Literature update week 08 (2019)

[1] *Sheng J, Xu J*. **Association of coronary artery disease with toll-like receptor 4 genetic variants: A meta-analysis**. Advances in clinical and experimental medicine : official organ Wroclaw Medical University 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30784241
ABSTRACT
BACKGROUND: Toll-like receptor 4 (TLR4) plays an important role in the formation of coronary atherosclerotic plaque and the pathogenesis of coronary artery disease (CAD). OBJECTIVES: The aim of the study was to conduct a meta-analysis assessing the relationship between 2 common genetic variants in the TLR4 gene (rs4986790 and rs4986791) and susceptibility to CAD. MATERIAL AND METHODS: A systematic search of Web of Science, Embase, Scopus, Pubmed, and Wanfang Med Online was undertaken. Case-control studies assessing the association of rs4986790 and rs4986791 with CAD risk were included. The odds ratio (OR) and 95% confidence interval (CI) were used as the metric of choice for the evaluation of risk. RESULTS: The literature search generated 427 studies, of which 14 met the inclusion criteria, for a total of 13,927 participants. Our meta-analysis revealed a significant association between rs4986791 and CAD risk in Asians using the dominant model (CT + TT vs CC: OR = 0.35, 95% CI = 0.21-0.56, $p < 0.001$), heterozygote contrast (CT vs CC: OR = 0.32, 95% CI = 0.19-0.57, $p < 0.001$) and allele contrast (T vs C: OR = 0.38, 95% CI = 0.25- 0.58, $p < 0.001$). No significant association between rs4986791 and CAD was observed among Caucasians. For rs4986790, the results provided no evidence of an association with CAD risk. CONCLUSIONS: Our analysis suggests that rs4986791 is negatively associated with CAD risk in Asians but not in Caucasians. No association between rs4986790 and CAD risk was found.

[2] *Li L, Wang S, Huang H et al.* **Effects of Rosuvastatin and Aspirin on Retinal Vascular Structures in Hypercholesterolemic Patients with Low-to-Moderate Risk of Coronary Artery Disease**. American journal of cardiovascular drugs : drugs, devices, and other interventions 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30793259
ABSTRACT
INTRODUCTION: Atherosclerosis erodes large elastic arteries and damages peripheral small vessels. Evaluating retinal vessel caliber enables exploration of the effect of improving microcirculation with statins. OBJECTIVE: We investigated whether rosuvastatin therapy improves retinal vasculature in hypercholesterolemic patients with a low-to-moderate risk of coronary artery disease (CAD). METHODS: This was a prospective, open-label, randomized study in which 127 patients were enrolled and randomized (ratio 1:1) into rosuvastatin and control groups. RESULTS: Rosuvastatin increased retinal arteriolar calibers by 3.560 microm at 12 months, decreased retinal venular calibers by 3.110 microm at 6 months and by 5.860 microm at 12 months, and increased the artery-vein ratio (AVR) by 2.68% at 6 months and by 5.90% at 12 months. Meanwhile, in the control group, retinal arteriolar calibers decreased by 1.110 microm at 12 months, retinal venular calibers increased by 1.020 microm at 6 months and by 1.04 microm at 12 months, and AVR decreased by 1.12% at 6 months and by 1.73% at 12 months. All the above parameters were statistically significant between groups, but there was no significant change in retinal arteriolar calibers at 6 months. The increased AVR correlated significantly with decreased C-reactive protein (CRP) at 6 months and decreased low-density

lipoprotein and CRP at 12 months. DISCUSSION: For patients with a low-to-moderate risk of CAD, we found a significant effect of rosuvastatin on retinal microvasculature, including AVR increase, venular constriction, and arteriolar dilation after 6-12 months of treatment. CLINICAL TRIAL REGISTRATION: Chinese Clinical Trial Registry identifier number ChiCTR-IOR-15006664.

[3] *Mooradian AD*. **Evidence-Based Cardiovascular Risk Management in Diabetes**. American journal of cardiovascular drugs : drugs, devices, and other interventions 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30793262
ABSTRACT
Multipronged risk management in diabetes has contributed to the recent decline in cardiovascular mortality. Few antihyperglycemic drugs have been conclusively shown to have cardioprotective effects. These include metformin, liraglutide, semaglutide, dulaglutide, and sodium-glucose cotransporter-2 inhibitors. Statins are the cornerstone of treatment for people with established coronary artery disease (CAD) or at risk of CAD. In patients with persistent low-density lipoprotein cholesterol (LDL-C) levels > 70 mg/dL, the addition of ezetimibe or proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors is recommended. In general, angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers should be included in the treatment regimen. The goal is to have blood pressure < 140/90 mmHg, whereas a lower goal of < 130/80 mmHg is recommended in patients with CAD or proteinuria (> 1 g/day). Aspirin antiplatelet therapy should be restricted for people with established CAD or those with multiple CAD risk factors. While antiobesity medications have a modest role in managing obesity, bariatric surgery in people with body mass index (BMI) >/= 40 or >/= 35 with comorbidities can substantially affect quality of life and may reduce cardiovascular risks. Prescribing therapeutic agents should take into consideration a variety of factors, including the patient's preferences and the drug's affordability, side effect profile, and proven cardiovascular benefit.

[4] *Terabe K, Takahashi N, Cobb M et al.* **Simvastatin promotes restoration of chondrocyte morphology and phenotype**. Archives of biochemistry and biophysics 2019; 665:1-11.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30776329
ABSTRACT
In this study we examined whether the action of simvastatin affects re-differentiation of passaged chondrocytes and if so, whether this was mediated via changes in cholesterol or cholesterol intermediates. Bovine articular chondrocytes, of varying passage number, human knee chondrocytes and rat chondrosarcoma chondrocytes were treated with simvastatin and examined for changes in mRNA and protein expression of markers of the chondrocyte phenotype as well as changes in cell shape, proliferation and proteoglycan production. In all three models, while still in monolayer culture, simvastatin treatment alone promoted changes in phenotype and morphology indicative of re-differentiation most prominent being an increase in SOX9 mRNA and protein expression. In passaged bovine chondrocytes, simvastatin stimulated the expression of SOX9, ACAN, BMP2 and inhibited the expression of COL1 and alpha-smooth muscle actin. Co-treatment of chondrocytes with simvastatin plus exogenous cholesterol-conditions that had previously reversed the inhibition on CD44 shedding, did not alter the effects of simvastatin on re-differentiation. However, the co-treatment of chondrocytes with simvastatin together with other pathway intermediates, mevalonate,

geranylgeranylpyrophosphate and to a lesser extent, farnesylpyrophosphate, blocked the pro-differentiation effects of simvastatin. Treatment with simvastatin stimulated expression of SOX9 and COL2a and enhanced SOX9 protein in human OA chondrocytes. The co-treatment of OA chondrocytes with mevalonate or geranylgeranylpyrophosphate, but not cholesterol, blocked the simvastatin effects. These results lead us to conclude that the blocking of critical protein prenylation events is required for the positive effects of simvastatin on the re-differentiation of chondrocytes.

[5] *Shek AB, Kurbanov RD, Alieva RB et al.* **Personalized rosuvastatin therapy in problem patients with partial statin intolerance**. Archives of medical sciences. Atherosclerotic diseases 2018; 3:e83-e89.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30775595
ABSTRACT
Introduction: The aim was to study the pharmacogenetic determinants of switching simvastatin-intolerant ethnic Uzbek patients with coronary artery disease (CAD) to rosuvastatin treatment. Material and methods: The study included 50 patients with CAD, who demonstrated statin-induced adverse liver symptoms, accompanied by an elevation in transaminase level (3-fold or more in 37 cases) or statin-induced adverse muscle symptoms, accompanied by elevations in serum (CK > 3 times above the upper limit of normal (ULN)) in simvastatin treatment with a dose of 10-20 mg/day. The control group consisted of 50 patients without side effects. Patients were genotyped for polymorphisms in the genes coding for the cytochrome P450 (CYP) metabolic enzymes CYP3A5(6986A>G), CYP2C9(430C>T), CYP2C9(1075A>C), and hepatic influx and efflux transporters SLCO1B1(521T>C) and BCRP(ABCG2, 421C>A) by means of the PCR-RFLP method. Results: When the 50 patients of the case group were switched to the starting rosuvastatin dose of 5 mg, intolerance symptoms were not observed in 29 (58%) versus 21 with adverse symptoms. In this case-control study, the groups differed significantly only in the prevalence of the *3/*3 genotype CYP3A5 (OR = 5.25; 95% CI: 1.6-17.8; p = 0.014). Conclusions: In a considerable proportion of ethnic Uzbek patients with CAD and simvastatin intolerance symptoms, serious side effects when switching to a starting dose of rosuvastatin were not observed, and it should be noted that in most cases (72.4%) this phenomenon was observed among the carriers of *3/*3 genotype of the CYP3A5 (6986A> G) gene.

