Literature update week 45 (2018)

[1] *Liu P, Liu Y, Li P et al.* **Rosuvastatin- and Heparin-Loaded Poly(L-Lactide-Co-Caprolactone) Nanofibre Aneurysm Stent Promotes Endothelialization via Vascular Endothelial Growth Factor Type A Modulation**. ACS applied materials & interfaces 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30403126
ABSTRACT
BACKGROUND AND PURPOSE: This study explored a new rosuvastatin calcium- and heparin-loaded poly(L-lactide-co-caprolactone) (PLCL) scaffold for covered stents in treating aneurysms. The mechanism of rosuvastatin-induced endothelialization via VEGF-A elevation was further explored. METHODS: Rosu50, Rosu75, Rosu100 and phosphate-buffered saline (PBS) nanofibrous scaffolds were fabricated by coaxial electrospinning and observed by electron microscopy. Anti-coagulation and pro-endothelialization properties were tested. Sixteen rabbits were selected for an in vivo assay and underwent microsurgery to establish a carotid aneurysm model. The animals were treated with covered stents and followed for four months using digital subtraction angiography (DSA), electron microscopy and histology. Rosuvastatin-treated human umbilical vein endothelial cell (HUVEC) viability, function and vascular endothelial growth factor (VEGF)-A modulation were further studied to understand the rosuvastatin pro-endothelialization mechanism. RESULTS: Our study demonstrates that rosuvastatin and heparin can be incorporated into PLCL nanofibres via electrospinning. Rosu100 nanofibre scaffolds exhibited significant anti-coagulation properties. The viability of HUVECs transferred to Rosu100 nanofibre scaffolds was increased significantly. In vivo, the Rosu100 group was superior to the PBS group under DSA. In addition, the Rosu100 stents induced more integrated endothelialization. Further study demonstrated that rosuvastatin promoted HUVEC viability and function in vitro. The effects of rosuvastatin may be attributed to an elevation in VEGF-A. CONCLUSIONS: We demonstrated that rosuvastatin- and heparin-loaded PLCL-covered stents show favourable anti-coagulation and pro-endothelialization properties in vitro and in vivo in a rabbit aneurysm model. VEGF-A elevation played a crucial role in the rosuvastatin-promoted endothelialization. This work provides an additional option for treating cerebral aneurysms with covered stents.

[2] *Guedeney P, Baber U, Claessen B et al.* **Temporal trends, determinants, and impact of high-intensity statin prescriptions after percutaneous coronary intervention: Results from a large single-center prospective registry**. American heart journal 2018; 207:10-18.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30404046
ABSTRACT
BACKGROUND: High-intensity statins (HIS) are recommended for secondary prevention following percutaneous coronary intervention (PCI). We aimed to describe temporal trends and determinants of HIS prescriptions after PCI in a usual-care setting. METHODS: All patients with age </=75 years undergoing PCI between January 2011 and May 2016 at an urban, tertiary care center and discharged with available statin dosage data were included. HIS were defined as atorvastatin 40 or 80 mg, rosuvastatin 20 or 40 mg, and simvastatin 80 mg. RESULTS: A total of 10,495 consecutive patients were included. Prevalence of HIS prescriptions nearly doubled from 36.6% in 2011 to 60.9% in 2016 (P < .001), with a stepwise increase each year after 2013. Predictors of HIS prescriptions included ST-segment elevation myocardial infarction/non-ST-segment elevation myocardial infarction (odds ratio [OR] 4.60, 95% CI 3.98-5.32, P < .001) and

unstable angina (OR 1.31, 95% CI 1.19-1.45, P < .001) as index event, prior myocardial infarction (OR 1.48, 95% CI 1.34-1.65, P < .001), and co-prescription of beta-blocker (OR 1.26, 95% CI 1.12-1.43, P < .001). Conversely, statin treatment at baseline (OR 0.86, 95% CI 0.77-0.96, P = .006), Asian races (OR 0.73, 95% CI 0.65-0.83, P< .001), and older age (OR 0.90, 95% CI 0.88-0.92, P < .001) were associated with reduced HIS prescriptions. There was no significant association between HIS prescriptions and 1-year rates of death, myocardial infarction, or target-vessel revascularization (adjusted hazard ratio 0.98, 95% CI 0.84-1.15, P = .84), although there was a trend toward reduced mortality (adjusted hazard ratio 0.71, 95% CI 0.50-1.00, P = .05). CONCLUSION: Although the rate of HIS prescriptions after PCI has increased in recent years, important heterogeneity remains and should be addressed to improve practices in patients undergoing PCI.

[3] *Osuna-Ramos JF, Reyes-Ruiz JM, Bautista-Carbajal P et al.* **Ezetimibe inhibits dengue virus infection in Huh-7 cells by blocking the cholesterol transporter Niemann-Pick C1-like 1 receptor**. Antiviral research 2018; 160:151-164.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30391500
ABSTRACT
Despite the importance of Dengue virus (DENV) infection in human health, there is not a fully effective vaccine or antiviral treatment against the infection. Since lipids such as cholesterol are required during DENV infection, its uptake and synthesis are increased in infected cells. Ezetimibe is an FDA-approved drug that reduces cholesterol uptake by inhibiting the endocytosis through Niemman-Pick C1-Like 1 (NPC1L1) receptor, expressed on the membrane of enterocytes and hepatocytes. Our results indicate that an increase in the amount of NPC1L1 occurs on the surface of Huh-7cells during DENV infection, which correlates with an increase in cholesterol levels. Blockage of NPC1L1 with ezetimibe in concentrations up to 50muM does not reduce cell viability but diminished total cellular cholesterol, the percentage of infected cells, viral yield, viral RNA and protein synthesis without affecting DENV binding and/or entry to Huh-7cells. Moreover, ezetimibe inhibited DENV replicative complex formation and lipid droplets accumulation. All these results indicate that ezetimibe is an excellent drug to inhibit DENV infection and confirm that cholesterol is a key target to inhibit viral infection.

