forms of established drugs (selective PPARα receptor modulators) are coming. The new procedures include fixed combinations of established drugs improving adherence and intensifying lipid modifying effects (statin + ezetimibe). The portfolio of lipid-lowering therapies today also includes monoclonal antibodies against PCSK9 (PCSK9 inhibitors). The main direction of future development is biotechnology using the principle of so-called antisense therapy, i.e. the use of specific oligonucleotide sequences blocking the translation of the selected protein. These novel therapies targeting, for example, apolipoprotein B, apolipoprotein CIII, or lipoprotein(a) are in various stages of clinical trials. A simi-lar (but not identical) principle is the use of RNA silencing - interference with gene expression using short sequences of double-stranded RNA (e.g. inclisiran siRNA against PCSK9). Innovations in the field of hypolipidemic pharmacotherapy in our country may also be inhibitors of microsomal triglyceride transfer protein (approved for use in homozygotes for familial hypercholesterolemia and experimentally also for familial chylomicronemia). The small molecule ATP citrate lyase inhibitor, bempedoic acid, decreases LDL-C by a further 20 % over and above the reduction achievable by a statin. In a broader sense, the novelty of hypolipidemic pharmacotherapy includes treatment options for some rare metabolic diseases (eg. enzyme replacement therapy for acid lysosomal lipase deficiency) manifested by lipoprotein metabolism abnormalities. All these new directions must aim at the common main goal of reducing the incidence of cardiovascular and gastrointestinal complications of dyslipidemia. Clinical research also aims to prove these effects.