[6] *van der Vorst EPC, Mandl M, Muller M et al.* **Hematopoietic ChemR23 (Chemerin Receptor 23) Fuels Atherosclerosis by Sustaining an M1 Macrophage-Phenotype and Guidance of Plasmacytoid Dendritic Cells to Murine Lesions**. Arteriosclerosis, thrombosis, and vascular biology 2019:Atvbaha119312386.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30786742
ABSTRACT
Objective- Expression of the chemokine-like receptor ChemR23 (chemerin receptor 23) has been specifically attributed to plasmacytoid dendritic cells (pDCs) and macrophages and ChemR23 has been suggested to mediate an inflammatory immune response in these cells. Because chemokine receptors are important in perpetuating chronic inflammation, we aimed to establish the role of ChemR23-deficiency on macrophages and pDCs in atherosclerosis. Approach and Results- ChemR23-knockout/knockin mice expressing eGFP (enhanced green

fluorescent protein) were generated and after crossing with apolipoprotein E-deficient (Apoe (-/-) ChemR23 (e/e)) animals were fed a western-type diet for 4 and 12 weeks. Apoe (-/) (-) ChemR23 (e/e) mice displayed reduced lesion formation and reduced leukocyte adhesion to the vessel wall after 4 weeks, as well as diminished plaque growth, a decreased number of lesional macrophages with an increased proportion of M2 cells and a less inflammatory lesion composition after 12 weeks of western-type diet feeding. Hematopoietic ChemR23-deficiency similarly reduced atherosclerosis. Additional experiments revealed that ChemR23-deficiency induces an alternatively activated macrophage phenotype, an increased cholesterol efflux and a systemic reduction in pDC frequencies. Consequently, expression of the pDC marker SiglecH in atherosclerotic plaques of Apoe (-/-) ChemR23 (e/e) mice was declined. ChemR23-knockout pDCs also exhibited a reduced migratory capacity and decreased CCR (CC-type chemokine receptor)7 expression. Finally, adoptive transfer of sorted wild-type and knockout pDCs into Apoe (-/-) recipient mice revealed reduced accumulation of ChemR23-deficient pDCs in atherosclerotic lesions. Conclusions- Hematopoietic ChemR23-deficiency increases the proportion of alternatively activated M2 macrophages in atherosclerotic lesions and attenuates pDC homing to lymphatic organs and recruitment to atherosclerotic lesions, which synergistically restricts atherosclerotic plaque formation and progression.

[7] *Rodriguez-Jimenez C, Gomez-Coronado D, Frias Vargas M et al.* **A new variant (c.1A>G) in LDLRAP1 causing autosomal recessive hypercholesterolemia: Characterization of the defect and response to PCSK9 inhibition**. Atherosclerosis 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30777337
ABSTRACT
BACKGROUND AND AIMS: Autosomal recessive hypercholesterolemia (ARH) is a rare disorder caused by mutations in LDLRAP1, which impairs internalization of hepatic LDL receptor (LDLR). ARH patients respond relatively well to statins or the combination of statins and Ezetimibe, but scarce and variable data on treatment with PCSK9 inhibitors is available. We aimed to identify and characterize the defect in a hypercholesterolemic patient with premature cardiovascular disease and determine the response to lipid-lowering treatment. METHODS AND RESULTS: Gene sequencing revealed a homozygous c.1A>G:p.? variant in LDLRAP1. Primary lymphocytes were isolated from the ARH patient, one control and two LDLR-defective subjects, one LDLR:p.(Cys352Ser) heterozygote and one LDLR:p.(Asn825Lys) homozygote. The patient had undetectable full-length ARH protein by Western blotting, but expressed a lower-than-normal molecular weight peptide. LDLR activity was measured by flow cytometry, which showed that LDL binding and uptake were reduced in lymphocytes from the ARH patient as compared to control lymphocytes, but were slightly higher than in those from the LDLR:p.(Cys352Ser) heterozygote. Despite the analogous internalization defect predicted in ARH and homozygous LDLR:p.(Asn825Lys) lymphocytes, LDL uptake was higher in the former than in the latter. LDL-cholesterol levels were markedly reduced by the successive therapy with Atorvastatin and Atorvastatin plus Ezetimibe, and the addition of Evolocumab biweekly decreased LDL-cholesterol by a further 39%. CONCLUSIONS: The LDLRAP1:c.1A>G variant is associated with the appearance of an N-terminal truncated ARH protein and to reduced, although still significant, LDLR activity in lymphocytes. Residual LDLR activity may be relevant for the substantial response of the patient to Evolocumab.

[8] *Sanvee GM, Panajatovic MV, Bouitbir J, Krahenbuhl S*. **Mechanisms of insulin resistance by simvastatin in C2C12 myotubes and in mouse skeletal muscle**. Biochem Pharmacol 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30796916

ABSTRACT
Statins inhibit cholesterol biosynthesis and lower serum LDL-cholesterol levels. They are generally well tolerated, but can cause insulin resistance in patients. Therefore, we investigated the mechanisms underlying the statin-induced insulin resistance. We used mice and C2C12 myotubes (murine cell line): mice (n=10) were treated with oral simvastatin (5 mg/kg/day) or water (control) for 21 days and C2C12 cells were exposed to 10 muM simvastatin for 24h. After intraperitoneal glucose application (2 g/kg), simvastatin-treated mice had higher glucose but equal insulin plasma concentrations than controls and lower glucose transport into skeletal muscle. Similarly, glucose uptake by C2C12 myotubes exposed to 10 muM simvastatin for 24h was impaired compared to control cells. In simvastatin-treated C2C12 myotubes, mRNA and protein expression of the insulin receptor (IR) beta-chain was increased, but the phosphorylation (Tyr1361) was impaired. Simvastatin decreased numerically Akt/PKB Thr308 phosphorylation (via insulin signaling pathway) and significantly Akt/PKB Ser473 phosphorylation (via mTORC2), which was explained by impaired phosphorylation of mTOR Ser2448. Reduced phosphorylation of Akt/PKB impaired downstream phosphorylation of GSK3beta, leading to impaired translocation of GLUT4 into plasma membranes of C2C12 myotubes. In contrast, reduced phosphorylation of AS160 could be excluded as a reason for impaired GLUT4 translocation. In conclusion, simvastatin caused insulin resistance in mice and impaired glucose uptake in C2C12 myotubes. The findings in myotubes can be explained by diminished activation of Akt/PKB by mTORC2 and downstream effects on GSK3beta, impairing the translocation of GLUT4 and the uptake of glucose.

[9] *Solberg OG, Stavem K, Ragnarsson A et al.* **Index of microvascular resistance to assess the effect of rosuvastatin on microvascular function in women with chest pain and no obstructive coronary artery disease: A double-blind randomized study**. Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30790446

ABSTRACT
INTRODUCTION: Many women undergoing coronary angiography for chest pain have no or only minimal coronary artery disease (CAD). However, despite the lack of obstructive CAD, they still have an increased risk of major adverse cardiovascular events. Pleiotropic effects of statins may influence microvascular function, but if statins improve microvascular function in unselected chest pain patients is not well studied. This study assessed microvascular function by using the thermodilution-derived test "the index of microvascular resistance" (IMR) with the aim of determining the (i) IMR level in women with chest pain and non-obstructive CAD and if (ii) IMR is modified by high-dose statin treatment in these patients. Additional objectives were to identify the influence of statins on the health status as assessed with generic health questionnaires and on biomarkers of endothelial activation. MATERIALS AND METHODS: The study was a randomized, double-blind, single-center trial comparing 6 months of rosuvastatin treatment with placebo. In total, 66 women without obstructive CAD were included. Mean age

was 52.7 years and 55.5 years in the placebo and rosuvastatin group, respectively. Microvascular function was assessed using the IMR, health status was assessed using the SF-36 and EQ-5D questionnaires, and biochemical values were assessed at baseline and 6 months later. RESULTS AND CONCLUSIONS: In the placebo group IMR was 14.6 (SD 5.7) at baseline and 14.4 (SD 6.5) at follow-up. In the rosuvastatin group IMR was 16.5 (SD 7.5) at baseline and 14.2 (SD 5.8) at follow-up. IMR did not differ significantly between the two study groups at follow-up controlled for preintervention values. C-reactive protein (CRP) was comparable between the groups at baseline, while at follow-up CRP was significantly lower in the rosuvastatin group compared to placebo [0.6 (+/-0.5) mg/L vs. 2.6 (+/-3.0) mg/L; p = 0.002]. Whereas rosuvastatin treatment for 6 months attenuated CRP levels, it did not improve microvascular function as assessed by IMR (Clinical Trials.gov NCT 01582165, EUDRACT 2011-002630-39.3tcAZ).