[4] *Zhao J, Cheng Q, Liu Y et al.* **Atorvastatin alleviates early hypertensive renal damage in spontaneously hypertensive rats**. Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie 2018; 109:602-609.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30399597
ABSTRACT
This study aimed to examine the effects of atorvastatin on early hypertensive renal damage and explored the underlying mechanisms. 12-week-old salt-loaded spontaneous hypertensive rats (SHRs) were divided into four groups: atorvastatin (AVT), losartan potassium (LP), atorvastatin combined with peroxisome proliferators-activated receptor gamma (PPAR-gamma) inhibitor (AVT + GW9662), and saline. During 10 weeks administration blood pressure and urea albumin creatinine ratio were determined. We also examined the renal function, pathological changes of kidney, inflammatory cytokines in the serum and the association of the change of inflammatory factors in the kidney tissue. AVT did not reduce the mortality of the SHRs. AVT

reduced the blood pressure of SHRs, but the effect was not comparable to that of LP. AVT significantly decreased urine protein. AVT and LP displayed comparable effects by significantly decreasing inflammatory cytokines (hs-CRP, IL-1beta, IL-6, TNF-alpha, and TGF-beta) levels in serum. AVT and LP both apparently improved renal pathological changes and significantly reduced the infiltration of macrophage in renal tubular interstitial. Both mRNA and protein expression levels of TLR4, NFkappaB, MCP-1 were significantly down regulated in AVT and LP groups. There was no significant change in macrophage polarity. The addition of PPAR-gamma inhibitor partially reduced the anti-inflammatory effect of AVT. These results mean that Atorvastatin can alleviates the pathology of hypertensive renal damage. Atorvastatin protects the kidney by reducing the apparent inflammation in salt-loaded SHRs. Atorvastatin alleviates inflammation partially by augmenting expression of PPAR-gamma.

[5] *Barale C, Frascaroli C, Senkeev R et al.* **Simvastatin Effects on Inflammation and Platelet Activation Markers in Hypercholesterolemia**. BioMed research international 2018; 2018:6508709.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30402489
ABSTRACT
Background: Beside the lipid-lowering effect, statins slow the progression of atherosclerosis by exerting anti-inflammatory and platelet inhibiting effects. We investigated whether platelet inhibition by simvastatin correlates with the statin effects on lipid lowering, inflammation, oxidative stress, and endothelial and platelet activation. Methods: In hypercholesterolemic patients allocated to diet (n=20) or a 2-month treatment with diet plus 40 mg simvastatin (n=25), we evaluated platelet aggregating responses to ADP, collagen, and arachidonic acid (AA), the effect of aspirin on AA-induced aggregation, pro- and anti-inflammatory and atherogenic mediators (IL-1beta, -5, -6, -7, -8, -9, -10, -12, and -13, IFN-gamma, IP-10, Eotaxin, and sRAGE), markers of endothelium (sE-selectin, VEGF, and MCP-1) and platelet activation (sP-selectin, sCD-40L, RANTES, and PDGF-bb), and oxidative stress (8-OH-2'-deoxyguanosine). Results: After treatment, beside the improvement of lipid profile, we observed the following: a reduction of platelet aggregation to ADP (p=0.0001), collagen (p=0.0001), AA (p=0.003); an increased antiaggregating effect of aspirin in the presence of AA (p=0.0001); a reduction of circulating levels of IL-6 (p=0.0034), IL-13 (p<0.0001), IFN-gamma (p<0.0001), VEGF (p<0.0001), sE-selectin (p<0.0001), sCD-40L (p<0.0001), sP-selectin (p=0.003), and 8-OH-2'-deoxyguanosine (p<0.0001); an increase of IL-10 and sRAGEs (p=0.0001 for both). LDL-cholesterol levels (i) positively correlated with IL-6, IFN-gamma, E-selectin, sCD-40L, 8-OH-2'-deoxyguanosine, platelet aggregation to ADP, collagen, AA, and aspirin IC-50 and (ii) negatively correlated with IL-10 and sRAGE. In multiple regression analyses, LDL-cholesterol was the strongest predictor for most parameters of platelet reactivity. Conclusion: In primary hypercholesterolemia, simvastatin treatment reduced platelet activation and subclinical inflammation and improved endothelial dysfunction. LDL-cholesterol levels were the major correlate of platelet reactivity; however, other effects of statins may contribute to reducing the progression of atherosclerosis.

[6] *Beckwitt CH, Clark AM, Ma B et al.* **Statins attenuate outgrowth of breast cancer metastases**. British journal of cancer 2018; 119:1094-1105.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30401978

ABSTRACT
BACKGROUND: Metastasis in breast cancer foreshadows mortality, as clinically evident disease is aggressive and generally chemoresistant. Disseminated breast cancer cells often enter a period of dormancy for years to decades before they emerge as detectable cancers. Harboring of these dormant cells is not individually predictable, and available information suggests that these micrometastatic foci cannot be effectively targeted by existing therapies. As such, long-term, relatively non-toxic interventions that prevent metastatic outgrowth would be an advance in treatment. Epidemiological studies have found that statins reduce breast cancer specific mortality but not the incidence of primary cancer. However, the means by which statins reduce mortality without affecting primary tumor development remains unclear. METHODS: We examine statin efficacy against two breast cancer cell lines in models of breast cancer metastasis: a 2D in vitro co-culture model of breast cancer cell interaction with the liver, a 3D ex vivo microphysiological system model of breast cancer metastasis, and two independent mouse models of spontaneous breast cancer metastasis to the lung and liver, respectively. RESULTS: We demonstrate that statins can directly affect the proliferation of breast cancer cells, specifically at the metastatic site. In a 2D co-culture model of breast cancer cell interaction with the liver, we demonstrate that atorvastatin can directly suppress proliferation of mesenchymal but not epithelial breast cancer cells. Further, in an ex vivo 3D liver microphysiological system of breast cancer metastasis, we found that atorvastatin can block stimulated emergence of dormant breast cancer cells. In two independent models of spontaneous breast cancer metastasis to the liver and to the lung, we find that statins significantly reduce proliferation of the metastatic but not primary tumor cells. CONCLUSIONS: As statins can block metastatic tumor outgrowth, they should be considered for use as long-term adjuvant drugs to delay clinical emergence and decrease mortality in breast cancer patients.

[7] *Fawzy Fahim V, Wadie W, Shafik AN, Ishak Attallah M*. **Role of simvastatin and insulin in memory protection in a rat model of diabetes mellitus and dementia**. Brain research bulletin 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30395886

ABSTRACT
OBJECTIVES: The memory protective role of simvastatin and/or insulin, in a rat model of diabetes mellitus (DM) and dementia was examined. METHODS: DM was induced by an intraperitoneal injection of streptozotocin. Diabetic rats were divided into untreated; insulin treated; simvastatin treated with 10 and 20 mg/kg/day; and combined insulin plus simvastatin treatment in the previous doses. Treatment started after blood glucose elevation and persisted for 6 weeks. Morris water maze and Y maze tests were held to detect behavioral changes. Serum glucose, cholesterol and insulin levels, the hippocampi insulin, amyloid beta (Ass) 1-42 and oxidative stress markers were measured. RESULTS: Insulin increased the time spent in the target quadrant in the Morris water maze test and the percentage of alternations in the Y maze test, despite the mild improvements in brain parameters demonstrated by amyloid beta 1-42, malondialdehyde and reduced glutathione levels; while simvastatin in both doses improved brain parameters with no positive impact on behavioral tests. Insulin combined with simvastatin 20 mg/kg/day was effective in enhancing the behavioral tests and the measured

brain parameters. CONCLUSIONS: Treatment with insulin and simvastatin could provide a promising memory protective effect in diabetics.

[8] *Hassan SMS, Rizk A, Thomann C et al.* **Preconditioning with atorvastatin against renal ischemic-reperfusion injury in non-diabetic versus diabetic rats**. Canadian journal of physiology and pharmacology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30412424
ABSTRACT
Acute renal failure complicates renal ischemic-reperfusion (I/R) due to reactive oxygen species production. Atorvastatin (ATO) has antiinflammatory and antioxidant properties. The current study investigated whether ATO alleviated damages induced by renal I/R injury in non-diabetic versus diabetic rat models. Thirty-six rats (18/group) were divided into non-diabetic and diabetic Groups, A and B, respectively: Group A1 (sham), Group A2 (I/R), Group A3 (ATO + I/R), Group B1 (sham), Group B2 (I/R), and Group B3 (ATO + I/R). All groups experienced 45 minutes of renal ischemia, bilaterally, followed by 24 hours of reperfusion. Groups A3 and B3 were treated with intraperitoneal single doses of ATO (10 mg/kg) 30 minutes before ischemia. Histological analysis of kidney tissues, immune expression of caspase 3 and CD44, kidney function tests, and oxidative stress markers, assessed tubular injury. Histological analysis revealed marked tubular damage in Groups A2 and B2 but improvement in Groups A3 and B3. Improvements were also found for immune expression of caspase 3 and CD44, kidney function tests, and oxidative stress markers. Our results suggested ATO may ameliorate renal I/R injury, differently between non-diabetic and diabetic rats.

[9] *Sanyour HJ, Li N, Rickel AP et al.* **Membrane cholesterol and substrate stiffness coordinate to induce the remodeling of the cytoskeleton and the alteration in the biomechanics of vascular smooth muscle cells**. Cardiovascular research 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30395154
ABSTRACT
Aims: Cholesterol not only deposits in foam cells at the atherosclerotic plaque, but also plays an important role as a regulator of cell migration in atherogenesis. In addition, the progression of atherosclerosis leads to arterial wall stiffening, and thus altering the micromechanical environment of vascular smooth muscle cells (VSMCs) in vivo. Our studies aim to test the hypothesis that membrane cholesterol and substrate stiffness coordinate to regulate VSMCs biomechanics, and thus potentially regulate VSMCs migration and atherosclerotic plaque formation. Methods and results: Methyl-beta-cyclodextrin (MbetaCD) was used to manipulate membrane cholesterol content in VSMCs isolated from the descending thoracic aorta of male Sprague Dawley rats and cultured on type I collagen (COL1)-coated polyacrylamide (PA) gel substrates with varying stiffness. Atomic force microscopy (AFM) was used to determine VSMCs stiffness and integrin-fibronectin (FN) adhesion. The alignment of submembranous actin filaments was visualized with AFM and confocal microscopy. The constriction force of rat aorta was measured ex vivo using a multi-wire myograph system. Our results demonstrated that cholesterol-depletion and substrate-softening induced a significant decrease in VSMCs stiffness and adhesion to FN, as well as cytoskeletal disorganization. In addition, the contractile force of rat aorta was reduced upon cholesterol-depletion. Cholesterol-enrichment resulted in an

increase in stiffness, adhesion to FN, cytoskeletal organization of VSMCs compared to the cholesterol-depleted cells and enhanced contractile force of rat aortas compared to the cholesterol-depleted vessel rings. Conclusions: Cell membrane cholesterol and substrate stiffness synergistically affect VSMCs elastic modulus (E-modulus) by regulating the organization of the actin cytoskeleton. Except for the 3.5 kPa gel substrate, cholesterol-depletion decreased VSMCs-FN adhesion force, adhesion loading rate, cytoskeletal orientation, and E-modulus compared to the control VSMCs. Conversely, cholesterol-enrichment significantly increased cytoskeleton orientation, stiffness, and VSMCs-FN cell adhesion force compared to both control and cholesterol-depleted VSMCs on a soft substrate.

[10] *Mengelberg A, Leathem J, Podd J*. **Fish oil supplement use in New Zealand: A cross-sectional survey**. Complementary therapies in clinical practice 2018; 33:118-123.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30396608
ABSTRACT
OBJECTIVE: The aims of the survey were to determine: (i) the percentage of fish oil supplement users in a sample population; (ii) why people take fish oil supplements; (iii) where fish oil supplements are stored as well as the average daily dosage; (iv) what dietary and lifestyle behaviours are associated with fish oil supplement use. DESIGN: An online cross-sectional survey. SETTING: New Zealand. RESPONDENTS: A total of 334 New Zealand residents over the age of 18. RESULTS: Fish oil supplements were taken by 21.9% of respondents. Reasons for taking fish oil supplements were - 72.6% for 'general well-being', 54.8% to 'improve brain function', 31.5% for 'pain/inflammation', 12.3% to 'lower cholesterol levels' and 11% for 'a dietary insufficiency'. Approximately 26% of fish oil users reported taking a dose of fish oil supplements that would meet the recommended daily intake of 400-600mg combined docosahexaenoic acid and eicosapentaenoic acid, and only 6.8% of fish oil users reported storing their fish oil supplements in the refrigerator. After controlling for other characteristics including age, gender, ethnicity and body mass index, fish oil supplementation use was most likely among respondents who already eat oily fish and least likely in respondents who regularly eat nuts and seeds. CONCLUSIONS: Fish oil supplements are a commonly used supplement in New Zealand, yet questions remain about the role of these supplements in improving health outcomes. Safety issues related to manufacturing and storage conditions indicate that there is an urgency in answering these questions.

[11] *Sinclair AJ, Abdelhafiz AH, Forbes A, Munshi M*. **Evidence-based diabetes care for older people with Type 2 diabetes: a critical review**. Diabetic medicine : a journal of the British Diabetic Association 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30411402
ABSTRACT
In our ageing society diabetes imposes a significant burden in terms of the numbers of people with the condition, diabetes-related complications including disability, and health and social care expenditure. Older people with diabetes can represent some of the more complex and difficult challenges facing the clinician working in different settings, and the recognition that we have only a relatively small (but increasing) evidence base to guide us in diabetes management is a limitation of our current approaches. Nevertheless, in this review we attempt to explore

what evidence there is to guide us in a comprehensive scheme of treatment for older adults, often in a high-risk clinical state, in terms of glucose lowering, blood pressure and lipid management, frailty care and lifestyle interventions. We strive towards individualized care and make a call for action for more high-quality research using different trial designs.