[10] *Ferguson JJ, Stojanovski E, MacDonald-Wicks L, Garg ML*. **High molecular weight oat beta-glucan enhances lipid-lowering effects of phytosterols. A randomised controlled trial**. Clinical nutrition (Edinburgh, Scotland) 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30792143
ABSTRACT
BACKGROUND & AIMS: Oat beta-glucan (OBG) and phytosterols (PS) are known to lower blood cholesterol levels via different mechanisms. Combination of high molecular weight (MW) OBG and PS in a single functional food could have complementary and/or synergistic effects for optimising heart health. The aim of this study was to investigate the effects of dietary supplementation with high-MW OBG with or without PS on plasma lipids in hypercholesterolaemic individuals. METHODS: In a double-blinded, placebo-controlled, 2 x 2 factorial trial, participants were randomised to receive biscuits fortified with either no PS or OBG (PL, n = 18) or 2 g PS (PS, n = 18), 3 g OBG (OBG, n = 18), or combination of 2 g PS and 3 g OBG (PS-OBG, n = 18) per day for 6 weeks. Primary outcome was fasting plasma total cholesterol (TC) and secondary outcomes were LDL-cholesterol, LDL-C; HDL-cholesterol, HDL-C; triglycerides, TG and TC to HDL-cholesterol (TC:HDL) ratio. RESULTS: TC and LDL-C were significantly lowered following PS (-4.6% and -7.6% respectively; $p < 0.05$), OBG (-5.7% and -8.6%; $p < 0.01$) and PS-OBG (-11.5% and -13.9%; $p < 0.0001$) administration. The reduction in TC in the PS-OBG group was significantly greater compared to PL ($p < 0.001$) and PS ($p < 0.05$). PS-OBG group had a significantly greater reduction in LDL-C compared to PL ($p < 0.01$) but not in comparison to PS or OBG groups. TC:HDL ratio was significantly reduced following PS-OBG (-8.9%; $p < 0.01$) only, and there was no significant difference found between groups. Plasma TG reduced by 8.4% following PS-OBG, however, this was statistically non-significant. Plasma HDL-C remained unchanged across all groups. CONCLUSIONS: Dietary supplementation with high-MW OBG and PS in a single functional food enhances their lipid-lowering potential. Blood cholesterol lowering by PS and OBG is additive. Delivery of these two bioactive nutrients in a single food allows optimisation of their lipid-lowering effects and may provide added heart health benefits with enhanced compliance. The trial was registered with the Australian New Zealand Clinical Trials Registry at http://www.anzctr.org.au/(ACTRN12618001455257).

Literature update week 08 (2019)

[11] *Luscher TF, Davies A*. **Inclusion of multiple inappropriate studies in a meta-analysis of randomized controlled trials of atorvastatin loading prior to percutaneous coronary intervention for acute coronary syndrome: editor's response**. European heart journal 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30783647
ABSTRACT

[12] *Turgeon RD, Althouse AD*. **Inappropriate inclusion of multiple studies in a meta-analysis of randomized controlled trials of atorvastatin loading prior to percutaneous coronary intervention for acute coronary syndrome**. European heart journal 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30783662
ABSTRACT

[13] *Lee SE, Sung JM, Andreini D et al.* **Differential association between the progression of coronary artery calcium score and coronary plaque volume progression according to statins: the Progression of AtheRosclerotic PlAque DetermIned by Computed TomoGraphic Angiography Imaging (PARADIGM) study**. European heart journal cardiovascular Imaging 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30789215
ABSTRACT
AIMS: Coronary artery calcium score (CACS) is a strong predictor of major adverse cardiac events (MACE). Conversely, statins, which markedly reduce MACE risk, increase CACS. We explored whether CACS progression represents compositional plaque volume (PV) progression differently according to statin use. METHODS AND RESULTS: From a prospective multinational registry of consecutive patients (n = 2252) who underwent serial coronary computed tomography angiography (CCTA) at a >/= 2-year interval, 654 patients (61 +/- 10 years, 56% men, inter-scan interval 3.9 +/- 1.5 years) with information regarding the use of statins and having a serial CACS were included. Patients were divided into non-statin (n = 246) and statin-taking (n = 408) groups. Coronary PVs (total, calcified, and non-calcified; sum of fibrous, fibro-fatty, and lipid-rich) were quantitatively analysed, and CACS was measured from both CCTAs. Multivariate linear regression models were constructed for both statin-taking and non-statin group to assess the association between compositional PV change and change in CACS. In multivariate linear regression analysis, in the non-statin group, CACS increase was positively associated with both non-calcified (beta = 0.369, P = 0.004) and calcified PV increase (beta = 1.579, P < 0.001). However, in the statin-taking group, CACS increase was positively associated with calcified PV change (beta = 0.756, P < 0.001) but was negatively associated with non-calcified PV change (beta = -0.194, P = 0.026). CONCLUSION: In the non-statin group, CACS progression indicates the progression of both non-calcified and calcified PV progression. However, under the effect of statins, CACS progression indicates only calcified PV progression, but not non-calcified PV progression. Thus, the result of serial CACS should be differently interpreted according to the use of statins.

[14] *Macchi C, Banach M, Corsini A et al.* **Changes in circulating pro-protein convertase subtilisin/kexin type 9 levels - experimental and clinical approaches with lipid-lowering agents**. European journal of preventive cardiology 2019:2047487319831500.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30776916

ABSTRACT
Regulation of pro-protein convertase subtilisin/kexin type 9 (PCSK9) by drugs has led to the development of a still small number of agents with powerful activity on low-density lipoprotein cholesterol levels, associated with a significant reduction of cardiovascular events in patients in secondary prevention. The Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) and Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab (ODYSSEY OUTCOMES) studies, with the two available PCSK9 antagonists, i.e. evolocumab and alirocumab, both reported a 15% reduction in major adverse cardiovascular events. Regulation of PCSK9 expression is dependent upon a number of factors, partly genetic and partly associated to a complex transcriptional system, mainly controlled by sterol regulatory element binding proteins. PCSK9 is further regulated by concomitant drug treatments, particularly by statins, enhancing PCSK9 secretion but decreasing its stimulatory phosphorylated form (S688). These complex transcriptional mechanisms lead to variable circulating levels making clinical measurements of plasma PCSK9 for cardiovascular risk assessment a debated matter. Determination of total PCSK9 levels may provide a diagnostic tool for explaining an apparent resistance to PCSK9 inhibitors, thus indicating the need for other approaches. Newer agents targeting PCSK9 are in clinical development with a major interest in those with a longer duration of action, e.g. RNA silencing, allowing optimal patient compliance. Interest has been expanded to areas not only limited to low-density lipoprotein cholesterol reduction but also investigating other non-lipid pathways raising cardiovascular risk, in particular inflammation associated to raised high-sensitivity C-reactive protein levels, not significantly affected by the present PCSK9 antagonists.

[15] *Shin J, Chung JW, Jang HS et al.* **Achieved low-density lipoprotein cholesterol level and stroke risk: A meta-analysis of 23 randomised trials**. European journal of preventive cardiology 2019:2047487319830503.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30782002
ABSTRACT
AIMS: Lowering the low-density lipoprotein cholesterol level reduces the risk of stroke, but it has not been clear whether the stroke risk would continuously decrease by lowering low-density lipoprotein cholesterol to a very low level. The purpose of this study was to evaluate the association between achieved low-density lipoprotein cholesterol levels and stroke risk. METHODS AND RESULTS: A systematic search of MEDLINE, EMBASE and Cochrane Library databases was conducted to identify randomised controlled trials that tested cholesterol-lowering pharmacological therapies and reported both achieved low-density lipoprotein cholesterol levels and stroke outcomes. A meta-regression analysis was conducted to assess the linear association between the achieved low-density lipoprotein cholesterol levels and stroke risk. In addition, we evaluated pooled estimates of low-density lipoprotein cholesterol-lowering effect stratified by achieved low-density lipoprotein cholesterol levels of active arms. A total of 222,149 participants in 23 trials (52 arms of 26 studies) were included. The meta-regression analysis showed that each 1 mmol/L decrease in the achieved low-density lipoprotein cholesterol level (down to 0.78 mmol/L) was associated with a significant reduction of 23.5% (slope 0.235, 95% confidence interval 0.007-0.464, P = 0.044) in stroke risk. Irrespective of achieved low-density lipoprotein cholesterol levels in the active arms, the effects of lowering

the low-density lipoprotein cholesterol level on stroke risk were significant and consistent (test for subgroup difference, P = 0.23, I(2) = 31%). However, there was no significant increase in haemorrhagic stroke risk with lower achieved low-density lipoprotein cholesterol levels. CONCLUSION: In this meta-analysis of randomised controlled trials, the stroke risk monotonically reduced with lowering of low-density lipoprotein cholesterol to very low levels.