[12] *Tabesh M, Magliano DJ, Tanamas SK et al.* **Cardiovascular disease management in people with diabetes outside North America and Western Europe in 2006 and 2015**. Diabetic medicine : a journal of the British Diabetic Association 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30402961
ABSTRACT
AIM: Optimal treatment of cardiovascular disease is essential to decrease mortality among people with diabetes, but information is limited on how actual treatment relates to guidelines. We analysed changes in therapeutic approaches to anti-hypertensive and lipid-lowering medications in people with Type 2 diabetes from 2006 and 2015. METHODS: Summary data from clinical services in seven countries outside North America and Western Europe were collected for 39 684 people. Each site summarized individual-level data from outpatient medical records for 2006 and 2015. Data included: demographic information, blood pressure (BP), total cholesterol levels and percentage of people taking statins, anti-hypertensive medication (angiotensin-converting enzyme inhibitors, calcium channel blockers, angiotensin II receptor blockers, thiazide diuretics) and antiplatelet drugs. RESULTS: From 2006 to 2015, mean cholesterol levels decreased in six of eight sites (range: -0.5 to -0.2), whereas the proportion with BP levels > 140/90 mmHg increased in seven of eight sites. Decreases in cholesterol paralleled increases in statin use (range: 3.1 to 47.0 percentage points). Overall, utilization of anti-hypertensive medication did not change. However, there was an increase in the use of angiotensin II receptor blockers and a decrease in angiotensin-converting enzyme inhibitors. The percentage of individuals receiving calcium channel blockers and aspirin remained unchanged. CONCLUSIONS: Our findings indicate that control of cholesterol levels improved and coincided with increased use of statins. The percentage of people with BP > 140/90 mmHg was higher in 2015 than in 2006. Hypertension treatment shifted from using angiotensin-converting enzyme inhibitors to angiotensin II receptor blockers. Despite the potentially greater tolerability of angiotensin II receptor blockers, there was no associated improvement in BP levels.

[13] *Itoh H, Komuro I, Takeuchi M et al.* **Achieving LDL-C target levels less than 70 mg/dL may provide extra cardiovascular protection in high-risk patients: exploratory analysis of the Standard Versus Intensive Statin Therapy for Patients With Hypercholesterolemia and Diabetic Retinopathy Study**. Diabetes Obes Metab 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30393955
ABSTRACT
AIMS: EMPATHY, a multicenter, randomized, open-label, blinded-endpoint study, assessed the benefits of intensive statin therapy on reducing cardiovascular (CV) events in type 2 diabetic patients with hyperlipidemia and retinopathy in primary prevention in Japan. Intensive therapy (targeting LDL-C <70 mg/dL) was no more effective than standard therapy (LDL-C >/=100 to

<120 mg/dL) in the intention-to-treat population. However, after 3 years, intergroup difference in LDL-C was only 27.7 mg/dL, and targeted levels were achieved in <50% of patients. We hypothesized that the intergroup difference in CV events would have been statistically significant if more patients had been successfully treated to target. MATERIALS AND METHODS: This exploratory post-hoc analysis focused on intergroup data from patients who achieved their target LDL-C levels. A Cox proportional hazards model was used to estimate HRs for incidence of the primary endpoint in patients who achieved target LDL-C levels in each group. RESULTS: Data were analyzed from 1909 patients (intensive: 703; standard: 1206) who achieved target LDL-C levels. LDL-C at 36 months was 59.7+/-11.6 mg/dL in the intensive group and 107.1+/-17.8 mg/dL in the standard group (P< .05). After adjusting for baseline prognostic factors, composite incidence of CV events or deaths associated with CV events was significantly lower in the intensive than the standard group (HR, 0.48; 95% CI, 0.28-0.82; P= .007). CONCLUSIONS: This post-hoc analysis suggests that achieving LDL-C target levels <70 mg/dL may more effectively reduce CV events than achieving target levels >/=100 to <120 mg/dL in patients with hypercholesterolemia and diabetic retinopathy.

[14] *Maged A, Abdelkhalek AA, Mahmoud AA et al.* **Mesenchymal stem cells associated with chitosan scaffolds loaded with rosuvastatin to improve wound healing**. Eur J Pharm Sci 2018; 127:185-198.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30412769
ABSTRACT
In this study we explored the role of rosuvastatin calcium in skin regeneration as statins play important role in the field of tissue engineering. Chitosan hydrochloride was crosslinked with different weight ratios of collagen, beta-glycerolphosphate and carboxymethyl cellulose to produce scaffolds by lyophilization technique. Subsequently, the fabricated scaffolds were examined for their morphology, water absorption capacity, water retention, friability and in-vitro drug release as well as in-vivo studies. The results revealed porous 3-D structured scaffolds with maximum water absorption values-ranging between 396 and 2993%. Scaffolds containing carboxymethyl cellulose revealed highest water absorption-values. In-vitro drug release results showed gradual drug release for 60h with mean dissolution time-values (MDT) between 13 and 21h. Combination of chitosan, collagen, carboxymethyl cellulose in weight ratio of 40:30:30, respectively achieved gradual disintegration of the scaffold in a simulating medium to an open wound after 4days. This selected scaffold loaded with rosuvastatin revealed increase proliferation of human dermal fibroblasts compared to placebo scaffold. After 30days of implantation of selected medicated scaffold loaded with/without mesenchymal stem cells and placebo scaffolds to induced wounds in Albino rats, enhanced skin regeneration and absence of scar formation for drug loaded scaffolds were observed. The histopathological study showed the advantage of stem cells-loaded scaffolds through the normal redistribution of collagen in the epidermal layer. In conclusion, rosuvastatin calcium and stem cells loaded in the tested scaffolds proved their potential effect in enhancing skin healing and regeneration.

[15] *Li T, Yao W*. **Therapeutic effect of irbesartan combined with atorvastatin calcium in the treatment of rats with coronary heart disease**. Experimental and therapeutic medicine 2018; 16:4119-4123.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30402154
ABSTRACT
This study aimed to investigate the therapeutic effect of irbesartan combined with atorvastatin calcium in the treatment of rats with coronary heart disease. One hundred sixty Wistar rats were selected to establish coronary heart disease model. Rats with coronary heart disease were randomly divided into 4 groups: Model, irbesartan, atorvastatin calcium and combination groups (irbesartan combined with atorvastatin calcium group). Rats in irbesartan group were treated with 50 mg/(kg.day) irbesartan; rats in atorvastatin calcium group were given atorvastatin calcium at a dose of 10 mg/(kg.day); rats in combination group were subjected to atorvastatin calcium at a dose of 10 mg/(kg.day) and irbesartan at a dose of 50 mg/(kg.day), while rats in model groups were given intragastric administration of normal saline at a dose of 2 ml/day. Serum lipids, including total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and TC/HDL-C, were measured by automatic biochemical analyzer. Expression of sPLA2-V in myocardium and aortic trunk of rats was detected by reverse transcription-PCR (RT-PCR) and western blot analysis. After treatment, levels of serum TC, TG, LDL-C, HDL-C and TC/HDL-C in rats of each treatment group were better than those in model group ($p<0.05$). Expression level of sPLA2-V in myocardium and aortic trunk in model group was significantly higher than that in other groups ($p<0.05$). Expression level of sPLA2-V in combination group was significantly lower than that in irbesartan and atorvastatin calcium groups ($p<0.05$). Combination of irbesartan and atorvastatin calcium is superior to irbesartan or atorvastatin calcium alone in the treatment of rats with coronary heart disease. The possible explanation is that the two drugs can reduce the expression of sPLA2-V in myocardium and aortic trunk, which in turn relieved atherosclerosis and achieved better therapeutic effect.

[16] *Tsentidis C, Bampilis A, Ntova V et al.* **Metabolic Syndrome as a Predictor of Adrenal Functional Status: A Discriminant Multivariate Analysis Versus Logistic Regression Analysis**. Hormone and metabolic research = Hormon- und Stoffwechselforschung = Hormones et metabolisme 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30406628
ABSTRACT
Patients harboring adrenal tumors are characterized by higher prevalence of metabolic syndrome (MetS) components and a higher incidence of cardiovascular complications, especially in cases of subclinical or overt hormonal hypersecretion. Early detection and referral of those patients in tertiary centers could prevent unfavorable outcomes. In this cross-sectional, retrospective study, we evaluated 111 consecutive patients with adrenal incidentalomas and 14 patients with known hypersecretory adrenal lesions (autonomous cortisol secretion, primary aldosteronism, and pheochromocytoma), who were investigated in our clinic. Based on the different distribution of MetS components in patients with non-functional and functional adrenal lesions we introduced a predictive model of hormonal hypersecretion using those components. We performed multivariate discriminant analysis and

compared predictive results with conventional multiple logistic regression analysis. Diabetes, impaired glucose tolerance, impaired fasting glucose, hypertension, body mass index, HDL-cholesterol levels, triglyceride levels, drug treatment for lipid disorder (statins, fenofibrate, and fish oils, alone or in combination), and maximal adrenal lesion diameter were used as discriminating covariates. Multivariate discriminant function exhibited a sensitivity of 77.27% and specificity of 73.08% in predicting adrenal hormonal hypersecretion. Receiver operating characteristic curve of discriminant predictive function had an area under the curve value of 0.785, S.E. 0.04. Logistic function delivered comparable results. MetS components exhibit a good predictive feature of hormonal hypersecretion in patients with adrenal tumors. Predictive functions may help in the search for an easy and generally available algorithm to validly predict the functional activity of adrenal masses.

[17] *Khuchua Z, Glukhov AI, Strauss AW, Javadov S*. **Elucidating the Beneficial Role of PPAR Agonists in Cardiac Diseases**. International journal of molecular sciences 2018; 19.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30400386

ABSTRACT

Peroxisome proliferator-activated receptors (PPARs) are nuclear hormone receptors that bind to DNA and regulate transcription of genes involved in lipid and glucose metabolism. A growing number of studies provide strong evidence that PPARs are the promising pharmacological targets for therapeutic intervention in various diseases including cardiovascular disorders caused by compromised energy metabolism. PPAR agonists have been widely used for decades as lipid-lowering and anti-inflammatory drugs. Existing studies are mainly focused on the anti-atherosclerotic effects of PPAR agonists; however, their role in the maintenance of cellular bioenergetics remains unclear. Recent studies on animal models and patients suggest that PPAR agonists can normalize lipid metabolism by stimulating fatty acid oxidation. These studies indicate the importance of elucidation of PPAR agonists as potential pharmacological agents for protection of the heart from energy deprivation. Here, we summarize and provide a comprehensive analysis of previous studies on the role of PPARs in the heart under normal and pathological conditions. In addition, the review discusses the PPARs as a therapeutic target and the beneficial effects of PPAR agonists, particularly bezafibrate, to attenuate cardiomyopathy and heart failure in patients and animal models.

[18] *Truong QA, Rinehart S, Abbara S et al.* **Coronary computed tomographic imaging in women: An expert consensus statement from the Society of Cardiovascular Computed Tomography**. Journal of cardiovascular computed tomography 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30392926

ABSTRACT

This expert consensus statement from the Society of Cardiovascular Computed Tomography (SCCT) provides an evidence synthesis on the use of computed tomography (CT) imaging for diagnosis and risk stratification of coronary artery disease in women. From large patient and population cohorts of asymptomatic women, detection of any coronary artery calcium that identifies females with a 10-year atherosclerotic cardiovascular disease risk of >7.5% may more effectively triage women who may benefit from pharmacologic therapy. In addition to accurate detection of obstructive coronary artery disease (CAD), CT angiography (CTA) identifies

nonobstructive atherosclerotic plaque extent and composition which is otherwise not detected by alternative stress testing modalities. Moreover, CTA has superior risk stratification when compared to stress testing in symptomatic women with stable chest pain (or equivalent) symptoms. For the evaluation of symptomatic women both in the emergency department and the outpatient setting, there is abundant evidence from large observational registries and multi-center randomized trials, that CT imaging is an effective procedure. Although radiation doses are far less for CT when compared to nuclear imaging, radiation dose reduction strategies should be applied in all women undergoing CT imaging. Effective and appropriate use of CT imaging can provide the means for improved detection of at-risk women and thereby focus preventive management resulting in long-term risk reduction and improved clinical outcomes.

[19] *Luan C, Chen X, Zhu Y et al.* **Potentiation of psoriasis-like inflammation by PCSK9**. The Journal of investigative dermatology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30395847
ABSTRACT
Psoriasis is a systemic inflammatory disease, associated with metabolic disorders, including high level of low-density lipoprotein(LDL). Proprotein convertase subtilisin/kexin 9 (PCSK9), promoting the degradation of LDL receptors, and therefore the increased concentration of circulating LDL, is also involved in inflammation. This study aims to examine the role of PCSK9 in psoriasis and to investigate the potential of topically applying siRNA targeting Pcsk9 as a psoriasis treatment. We investigated the expression of PCSK9 in lesions of psoriasis patients, the imiquimod (IMQ) induced psoriatic reactions in Pcsk9 knockout and Pcsk9 siRNA treated mice, and also used cultured human keratinocytes to investigate the role of PCSK9 on regulating cell proliferation and apoptosis. We found that PCSK9 is overexpressed in psoriatic lesions, suppressing Pcsk9 can decrease the inflammatory reaction induced by IMQ treatment and inhibit hyper-proliferation of keratinocytes. We also found that suppressing PCSK9 can significantly alter the cell cycle and induce apoptosis of human keratinocytes. Taken together, our findings indicate that PCSK9 plays an important role in psoriasis, and may be a therapeutic target.