[16] *Haque T, Bhaheetharan S, Khan BV*. **Is there a role for pleiotropic effects of atorvastatin and fenofibrate in the metabolic syndrome and prediabetes?** Expert review of endocrinology & metabolism 2010; 5:835-837.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30780833
ABSTRACT
Evaluation of: Krysiak R, Gdula-Dymek A, Bachowski R, Okopien B. Pleiotropic effects of atorvastatin and fenofibrate in metabolic syndrome and different types of prediabetes. Diabetes Care 33(10), 2266-2270 (2010). The beneficial use of fibrates and statins has been observed in previous studies among patients with dyslipidemia, including those with glucose metabolism abnormalities. The paper under evaluation highlights these benefits and provides insight. Specifically, these findings are observed in patients who have prediabetes and metabolic syndrome (MS), and are taking atorvastatin or fenofibrate. The paper documents that both drugs have multiple pleiotropic effects on MS patients. Furthermore, these effects may be determined by prediabetes type. The results strengthen previous knowledge and offer new understanding, as no previous study has investigated whether the type of prediabetes can determine extra-lipid effects and cardiovascular risk factors in MS patients.

[17] *Viljoen A, Wierzbicki AS*. **Colesevelam: an improved bile acid sequestrant for treating hypercholesterolemia and improving diabetes**. Expert review of endocrinology & metabolism 2010; 5:825-834.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30780836
ABSTRACT
There is a well-established association between serum cholesterol and coronary heart disease. Statins are the first-line agents for the treatment of hypercholesterolemia, yet combination therapy is required to achieve the desired reduction in low-density lipoprotein cholesterol (LDL-C). Niacin and bile acid sequestrants were among the first lipid-lowering drugs developed to lower LDL-C and have been established to be effective both in monotherapy and in combination therapy. However, tolerability and compliance issues have limited their use. Colesevelam HCl is the newest bile acid sequestrant and reduces LDL-C by 16-22% in monotherapy and adds 12-14% in combination dual therapy with statins, fibrates and ezetimibe or in triple therapy with statin and ezetimibe. It reduces C-reactive protein levels by 16-19% in monotherapy or by 23% in combination with statins and other lipid-lowering therapies. In addition, it consistently reduces hemoglobin A1c by 0.5% in addition to other hypoglycemic drugs in studies of patients with diabetes. Compared with other bile acid sequestrants it has a higher bile acid-binding capacity, reduced adverse effects and, therefore, has better compliance. Colesevelam HCl is thus a useful addition to the lipid-lowering formulary as a second-line agent, particularly for patients with metabolic syndrome requiring extra reduction in LDL-C.

[18] *Konishi T, Kashiwagi Y, Funayama N et al.* **Obstructive sleep apnea is associated with increased coronary plaque instability: an optical frequency domain imaging study**. Heart Vessels 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30790035
ABSTRACT
Obstructive sleep apnea (OSA) is associated with coronary artery disease (CAD) and with an increased risk for myocardial infarction, stroke or death due to cardiovascular disease. Optical frequency-domain imaging (OFDI) is a useful modality for evaluating the characteristics of atherosclerotic plaque. The purpose of the study was to use OFDI to investigate the association of OSA with coronary plaque characteristics in patients undergoing percutaneous coronary intervention (PCI). We retrospectively analyzed OFDI data for coronary artery plaques from 15 patients with OSA and 35 non-OSA patients treated between October 2015 and October 2018. Plaque morphology was evaluated for 70 lesions, including 21 from patients with OSA and 49 from non-OSA patients. Compared with the non-OSA group, patients with OSA had significantly higher prevalences of thinned cap fibroatheroma (TCFA) (67% vs. 35%, P = 0.014) and microchannels (86% vs. 55%, P = 0.014); a significantly higher mean lipid index (1392 +/- 982 vs. 817 +/- 699, P = 0.021), macrophage grade (8.4 +/- 6.4 vs. 4.8 +/- 4.5, P = 0.030), and maximum number of microchannels (1.5 +/- 1.0 vs. 0.7 +/- 0.7, P = 0.001); and a significantly lower mean minimum fibrous cap thickness (69.4 +/- 28.7 vs. 96.1 +/- 51.8 mum, P = 0.008). This OFDI analysis suggests that OSA is associated with unstable plaque characteristics in patients with CAD. More intensive medical management for stabilization of coronary atherosclerotic plaque is required in patients with OSA.

[19] *Di Daniele N, Celotto R, Alunni Fegatelli D et al.* **Common Carotid Artery Calcification Impacts on Cognitive Function in Older Patients**. High blood pressure & cardiovascular prevention : the official journal of the Italian Society of Hypertension 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30779026
ABSTRACT
INTRODUCTION: Cognitive impairment and dementia represent an emerging health problem. Cardiovascular (CV) risk factors contribute to cognitive impairment. AIM: To investigate the effect of vascular calcification on cognitive impairment and dementia, independently of plaque and traditional CV risk factors. METHODS: Four hundred and sixty-nine patients (age of 78.6 +/- 6.1 years, 74.4% women) were studied. Traditional CV risk factors levels, cognitive function (MMSE), brain CT scan, and other vascular parameters were measured. Common Carotid Artery (CCA) plaque and calcification were evaluated by ultrasound. RESULTS: CCA calcification was associated with a lower MMSE score than in subjects with no CCA calcification (23.7 +/- 0.3 versus 25.5 +/- 0.8; p = 0.015), after controlling for age, sex, education, blood pressure levels, diabetes, creatinine, lipid lowering therapy, neuroimaging alteration, and CCA plaque. Similarly, CCA calcification was associated with higher odds of dementia regardless of the presence of CCA plaque (OR 1.70, 95% CI 1.01-2.94, p < 0.05). This trend was not observed when stratifying patients according to the presence of CCA plaque. CONCLUSION: CCA calcification is associated with cognitive impairment and dementia, independently of established CV risk factors and CCA plaque. The impact of arterial calcification on cognition seems largely independent of arterial stiffness.

[20] *Thomson SR, Chogtu B, Shetty R, Devasia T*. **Analysis of glycemic status in diabetes-naive patients on statins: A hospital-based cross-sectional study**. Indian journal of pharmacology 2018; 50:320-325.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30783324

ABSTRACT
INTRODUCTION: Randomized controlled trials, observational studies, and meta-analysis suggest risk of hyperglycemia in patients on statins, and this association is being viewed with renewed interest globally. The present study has tried to explore the possible diabetogenic effect of statins, the mechanism of this effect, and various comorbidities associated with this causation. MATERIALS AND METHODS: This cross-sectional study was carried out at the Department of Cardiology from October 2015 to March 2017. Patients on statins for at least 1 year and normoglycemic at the time of statin initiation were recruited in the study. The outcome of the present study was development of new-onset diabetes mellitus (NODM). Blood glucose levels and insulin levels were estimated. Other adverse reactions of statins and associated comorbidities in the patients were recorded. Descriptive statistics were used to analyze adverse drug reactions. RESULTS: A total of 104 patients met the inclusion criteria, of which eight patients (7.7%) developed NODM and 4 (3.8%) developed prediabetes. Atorvastatin 40 mg was most commonly prescribed statin. About 25% of patients taking atorvastatin 80 mg developed diabetes. CONCLUSION: Statins have a mild-to-moderate risk of developing NODM. The dose of statins is an important factor that increases the risk of diabetes in statin users.

[21] *Zhang J, Xu X, Zhu H et al.* **Dietary fish oil supplementation alters liver gene expressions to protect against LPS-induced liver injury in weanling piglets**. Innate immunity 2019; 25:60-72.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30782046

ABSTRACT
Here, the potential mechanisms of the protective effects of fish oil against LPS-induced liver injury in a piglet model were investigated by using RNA sequencing. Twenty-four piglets were used in a 2 x 2 factorial design, and the main factors included diet (5% corn oil or 5% fish oil) and immunological challenge (LPS or saline, on d 19). All piglets were slaughtered at 4 h after challenge, and liver samples were collected. Fish oil improved liver morphology and reduced TNF-alpha, IL-1beta and IL-6 productions after LPS challenge. RNA sequencing analysis showed fish oil had significant effect on the expressions of genes involved in immune response during LPS-induced inflammation. Selected gene expression changes were validated using quantitative RT-PCR. Fish oil reduced the expressions of pro-inflammatory genes IL1R1, IL1RAP, CEBPB and CRP, and increased that of anti-inflammatory genes IL-18BP, NFKBIA, IFIT1, IFIT2 and ATF3. Moreover, fish oil restored the expressions of some lipid metabolism-related genes, such as ACAA1, ACACA, ACADS and ACADM, which were only decreased in pigs fed a corn oil diet after LPS challenge. Our RNA sequencing reveals novel gene-nutrient interactions following fish oil supplementation and evoked inflammation, which add to the current understanding of the benefits of n-3 polyunsaturated fatty acids against liver injury.