[20] *Ahmad F, Leake DS*. **Lysosomal oxidation of LDL alters lysosomal pH, induces senescence and increases secretion of pro-inflammatory cytokines in human macrophages**. Journal of lipid research 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30397186
ABSTRACT
Objective We have shown that aggregated low density lipoproteins (LDL) is internalised by macrophages and oxidised in lysosomes by redox-active iron. We have now investigated if the lysosomal oxidation of LDL impairs lysosomal function and if a lysosomotropic antioxidant can prevent these alterations. Approach and Results LDL aggregated by sphingomyelinase (SMase-LDL) caused increased lysosomal lipid peroxidation in human monocyte-derived macrophages or THP-1 macrophage-like cells, as shown by a fluorescent probe, Foam-LPO. The pH of the lysosomes was increased considerably by lysosomal LDL oxidation as shown by Lysosensor Yellow/Blue and LysoTracker Red. SMase-LDL induced senescence-like properties in the cells as shown by beta-galactosidase staining and levels of p53 and p21. Inflammation plays a key role

in atherosclerosis. SMase-LDL treatment increased the LPS-induced secretion of TNF-alpha, IL-6 and MCP-1. The lysosomotropic antioxidant, cysteamine inhibited all of the above changes. Conclusions Targeting lysosomes with antioxidants, such as cysteamine, to prevent the intralysosomal oxidation of LDL might be a novel therapy for atherosclerosis.

[21] *Wang C, Venick RS, Shew SB et al.* **Long-Term Outcomes in Children With Intestinal Failure-Associated Liver Disease Treated With 6 Months of Intravenous Fish Oil Followed by Resumption of Intravenous Soybean Oil**. JPEN. Journal of parenteral and enteral nutrition 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30411372
ABSTRACT
BACKGROUND: Intravenous soybean oil (SO) is a commonly used lipid emulsion for children with intestinal failure (IF); however, it is associated with IF-associated liver disease (IFALD). Studies have demonstrated that intravenous fish oil (FO) is an effective treatment for IFALD. However, there is a lack of long-term data on children who stop FO and resume SO. This study's objective was to investigate our institution's outcomes for children with IFALD treated with 6 months of FO and who then restarted SO. METHODS: Inclusion criteria for FO included children with IFALD. Parenteral nutrition (PN)-dependent children resumed SO after FO and were prospectively followed for 4.5 years or until death, transplant, or PN discontinuation. The primary outcome was the cumulative incidence rate (CIR) for cholestasis after FO. RESULTS: Forty-eight subjects received FO, and conjugated bilirubin decreased over time (-0.22 mg/dL/week; 95% confidence interval [CI]: -0.25, -0.19; P < .001). The CIR for cholestasis resolution after 6 months of FO was 71% (95% CI: 54%, 82%). Twenty-seven subjects resumed SO and were followed for a median of 16 months (range 3-51 months). While the CIR for enteral autonomy after 3 years of follow-up was 40% (95% CI: 17%, 26%), the CIR for cholestasis and transplant was 26% (95% CI: 8%, 47%) and 6% (95% CI: 0.3%, 25%), respectively. CONCLUSION: In this study, FO effectively treated cholestasis, and SO resumption was associated with cholestasis redevelopment in nearly one-fourth of subjects. Long-term FO may be warranted to prevent end-stage liver disease.

[22] *Reiner Z*. **Triglyceride-Rich Lipoproteins and Novel Targets for Anti-atherosclerotic Therapy**. Korean circulation journal 2018; 48:1097-1119.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30403015
ABSTRACT
Although elevated serum low-density lipoprotein-cholesterol (LDL-C) is without any doubts accepted as an important risk factor for cardiovascular disease (CVD), the role of elevated triglycerides (TGs)-rich lipoproteins as an independent risk factor has until recently been quite controversial. Recent data strongly suggest that elevated TG-rich lipoproteins are an independent risk factor for CVD and that therapeutic targeting of them could possibly provide further benefit in reducing CVD morbidity, events and mortality, apart from LDL-C lowering. Today elevated TGs are treated with lifestyle interventions, and with fibrates which could be combined with omega-3 fatty acids. There are also some new drugs. Volanesorsen, is an antisense oligonucleotid that inhibits the production of the Apo C-III which is crucial in regulating TGs metabolism because it inhibits lipoprotein lipase (LPL) and hepatic lipase activity

but also hepatic uptake of TGs-rich particles. Evinacumab is a monoclonal antibody against angiopoietin-like protein 3 (ANGPTL3) and it seems that it can substantially lower elevated TGs levels because ANGPTL3 also regulates TGs metabolism. Pemafibrate is a selective peroxisome proliferator-activated receptor alpha modulator which also decreases TGs, and improves other lipid parameters. It seems that it also has some other possible antiatherogenic effects. Alipogene tiparvovec is a nonreplicating adeno-associated viral vector that delivers copies of the LPL gene to muscle tissue which accelerates the clearance of TG-rich lipoproteins thus decreasing extremely high TGs levels. Pradigastat is a novel diacylglycerol acyltransferase 1 inhibitor which substantially reduces extremely high TGs levels and appears to be promising in treatment of the rare familial chylomicronemia syndrome.

[23] *Bonaca MP, Gutierrez JA, Cannon C et al.* **Polyvascular disease, type 2 diabetes, and long-term vascular risk: a secondary analysis of the IMPROVE-IT trial**. The lancet. Diabetes & endocrinology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30396865

ABSTRACT
BACKGROUND: Polyvascular disease and type 2 diabetes are each associated with increased cardiovascular risk, but whether these risks are additive is unknown. In this exploratory analysis of a randomised trial, we explored the long-term cardiovascular risk associated with polyvascular disease, type 2 diabetes, and their combination in patients with acute coronary syndrome, and assessed the effect of ezetimibe given on top of statin therapy in patients with these concomitant conditions. METHODS: IMPROVE-IT was a multicentre, double-blind, randomised, placebo-controlled trial assessing the effect of ezetimibe added to statin therapy after acute coronary syndrome. Recruitment was from Oct 26, 2005, to July 8, 2010, and the trial was done at 1158 sites in 39 countries. 18 144 patients aged 50 years and older who had been stabilised after an acute coronary syndrome were randomly assigned to 40 mg per day simvastatin plus either 10 mg per day ezetimibe or matched placebo, for a median duration of 6 years. In this post-hoc exploratory analysis, we assessed the prespecified endpoints of the trial, including the primary composite endpoint (cardiovascular death, a major coronary event [non-fatal myocardial infarction, documented unstable angina requiring hospital admission, or coronary revascularisation occurring at least 30 days after randomisation], or stroke [ischaemic or haemorrhagic]) by concomitant polyvascular disease at baseline (peripheral artery disease or previous stroke or transient ischaemic attack) and stratified by concomitant type 2 diabetes. Efficacy analyses were done according to intention to treat and event rates. IMPROVE-IT is registered with ClinicalTrials.gov, number NCT00202878. FINDINGS: 1005 patients (6%) had peripheral artery disease and 1071 (6%) had stroke or transient ischaemic attack at baseline. Of these, 388 (39%) and 409 (38%) also had concomitant type 2 diabetes, respectively. At 7 years, patients with either polyvascular disease or type 2 diabetes had similar rates of the primary endpoint (39.8% and 39.9%, respectively), which were higher than patients without polyvascular disease or diabetes (29.6%). Polyvascular disease with concomitant type 2 diabetes was associated with further heightened risk (60.0% 7-year Kaplan-Meier rate, adjusted hazard ratio versus those with polyvascular disease 1.60, 95% CI 1.38-1.85; p<0.0001). Ezetimibe reduced cardiovascular risk consistently across groups with greater numerical absolute risk reductions in the highest-risk subgroups. INTERPRETATION: In patients with

coronary artery disease, concomitant polyvascular disease or type 2 diabetes are associated with increased long-term cardiovascular risk. The combination of polyvascular disease and diabetes is additive, resulting in very high risk. The benefit of ezetimibe is consistent in patients with and without polyvascular disease and type 2 diabetes; however, by nature of their higher risk patients with one, or especially both, of these diseases might derive the greatest absolute benefits. FUNDING: Merck.

[24] *AbuMweis SS, Panchal SK, Jones PJH*. **Triacylglycerol-Lowering Effect of Docosahexaenoic Acid Is Not Influenced by Single-Nucleotide Polymorphisms Involved in Lipid Metabolism in Humans**. Lipids 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30407633
ABSTRACT
The triacylglycerol (TAG)-lowering effects of long-chain n-3 fatty acids, and in particular docosahexaenoic acid (DHA), are well documented, although these effects manifest large interindividual variability. The objective of this secondary analysis is to investigate whether common single-nucleotide polymorphisms (SNP) in genes involved in DHA synthesis and TAG metabolism are associated with the responsiveness of blood lipids, lipoprotein, and apolipoprotein concentration to dietary treatment by DHA supplied in high-oleic canola oil (HOCO). In a randomized, crossover-controlled feeding trial, 129 subjects with metabolic syndrome received high-oleic canola oil (HOCO) and high-oleic canola oil supplemented with DHA (HOCO-DHA), each for 4 weeks. During the HOCO-DHA phase, the intake of DHA ranged from 1 to 2.5 g/day. The subjects were genotyped for apolipoprotein E (APOE) isoforms, and SNP including FADS1-rs174561, FADS2-rs174583, ELOVL2-rs953413, ELOVL5-rs2397142, CETP-rs5882, SCD1-rs2234970, PPARA-rs6008259, and LIPF-rs814628 were selected as important genes controlling fatty acid metabolism. Overall, consumption of HOCO-DHA oil reduced blood concentrations of TAG by 24% compared to HOCO oil. The reduction in TAG was independent of genetic variations in the studied genes. Similarly, no treatment-by-gene interactions were evident in the response to other lipids, lipoproteins, or apolipoproteins to DHA supplementation. Nevertheless, a lower interindividual variation in the TAG response to DHA supplementation compared to other studies was observed in this analysis. The TAG-lowering effect of a supplemental body-weight-based dose of DHA was not influenced by genetic variations in APOE, FADS1, FADS2, ELOVL2, ELOVL5, CETP, SCD1, PPARA, and LIPF.

[25] *Sun D, Zhou BY, Li S et al.* **Genetic basis of index patients with familial hypercholesterolemia in Chinese population: mutation spectrum and genotype-phenotype correlation**. Lipids in health and disease 2018; 17:252.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30400955
ABSTRACT
BACKGROUND: Although there have been many reports in the genetics of familial hypercholesterolemia (FH) worldwide, studies in regard of Chinese population are lacking. In this multi-center study, we aim to characterize the genetic spectrum of FH in Chinese population, and examine the genotype-phenotype correlations in detail. METHODS: A total of 285 unrelated index cases from China with clinical FH were consecutively recruited. Next-generation sequencing and bioinformatics tools were used for mutation detection of LDLR,

APOB and PCSK9 genes and genetic analysis. RESULTS: Overall, the detection rate is 51.9% (148/285) in the unrelated index cases with a total of 119 risk variants identified including 84 in the LDLR gene, 31 in APOB and 4 in PCSK9 gene. Twenty-eight variants were found in more than one individual and LDLR c.1448G > A (p. W483X) was most frequent one detected in 9 patients. Besides, we found 8 (7 LDLR and 1 APOB) novel variants referred as "pathogenic (or likely pathogenic) variants" according to in silico analysis. In the phenotype analysis, patients with LDLR null mutation had significantly higher LDL cholesterol level than LDLR defective and APOB/PCSK9 mutation carriers and those with no mutations ($p < 0.001$). Furthermore, 13 double heterozygotes, 16 compound heterozygotes and 5 true LDLR homozygotes were identified and the true LDLR homozygotes had the most severe phenotypes. CONCLUSIONS: The present study confirmed the heterogeneity of FH genetics in the largest Chinese cohort, which could replenish the knowledge of mutation spectrum and contribute to early screening and disease management.

[26] *Ravnskov U, de Lorgeril M, Kendrick M, Diamond DM*. **Inborn coagulation factors are more important cardiovascular risk factors than high LDL-cholesterol in familial hypercholesterolemia**. Medical hypotheses 2018; 121:60-63.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30396495
ABSTRACT
High low-density-lipoprotein cholesterol (LDL-C) is routinely described as the main cause of cardiovascular disease (CVD) in familial hypercholesterolemia (FH). However, numerous observations are in conflict with Bradford Hill's criteria for causality: a) degree of atherosclerosis is not associated with LDL-C; b) on average the life span of people with FH is about the same as for other people; c) LDL-C of people with FH without CVD is almost as high as in FH patients of the same age with CVD; and d) questionable benefit or none at all have been achieved in the controlled, randomized cholesterol-lowering trials that have included FH individuals only. Obviously, those individuals with FH who suffer from CVD may have inherited other and more important risk factors of CVD than high LDL-C. In accordance, several studies of FH individuals have shown that various coagulation factors may cause CVD. Equally, some non-FH members of an FH kindred with early CVD, have been found to suffer from early CVD as well. Cholesterol-lowering has only been successful in an animal experiment by using probucol, which has anticoagulant effects as well. We conclude that systematic studies of all kinds of risk factors among FH individuals are urgently required, because today millions of people with FH are treated with statins, the benefit of which in FH is unproven, and which have many serious side effects. We predict that treatment of FH individuals with elevated coagulation factors with anticoagulative drugs is more effective than statin treatment alone.