Literature update week 08 (2019)

[22] *Rahbar AR, Safavi E, Rooholamini M et al.* **Effects of Intermittent Fasting during Ramadan on Insulin-like Growth Factor-1, Interleukin 2, and Lipid Profile in Healthy Muslims**.
International journal of preventive medicine 2019; 10:7.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30774841
ABSTRACT
Background: Insulin-like growth factor-1 (IGF-1) and interleukin-2 (IL-2) play an essential role in pathophysiology of several chronic diseases. As a stressor, fasting in Ramadan may increase inflammatory markers such as IGF-1 and IL-2 in Muslims. The aim of this before-after study was to investigate the effects of fasting in Ramadan on IGF-1 and IL-2 levels in individuals. Methods: In all, 34 men age 16-64 years were selected out of the overall number of individuals who were ready for fasting entirely throughout Ramadan. A sample of blood was drawn from the contributors before and after Ramadan, and plasma IGF-1, IL-2, total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) were determined. To identify differences between the initial and final values of test results of the study for plasma IGF-1, IL-2, and lipid parameters, we used paired sample T-test. Results: Paired sample T-test illustrated a significant decrease in IGF-1 and IL-2 levels after Ramadan fasting compared to before Ramadan. The concentration of TG, cholesterol, and LDL-C levels underwent significant decreases over the period of the study. HDL-C levels did not change significantly during the study. A significant decrease in weight, waist circumferences, calorie, carbohydrate, and fat intake were observed in participants during Ramadan fasting. Conclusions: It is concluded that fasting in Ramadan independent of anthropometric measures attenuates inflammation and is beneficiary to health.

[23] *Sozen E, Demirel T, Ozer NK*. **Vitamin E: Regulatory role in the cardiovascular system**.
IUBMB life 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30779288
ABSTRACT
Cardiovascular disease (CVD) is one of the major causes of morbidity and mortality, all around the world. Vitamin E is an important nutrient influencing key cellular and molecular mechanisms as well as gene expression regulation centrally involved in the prevention of CVD. Cell culture and animal studies have focused on the identification of vitamin E regulated signaling pathways and involvement on inflammation, lipid homeostasis, and atherosclerotic plaque stability. While some of these vitamin E functions were verified in clinical trials, some of the positive effects were not translated into beneficial outcomes in epidemiological studies. In recent years, the physiological metabolites of vitamin E, including the liver derived (long- and short-chain) metabolites and phosphorylated (alpha-, gamma-tocopheryl phosphate) forms, have also provided novel mechanistic insight into CVD regulation that expands beyond the vitamin E precursor. It is certain that this emerging insight into the molecular and cellular action of vitamin E will help to design further studies, either in animal models or clinical trials, on the reduction of risk for CVDs. This review focuses on vitamin E-mediated preventive cardiovascular effects and discusses novel insights into the biology and mechanism of action of vitamin E metabolites in CVD. (c) 2019 IUBMB Life, 2019.

[24] *Hsu CL, Hou YH, Wang CS et al.* **Antiobesity and Uric Acid-Lowering Effect of Lactobacillus plantarum GKM3 in High-Fat-Diet-Induced Obese Rats**. Journal of the American College of Nutrition 2019:1-10.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30794474
ABSTRACT
OBJECTIVE: Obesity has become one of the world's biggest issues. This condition has a great impact on several metabolic and chronic diseases. For example, obesity is often accompanied by hyperuricemia or gout. However, few drugs are available for the treatment of obesity. The present study is to evaluate the antiobesity effect of Lactobacillus plantarum GKM3 in high-fat-diet-induced obese rats and whether taking L plantarum GKM3 can effectively reduce uric acid accumulation caused by obesity and ameliorate other harmful factors. METHOD: Sixty male Wistar rats were divided into five groups as follows: (1) ND group, fed normal diet; (2) HFC group, fed AIN93G-based high-fat diet containing 65% solids, 7% soybean oil, and 25% lard; (3) HFL group, fed AIN93G-based high-fat diet supplemented with 102.7 mg/kg/d L plantarum GKM3; (4) HFM group, fed AIN93G-based high-fat diet supplemented with 205.4 mg/kg/d L plantarum GKM3; and (5) HFH group, fed AIN93G-based high-fat diet supplemented with 513.5 mg/kg/d L plantarum GKM3. After 6 weeks, the body, organ, and fat weights; food intake; blood serum levels; and adipocyte size were measured. RESULTS: Results showed that rats fed on the high-fat diet showed more body weight, increased feed efficiency, higher fat deposition, higher total liver weight, elevated serum lipid levels, and increased adipocyte size compared with those on the normal diet. All these effects were reversed by supplementation of L plantarum GKM3. CONCLUSIONS: In conclusion, we suggest that the L plantarum GKM3 supplement may have beneficial antiobesity and uric acid-lowering effects.

[25] *Huang RC, Lillycrop KA, Beilin LJ et al.* **Epigenetic age acceleration in adolescence associates with BMI, inflammation and risk score for middle age cardiovascular disease**. The Journal of clinical endocrinology and metabolism 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30785999
ABSTRACT
BACKGROUND: 'Accelerated ageing', assessed by adult DNA methylation predicts cardiovascular disease (CVD). Adolescent accelerated aging might predict CVD earlier. We investigated whether epigenetic age acceleration (assessed age 17-years) associated with adiposity/CVD-risk measured (ages 17, 20, 22-years), and projected CVD by middle-age. METHODS: DNA methylation measured in peripheral blood provided 2 estimates of epigenetic age acceleration; intrinsic (IEAA, (preserved across cell types) and extrinsic (EEAA, dependent on cell admixture and methylation levels within each cell type).Adiposity was assessed by anthropometry, ultrasound and DEXA (ages 17, 20, 22 years). CVD-risk factors (lipids, HOMA-IR, blood pressure, inflammatory markers) were assessed at age 17-years. CVD development by age 47 years was calculated by Framingham algorithms. Results are presented as regression coefficients/5-year epigenetic age acceleration (IEAA/EEAA) for adiposity, CVD-risk factors and CVD development. RESULTS: In 995 participants (49.6% female, age 17.3+/-0.6 years), EEAA (/5-years) was associated with increased BMI of 2.4% (95%CI 1.2-3.6%) and 2.4% (0.8-3.9%) at 17 and 22 years, respectively. EEAA was associated with increases of 23% (3-33%) in hsCRP, 10% (4-17%) in interferon-gamma induced protein (IP-10) and 4% (2-6%) in tumour necrosis factor receptor 2

(sTNFR2), adjusted for BMI and HOMA-IR. EEAA(/5-years) results in a 4% increase in hard endpoints of CVD by 47 years old and a 3% increase, after adjustment for conventional risk factors. CONCLUSIONS: Accelerated epigenetic age in adolescence was associated with inflammation, BMI measured 5 years later, and probability of middle-age CVD. Irrespective whether this is cause or effect, assessing epigenetic age might refine disease prediction.

[26] *Luirink IK, Braamskamp M, Wiegman A et al.* **The clinical and molecular diversity of homozygous familial hypercholesterolemia in children: Results from the GeneTics of clinical homozygous hypercholesterolemia (GoTCHA) study**. Journal of clinical lipidology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30795984
ABSTRACT
BACKGROUND: Homozygous familial hypercholesterolemia (hoFH) is either diagnosed on the identification of pathogenic genetic variants in LDLR, APOB, or PCSK9 or by phenotypic parameters of which an extremely elevated LDL-C level >13 mmol/L (>500 mg/dL) is the most prominent hallmark. Little is known about the clinical spectrum in children with hoFH. OBJECTIVE: We set out to investigate the phenotypical spectrum of genetically defined hoFH in our pediatric cohort and evaluated how many pediatric patients, now classified as heterozygous, carry a second mutation, which would reclassify these patients as hoFH. METHODS: We analyzed the data of a total of 1903 children with molecularly proven FH. Subsequently we performed candidate gene sequencing in the cohort of heterozygous familial hypercholesterolemia children in whom the LDL-C level was above the lowest level measured in the pediatric patients with hoFH. RESULTS: Of our 13 hoFH children, 8 (62%) had LDL-C levels below the clinical hoFH criteria of 13 mmol/L (500 mg/dL). In the remaining 1890 patients with heterozygous familial hypercholesterolemia, 64 (3.4%) had LDL-C levels equal to or above the lowest LDL-C level in a patient with hoFH carrying 2 deleterious variants (8.36 mmol/L or 323.3 mg/dL). No additional pathogenic variants in LDLR and APOB were identified. In 2 related patients, a PCSK9 gain of function mutation was found. CONCLUSION: We show that LDL-C levels vary among pediatric patients with molecularly proven hoFH, and that most of these patients do not meet the clinical LDL-C criteria for hoFH. The levels overlap with LDL-C levels in true heterozygous patients. This warrants a critical reappraisal of the current LDL-C cutoffs for the phenotypic diagnosis of hoFH in children.

[27] *Su X, Shao Y, Lin Y et al.* **Clinical features, molecular characteristics, and treatments of a Chinese girl with sitosterolemia: A case report and literature review**. Journal of clinical lipidology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30782472
ABSTRACT
Sitosterolemia is a rare autosomal recessive disease characterized by a significant increase in blood plant sterol levels. Clinical manifestations usually include xanthomas, hypercholesterolemia,premature atherosclerosis and hematological abnormalities. We report here a sitosterolemia patient who presented with multiple xanthomas and profound hypercholesterolemia since 3 years old. The girl was mistreated as familial hypercholesterolemia for 6 years until correct diagnosis was made by detecting serum plant cholesterol levels. Sequence analysis revealed compound heterozygous mutations in ABCG5

gene, including the previously reported mutation c.904+1GA and a novel missense mutation c.1528CA. Although cholestyramine therapy reduced cholesterol level in association with marked regress of the xanthomas, serum plant sterol levels still remain high. Our study suggests that patients develop severe hypercholesterolemia and xanthomas at early age should be suspected of sitosterolemia. In addition, we also describe a novel missense mutation in exon 11 of the ABCG5 gene, which enriches the genetic mutation spectrum of sitosterolemia.

[28] *Upreti S, Fayyaz B, Bongu RP*. **Anti-HMG-CoA reductase myopathy, an undesirable evolution of statin induced myopathy: a case report**. Journal of community hospital internal medicine perspectives 2019; 9:33-35.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30788073
ABSTRACT
Statins are commonly used lipid lowering agents which play a pivotal role in reducing cardiovascular morbidity and mortality. Often well tolerated, these HMG-CoA reductase (HMGCR) inhibitors can sometimes cause severe muscle weakness and elevated creatinine kinase (CK) often labeled as statin intolerance or statin induced myopathy. These symptoms improve after discontinuation of the offending drug along with normalization of the enzyme levels. However, an entity called Immune Mediated Necrotizing Myopathy (IMNM), a type of autoimmune mediated myopathy, has been recognized and characterized in patients with history of statin exposure where there is persistence of proximal muscle weakness, CK elevation and myofiber necrosis can be seen on muscle biopsy even after stopping statins. With the increased use of statins, there seems to be a higher incidence of IMNM cases in recent years. Here we discuss a case of anti-HMG-CoA myopathy, one of the three recognized types of IMNM that has been more commonly associated with statin exposure and highly responsive to immunotherapy.

[29] *Tarpley AJ*. **New Frontier in Lipids: PCSK9 Inhibitors and Implications for the Life Insurance Industry**. Journal of insurance medicine (New York, N.Y.) 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30789783
ABSTRACT
Since the Framingham Heart Study solidified cholesterol as a causative agent in the development of coronary heart disease there has been an explosion of research in the field of lipidology. Many therapeutic options have come and gone as we have been refining the goals of therapy to match the mortality outcome data of large clinical trials. A new frontier has emerged with the introduction of the PCSK9 inhibitors that are able with monthly injections to lower LDL cholesterol >60% with favorable side effect profiles and recently published favorable mortality data. This ushers in a whole new era of cholesterol management. Life insurance medical directors will need to be informed of how these drugs are being used and for conditions such as homozygous hypercholesterolemia, a condition with a very high mortality risk, and for new genetic analysis of affected patients, who are not as rare as once thought. This article provides the background about the development of these drugs, their expanded indications, how they may slip through the cracks of prescription drug (Rx) database inquiries, and touches on therapies in development beyond this class of medications. Medicine is an evolving field. With the new gene editing CRISPR technology it will truly be transformational for these genetically

driven conditions with the potential for curative therapy. If curative therapy comes to pass it will, of course, have favorable implications for our evolving life insurance guidelines.

[30] *Romani M, Hofer DC, Katsyuba E, Auwerx J*. **Niacin: an old lipid drug in a new NAD+ dress**. Journal of lipid research 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30782960
ABSTRACT
Niacin, the first anti-dyslipidemic drug, has been at the centerstage of lipid research for many decades before the discovery of statins. However, to date, despite its remarkable effects on lipid profiles, the clinical outcomes of niacin treatment on cardiac events is still debated. In addition to its historically well-defined interactions with central players of lipid metabolism, niacin can be processed by eukaryotic cells to synthesize a crucial cofactor, nicotinamide adenine dinucleotide (NAD+). NAD+ acts as a cofactor in key cellular processes, including oxidative phosphorylation, glycolysis and DNA repair. More recently evidence emerged that NAD+ also is an essential co-substrate for the sirtuin family of protein deacylases, and thereby impact on a wide range of cellular processes, most notably mitochondrial homeostasis, energy homeostasis and lipid metabolism. NAD+ achieves these remarkable effects through sirtuin-mediated deacetylation of key transcriptional regulators, such as PGC-1alpha, LXR and SREBPs, that control these cellular processes. Here we present an alternative point of view to explain niacin's mechanism of action, with a strong focus on the importance of how this old drug acts as a control switch of NAD+/sirtuin-mediated control of metabolism.

[31] *Tall AR, Westerterp M*. **Inflammasomes, Neutrophil Extracellular Traps, and Cholesterol**. Journal of lipid research 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30782961
ABSTRACT
Activation of macrophage inflammasomes leads to interleukin (IL)-1b and IL-18 secretion and promotes atherosclerosis and its complications in mice and humans. However, the specific role and underlying mechanisms of the inflammasome in atherogenesis are topics of active research. Several studies in hyperlipidemic mouse models found that the NLRP3 inflammasome contributes to atherosclerosis, but recent work suggests that a second hit, such as defective cholesterol efflux or accumulation of oxidized mitochondrial DNA, may be required for significant inflammasome activation. Cholesterol crystal uptake or formation in lysosomes may damage membranes and activate NLRP3 inflammasomes. Alternatively, plasma or endoplasmic reticulum membrane cholesterol accumulation may condition macrophages for inflammasome activation in the presence of danger-associated molecular patterns, such as oxidized LDL. Inflammasome activation in macrophages or neutrophils leads to Gasdermin-D cleavage that induces membrane pore formation, releasing IL-1b and IL-18, and eventuating in pyroptosis or neutrophil extracellular trap formation (NETosis). In humans, inflammasome activation and NETosis may contribute to atherosclerotic plaque erosion and thrombosis, especially in patients with type 2 diabetes, chronic kidney disease, or clonal hematopoiesis. Suppression of the inflammasome by activation of cholesterol efflux or by direct inhibition of inflammasome components may benefit patients with cardiovascular disease and underlying susceptibility to inflammasome activation.

[32] *Yang L, Kraemer M, Fang XF et al.* **LPA Receptor 4 deficiency attenuates experimental atherosclerosis**. Journal of lipid research 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30796085
ABSTRACT
The widely expressed lysophosphatidic acid (LPA) selective receptor 4 (LPAR4) contributes to vascular development in mice and zebrafish. LPAR4 regulates endothelial permeability, lymphocyte migration, and hematopoiesis, which could contribute to atherosclerosis. We investigated the role of LPAR4 in experimental atherosclerosis elicited by adeno-associated virus expressing PCSK9 to lower LDL receptor levels. After 20 weeks on Western diet, cholesterol levels and lipoprotein distribution were similar in wild-type male and Lpar4Y/- mice (P = 0.94). Atherosclerotic lesion area in proximal aorta and arch was ~25% smaller in Lpar4Y/- mice (P = 0.009), and less atherosclerosis was detected in Lpar4Y/- mice at any given plasma cholesterol. Neutral lipid accumulation in aortic root sections occupied ~40% less area in Lpar4Y/- mice (P = 0.001), and CD68 ~ 25% lower (P = 0.045). No difference in smooth muscle alpha;-actin staining was observed. Bone marrow derived macrophages isolated from Lpar4Y/- mice displayed significantly increased upregulation of the M2 marker Arg1 in response to LPA compared to wild-type cells. In aortic root sections from Lpar4Y/- mice, heightened M2 repair macrophage marker expression was detected by CD206 staining (P = 0.03). These results suggest that LPAR4 may regulate recruitment of specific sets of macrophages or their phenotypic switching in a manner that could influence the development of atherosclerosis.

[33] *Hosseinzadeh A, Bahrampour Juybari K, Kamarul T, Sharifi AM*. **Protective effects of atorvastatin on high glucose-induced oxidative stress and mitochondrial apoptotic signaling pathways in cultured chondrocytes**. Journal of physiology and biochemistry 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30796627
ABSTRACT
The high glucose concentration is able to disturb chondrocyte homeostasis and contribute to OA pathogenesis. This study was designed to investigate the protective effects of atorvastatin (ATO) on high glucose (HG)-mediated oxidative stress and mitochondrial apoptosis in C28I2 human chondrocytes. The protective effect of ATO (0.01 and 0.1 muM) on HG (75 mM)-induced oxidative stress and apoptosis was evaluated in C28I2 cells. The effects of ATO on HG-induced intracellular ROS production and lipid peroxidation were detected and the protein expression levels of Bax, Bcl-2, caspase-3, total and phosphorylated JNK and P38 MAPKs were analyzed by Western blotting. The mRNA expression levels of antioxidant enzymes including heme oxygenase-1, NAD(P)H quinine oxidoreductase, glutathione S-transferase-P1, catalase, superoxide dismutase-1, glutathione peroxidase-1, -3, -4 were evaluated by reverse transcription-polymerase chain reaction. Pretreatment with ATO remarkably increased the gene expression levels of antioxidant enzymes and reduced HG-induced elevation of ROS, lipid peroxidation, Bax/Bcl-2 ratio, caspase-3 activation, and JNK and P38 phosphorylation. Atorvastatin could considerably reduce HG-induced oxidative stress and mitochondrial apoptosis through increasing the expression of antioxidant enzymes. Atorvastatin may be considered as a promising agent to prevent high glucose-induced cartilage degradation in OA patients.

[34] *Jansen SCP, Hoorweg BBN, Hoeks SE et al.* **A systematic review and meta-analysis of the effects of supervised exercise therapy on modifiable cardiovascular risk factors in intermittent claudication**. Journal of vascular surgery 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30777692
ABSTRACT
OBJECTIVE: Cardiovascular events, such as myocardial infarction and stroke, contribute significantly to the prognosis of patients with peripheral artery disease. Therefore cardiovascular risk reduction is a vital element of treatment in patients with intermittent claudication (IC). The cardiovascular risk is largely determined by modifiable risk factors, which can be treated with medical care and lifestyle adjustments, such as increasing physical activity. The objective of this study was to determine the effects of supervised exercise therapy (SET) on modifiable cardiovascular risk factors in IC patients. METHODS: This is a systematic review and meta-analysis of prospective studies on the effects of SET on cardiovascular risk factors in symptomatic IC patients. Studies were eligible if they presented baseline and follow-up values for at least one of the following risk factors: blood pressure (systolic or diastolic), heart rate, lipid profile (total cholesterol, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol), glucose, glycated hemoglobin, body weight, body mass index, or cigarette smoking. Pooled mean differences between follow-up and baseline were analyzed using a random-effects model. Data were classified into short-term results (6 weeks-3 months) and midterm results (6-12 months). Statistical heterogeneity was presented as I(2) and Q statistic. RESULTS: Twenty-seven studies with a total of 808 patients were included in this review. In the short term, SET resulted in significant improvements of systolic blood pressure (decrease of 4 mm Hg; 10 studies; 95% confidence interval [CI], -6.40 to -1.76; I(2), 0%) and diastolic blood pressure (decrease of 2 mm Hg; 8 studies; 95% CI, -3.64 to -0.22; I(2), 35%). In the midterm, SET contributed to significant lowering of levels of low-density lipoprotein cholesterol (decrease of 0.2 mmol/L; four studies; 95% CI, -0.30 to -0.12; I(2), 29%) and total cholesterol (decrease of 0.2 mmol/L, four studies; 95% CI, -0.38 to -0.10; I(2), 36%). No significant effects of SET were identified for heart rate, triglycerides, high-density lipoprotein cholesterol, glucose, glycated hemoglobin, body weight, body mass index, or cigarette smoking. CONCLUSIONS: This systematic review and meta-analysis shows favorable effects of SET on modifiable cardiovascular risk factors, specifically blood pressure and cholesterol levels. Despite the moderate quality, small trial sample sizes, and study heterogeneity, these findings support the prescription of SET programs not only to increase walking distances but also for risk factor modification. Future studies should address the potential effectiveness of SET to promote a healthier lifestyle and to improve cardiovascular outcomes in patients with claudication.

[35] *Kwiecinski J, Dey D, Cadet S et al.* **Peri-Coronary Adipose Tissue Density Is Associated With (18)F-Sodium Fluoride Coronary Uptake in Stable Patients With High-Risk Plaques**. JACC. Cardiovascular imaging 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30772226
ABSTRACT
OBJECTIVES: This study aimed to assess the association between increased lesion peri-coronary adipose tissue (PCAT) density and coronary (18)F-sodium fluoride ((18)F-NaF) uptake on

positron emission tomography (PET) in stable patients with high-risk coronary plaques (HRPs) shown on coronary computed tomography angiography (CTA). BACKGROUND: Coronary (18)F-NaF uptake reflects the rate of calcification of coronary atherosclerotic plaque. Increased PCAT density is associated with vascular inflammation. Currently, the relationship between increased PCAT density and (18)F-NaF uptake in stable patients with HRPs on coronary CTA has not been characterized. METHODS: Patients who underwent coronary CTA were screened for HRP, which was defined by 3 concurrent plaque features: positive remodeling; low attenuation plaque (LAP; <30 Hounsfield units [HU]) and spotty calcification; and obstructive coronary stenosis >/=50% (plaque volume >100 mm(3)). Patients with HRPs were recruited to undergo (18)F-NaF PET/CT. In lesions with stenosis >/=25%, quantitative plaque analysis, mean PCAT density, maximal coronary motion-corrected (18)F-NaF standard uptake values (SUVmax), and target-to-background ratios (TBR) were measured. RESULTS: Forty-one patients (age 65 +/- 6 years; 68% men) were recruited. Fifty-one lesions in 23 patients (56%) showed increased coronary (18)F-NaF activity. Lesions with (18)F-NaF uptake had higher surrounding PCAT density than those without (18)F-NaF uptake (-73 HU; interquartile range -79 to -68 vs. -86 HU; interquartile range -94 to -80 HU; p < 0.001). (18)F-NaF TBR and SUVmax were correlated with PCAT density (r = 0.63 and r = 0.68, respectively; all p < 0.001). On adjusted multiple regression analysis, increased lesion PCAT density and LAP volume were associated with (18)F-NaF TBR (beta = 0.25; 95% confidence interval: 0.17 to 0.34; p < 0.001 for PCAT, and beta = 0.07; 95% confidence interval: 0.03 to 0.11; p = 0.002 for LAP). CONCLUSIONS: In patients with HRP features on coronary CTA, increased density of PCAT was associated with focal (18)F-NaF PET uptake. Simultaneous assessment of these imaging biomarkers by (18)F-NaF PET and CTA might refine cardiovascular risk prediction in stable patients with HRP features.

[36] *Safarova MS, Satterfield BA, Fan X et al.* **A phenome-wide association study to discover pleiotropic effects of PCSK9, APOB, and LDLR**. NPJ genomic medicine 2019; 4:3.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30774981

ABSTRACT

We conducted an electronic health record (EHR)-based phenome-wide association study (PheWAS) to discover pleiotropic effects of variants in three lipoprotein metabolism genes PCSK9, APOB, and LDLR. Using high-density genotype data, we tested the associations of variants in the three genes with 1232 EHR-derived binary phecodes in 51,700 European-ancestry (EA) individuals and 585 phecodes in 10,276 African-ancestry (AA) individuals; 457 PCSK9, 730 APOB, and 720 LDLR variants were filtered by imputation quality (r (2) > 0.4), minor allele frequency (>1%), linkage disequilibrium (r (2) < 0.3), and association with LDL-C levels, yielding a set of two PCSK9, three APOB, and five LDLR variants in EA but no variants in AA. Cases and controls were defined for each phecode using the PheWAS package in R. Logistic regression assuming an additive genetic model was used with adjustment for age, sex, and the first two principal components. Significant associations were tested in additional cohorts from Vanderbilt University (n = 29,713), the Marshfield Clinic Personalized Medicine Research Project (n = 9562), and UK Biobank (n = 408,455). We identified one PCSK9, two APOB, and two LDLR variants significantly associated with an examined phecode. Only one of the variants was associated with a non-lipid disease phecode, ("myopia") but this association was not significant in the replication cohorts. In this large-scale PheWAS we did not find LDL-C-related variants in

PCSK9, APOB, and LDLR to be associated with non-lipid-related phenotypes including diabetes, neurocognitive disorders, or cataracts.

[37] *Pan R, Li Y, Zhou H*. **Efficacy and safety of different doses of alirocumab in reducing low-density lipoprotein cholesterol levels: a network meta-analysis**. Pharmazie 2019; 74:8-14.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30782243
ABSTRACT
This study aimed to conduct a network meta-analysis of the efficacy and safety of different doses of alirocumab in reducing low-density lipoprotein cholesterol levels. In the present study, a total of 16 studies were selected, published between January 2012 and October 2016. Pair-wise and network meta-analyses was used to carry out a direct and indirect comparison of the three treatment strategies of alirocumab in patients with hypercholesterolemia. The efficacy and safety of these different treatment strategies were analyzed. Results revealed that alirocumab could significantly reduce LDL-c levels, compared with placebo (relative effect 95 % CI: -71.45 [-91.16, -50.44], -74.32 [-90.40, -58.63] and -77.28 [-92.21, -61.90]) and ezetimibe (EZE) (relative effect 95 % CI: -37.2 [-61.21, -12.41], -40.07 [-56.92, -24.22] and -43.00 [-68.39, -17.91]). The comparison of the three treatment strategies of alirocumab indicated no significant differences in reducing the levels of LDL-c, TGs, TC, Lp (a), Apo B and SAEs, LTTD, IST, ACE, MD and NC. For the probabilities of 75 mg, 75-150 mg and 150 mg of alirocumab, the best treatment for EZE and placebo were 50 %, 68 %, 82 %, 1 % and 0 %, according to LDL-c level. The results of the benefit-risk analysis of efficacy and safety revealed that the logarithmic scale was 0.016 for 75 mg vs. 75-150 mg of alirocumab and 0.125 for 75-150 mg vs. 150 mg of alirocumab. The PCSK9 inhibitor alirocumab presents a significantly greater reducing effect on the levels of LDL-c compared with EZE, and the different doses of alirocumab exhibited no significant difference in the efficacy of LDL-c for hypercholesterolemia. An alirocumab dose of 75-150 mg Q2W might be the best choice due to its most favorable balance between efficacy and safety.

[38] *Cherny SS, Freidin MB, Williams FMK, Livshits G*. **The analysis of causal relationships between blood lipid levels and BMD**. PloS one 2019; 14:e0212464.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30794634
ABSTRACT
Bone mineral density (BMD) and lipid levels are two of the most extensively studied risk factors for common diseases of aging, such as cardiovascular disease (CVD) and osteoporosis (OP). These two risk factors are also correlated with each other, but little is known about the molecular mechanisms behind this correlation. Recent studies revealed that circulating levels of several metabolites involved in the biosynthesis of androsterone correlate significantly with BMD and have the capacity to affect cholesterol and lipids levels. A main aim of the present study was to investigate the hypothesis that androsterone-related metabolites could provide a link between CVD and OP, as a common cause of lipid levels and BMD. The present study employed data from the NIHR BRC TwinsUK BioResource, comprising 1909 and 1994 monozygotic and dizygotic twin pairs, respectively, to address the causal relationships among BMD and lipids, and their associated metabolites, using reciprocal causation twin modelling, as well as Mendelian randomization (MR) using large publicly-available GWAS datasets on lipids

and BMD, in conjunction with TwinsUK metabolite data. While results involving the twin modelling and MR analyses with metabolites were unable to establish a causal link between metabolite levels and either lipids or BMD, MR analyses of BMD and lipids suggest that lipid levels have a causal impact on BMD, which is consistent with findings from clinical trials of lipid-lowering drugs, which have also increased BMD.

[39] *Limwattananon C, Waleekhachonloet O*. **Access to and price trends of antidiabetic, antihypertensive, and antilipidemic drugs in outpatient settings of the Universal Coverage Scheme in Thailand**. PloS one 2019; 14:e0211759.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30785916
ABSTRACT
Under the Universal Coverage Scheme (UCS) with payment per capita for outpatient (OP) services, hospitals' financial risks will rise if access to essential drugs increases. This study examined trends in access to and price of essential drugs for noncommunicable diseases (NCDs) and an overall purchasing price index (PPI) for an OP drug basket from public hospitals. To examine drug access, OP prescription data from 2010-2012 were obtained from the UCS. Access to thirteen drugs for diabetes, hypertension, and dyslipidemia was examined for trend using a time-series analysis. To calculate the PPI, drugs in the same dataset in 2010 that each contributed at least 0.2% of the total OP drug expenditure (N = 118 items) were selected together with drugs expected for near future growth (N = 48 items). The PPI was constructed from purchasing prices in 16 hospitals using a standard method developed by the International Labour Organization. Based on 166 drug items accounting for 75% of OP drug expenditures, the overall PPI continually declined by 6.8% from 2010 to 2012. Access to the 13 selected NCD drugs, accounting for 22% of the total OP drug expenditure increased from 22 to 30 per 1,000 population for antidiabetics, 27 to 47 for antihypertensive agents, and 32 to 53 for antilipidemics from 2010-2012. Growth in the study drug recipients was relatively higher than that in the population and diagnosed patients. Due to generic market competition, metformin, glipizide, amlodipine, losartan, simvastatin, atorvastatin, and fenofibrate prices decreased by 6-22%. Antiretrovirals and risperidone prices decreased by more than 10% due to price negotiation by the UCS. Access to essential drugs for diabetes, hypertension and dyslipidemia has increased. A decline in the PPI could contain essential drug expenditure when the demand for the drugs increased. Generic market competition and price negotiation by the UCS led to price reduction.

[40] *Lammi C, Sgrignani J, Arnoldi A, Grazioso G*. **Biological Characterization of Computationally Designed Analogs of peptide TVFTSWEEYLDWV (Pep2-8) with Increased PCSK9 Antagonistic Activity**. Scientific reports 2019; 9:2343.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30787312
ABSTRACT
The inhibition of the PCSK9/LDLR protein-protein interaction (PPI) is a promising strategy for developing new hypocholesterolemic agents. Recently, new antibodies have been approved for therapy, but the high cost and low patients' compliance stimulate the development of alternatives. Starting from the structural information available for the complex between PCSK9 and TVFTSWEEYLDWV (Pep2-8) peptide inhibitor and using computational methods, in this

work we identified two Pep2-8 analogs as potential inhibitors of the PCSK9/LDLR PPI. Their biological characterization confirmed the theoretical outcomes. Remarkably, the treatment of HepG2 cells with these peptides increased the LDLR protein level on the cellular membrane, with activities that were 100 and 50 times better than the one of Pep2-8 tested at a 50 muM concentration. Moreover, they were 50 and 5 times more active than Pep2-8 in improving the functional ability of HepG2 cells to uptake extracellular LDL.

[41] *Poh KK, Chin CT, Tong KL et al.* **Cholesterol goal achievement and lipid-lowering therapy in patients with stable or acute coronary heart disease in Singapore: results from the Dyslipidemia International Study II**. Singapore medical journal 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30773600
ABSTRACT
INTRODUCTION: Dyslipidaemia is a major risk factor for coronary heart disease (CHD). There is a lack of data on the extent of lipid abnormalities and lipid-lowering therapy (LLT) in Singapore. METHODS: The Dyslipidemia International Study (DYSIS) II was a multinational observational study of patients with stable CHD and hospitalised patients with an acute coronary syndrome (ACS). A full lipid profile and use of LLT were documented at baseline, and for the ACS cohort, at four months post-hospitalisation. RESULTS: 325 patients were recruited from four sites in Singapore; 199 had stable CHD and 126 were hospitalised with an ACS. At baseline, 96.5% of the CHD cohort and 66.4% of the ACS cohort were being treated with LLT. In both cohorts, low-density lipoprotein cholesterol (LDL-C) levels were lower for the treated than the non-treated patients; accordingly, a higher proportion met the LDL-C goal of < 70 mg/dL (CHD: 28.1% vs. 0%, p = 0.10; ACS: 20.2% vs. 0%, p < 0.01). By the four-month follow-up, a higher proportion of the ACS patients that were originally not treated with LLT had met the LDL-C goal (from 0% to 54.5%), correlating with the increased use of medication. However, there was negligible improvement in the patients who were treated prior to the ACS. CONCLUSION: Dyslipidaemia is a significant concern in Singapore, with few patients with stable or acute CHD meeting the recommended European Society of Cardiology/European Atherosclerosis Society goal. LLT was widely used but not optimised, indicating considerable scope for improved management of these very-high-risk patients.

[42] *Hori E, Kikuchi C, Imaeda K et al.* **[Effect of Statins on Glycemic Status and Plasma Adiponectin Concentrations in Patients with Type 2 Diabetes Mellitus and Hypercholesterolemia]**. Yakugaku Zasshi 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30773524
ABSTRACT
It is reported that statins have inconsistent effects on glycemic status and adiponectin concentrations in patients with type 2 diabetes mellitus (T2DM). We aimed to investigate the effect of statins on these variables in patients with T2DM and hypercholesterolemia. A control group comprising 24 patients with T2DM but without hypercholesterolemia was observed for more than 12 weeks, while 24 patients with T2DM and hypercholesterolemia were treated with statins for the same period (statin group). The percentage changes in the glycemic status (blood glucose and glycated hemoglobin [HbA1c]), and levels of plasma adiponectin (total and high molecular weight [HMW]) were compared between the two groups. The statin group had

reduced percentage changes in HbA1c, blood glucose, and total and HMW-adiponectin concentration percentage changes that were similar to those in the control group. However, when matched for sex, age (+/- 5 years) and HbA1c (+/- 0.5%) with the control group, the pravastatin group had reduced percentage changes in the plasma HMW-adiponectin concentrations than the matched controls ($p = 0.023$). However, there were no differences in the percentage changes in the plasma total adiponectin ($p = 0.137$), HbA1c ($p = 0.202$), or blood glucose concentrations ($p = 0.450$) between the two groups. Pravastatin treatment had no effect on the glycemic status of patients with T2DM and hypercholesterolemia, but may reduce the percentage changes in the plasma HMW-adiponectin concentrations. Hence, patients with T2DM and hypercholesterolemia receiving long-term treatment with pravastatin might experience increased insulin resistance.