[27] *Cacciapaglia F, Anelli MG, Rinaldi A et al.* **Lipids and Atherogenic Indices Fluctuation in Rheumatoid Arthritis Patients on Long-Term Tocilizumab Treatment**. Mediators of inflammation 2018; 2018:2453265.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30405318
ABSTRACT
Rheumatoid arthritis (RA) patients are at high risk of cardiovascular (CV) events, and the chronic inflammatory state may generate quantitative and qualitative changes in lipoprotein fractions.

The anti-IL-6 receptor tocilizumab (TCZ), even if effective in inflammation and joint damage prevention, determined significant alterations to RA patients' lipid levels in randomized controlled trials, but real-world data are lacking. We evaluated the changes in lipid fraction levels and disease activity in a longitudinal cohort of RA patients on long-term treatment with tocilizumab (TCZ) in a community setting. We retrospectively selected 40 naive-biologic RA patients on treatment with intravenous TCZ compared to 20 RA patients on methotrexate treatment as the control group. Total cholesterol (Tot-Chol), low-density lipoproteins (LDL), high-density lipoprotein (HDL), and triglyceride (TG) levels were measured at the baseline and at 12, 24, and 52 weeks thereafter. At the same points, 28-joint disease activity score (DAS28), clinical disease activity index (CDAI), and EULAR clinical responses were also assessed. During the first 24 weeks, we observed in TCZ-treated patients a progressive statistically significant ($p < 0.001$) increase in Tot-Chol, LDL, HDL, and TG, which returned close to the baseline at 52 weeks. But no changes in the lipid-related CV risk indices Tot-Chol/HDL and LDL/HDL ratios and the atherogenic index (log10 TG/HDL) were detectable. Notably, we observed a statistically significant negative correlation between changes in lipid fractions and DAS28 or CDAI. The prolonged treatment with TCZ was associated to a transient increase in cholesterol's fractions during the first 6 months of treatment, with inverse correlation to disease activity, but with no impact on surrogate lipid indices of atherogenic risk. These findings may aid clinicians in interpreting the RA patient's lipid profile in daily clinical practice.

[28] *Schwartz GG, Steg PG, Szarek M et al.* **Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome**. The New England journal of medicine 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30403574

ABSTRACT

BACKGROUND: Patients who have had an acute coronary syndrome are at high risk for recurrent ischemic cardiovascular events. We sought to determine whether alirocumab, a human monoclonal antibody to proprotein convertase subtilisin-kexin type 9 (PCSK9), would improve cardiovascular outcomes after an acute coronary syndrome in patients receiving high-intensity statin therapy. METHODS: We conducted a multicenter, randomized, double-blind, placebo-controlled trial involving 18,924 patients who had an acute coronary syndrome 1 to 12 months earlier, had a low-density lipoprotein (LDL) cholesterol level of at least 70 mg per deciliter (1.8 mmol per liter), a non-high-density lipoprotein cholesterol level of at least 100 mg per deciliter (2.6 mmol per liter), or an apolipoprotein B level of at least 80 mg per deciliter, and were receiving statin therapy at a high-intensity dose or at the maximum tolerated dose. Patients were randomly assigned to receive alirocumab subcutaneously at a dose of 75 mg (9462 patients) or matching placebo (9462 patients) every 2 weeks. The dose of alirocumab was adjusted under blinded conditions to target an LDL cholesterol level of 25 to 50 mg per deciliter (0.6 to 1.3 mmol per liter). The primary end point was a composite of death from coronary heart disease, nonfatal myocardial infarction, fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization. RESULTS: The median duration of follow-up was 2.8 years. A composite primary end-point event occurred in 903 patients (9.5%) in the alirocumab group and in 1052 patients (11.1%) in the placebo group (hazard ratio, 0.85; 95% confidence interval [CI], 0.78 to 0.93; P<0.001). A total of 334 patients (3.5%) in the alirocumab group and 392 patients (4.1%) in the placebo group died (hazard ratio, 0.85; 95% CI, 0.73 to 0.98). The

absolute benefit of alirocumab with respect to the composite primary end point was greater among patients who had a baseline LDL cholesterol level of 100 mg or more per deciliter than among patients who had a lower baseline level. The incidence of adverse events was similar in the two groups, with the exception of local injection-site reactions (3.8% in the alirocumab group vs. 2.1% in the placebo group). CONCLUSIONS: Among patients who had a previous acute coronary syndrome and who were receiving high-intensity statin therapy, the risk of recurrent ischemic cardiovascular events was lower among those who received alirocumab than among those who received placebo. (Funded by Sanofi and Regeneron Pharmaceuticals; ODYSSEY OUTCOMES ClinicalTrials.gov number, NCT01663402 .).

[29] *Sage AP, Tsiantoulas D, Binder CJ, Mallat Z*. **The role of B cells in atherosclerosis**. Nature reviews. Cardiology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30410107
ABSTRACT
The cardiovascular system is subject to hyperlipidaemic, inflammatory, and pro-oxidant stressors. Over time, these factors drive prevalent chronic diseases, of which atherosclerosis is most prominent and accounts for the majority of deaths globally. Antibody-producing B cells perform a unique role in responses to stress, injury, and infection. The power, inducibility, and adaptability of the antibody repertoire require an equally complex range of control measures. Defects and chronic perturbations in these checkpoints lead to inappropriate antibody responses, which might have important roles in shaping the development and outcome of atherosclerotic disease. A unique aspect related to atherosclerosis is the prominent role of natural antibodies, specifically those binding to the oxidized epitopes that are abundant on modified lipoproteins and cellular debris. B cells control cellular immune responses through cell-cell contact, antigen presentation, and cytokine production, and thereby participate in systemic and local immune responses in atherosclerotic arteries. To date, both proatherogenic and antiatherogenic properties have been assigned to B cells, depending on subsets and how they are functionally targeted. For these reasons, a deeper understanding of how B cells influence atherosclerotic plaque development is being pursued with the hope of providing novel B cell-targeted interventions to prevent inflammation-driven cardiovascular events.

[30] *Meng L, Wang Y, Li T et al.* **Dietary Diversity and Food Variety in Chinese Children Aged 3(-)17 Years: Are They Negatively Associated with Dietary Micronutrient Inadequacy?** Nutrients 2018; 10.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30400573
ABSTRACT
Micronutrient inadequacy remains a nutritional problem in Chinese children. However, the associations between dietary diversity and inadequate micronutrient intake have not been extensively studied. A total of 2012 children aged 3(-)17 years from the China Health and Nutrition Survey were included for analysis. Dietary diversity score (DDS) and food variety scores (FVS) were assessed based on three 24-h recall periods. The nutrient adequacy ratio (NAR) was used to determine the micronutrient adequacy of the diet. The mean adequacy ratio (MAR, %) was defined as the sum of each NAR divided by the number of involved micronutrients. Overall micronutrient inadequacy (OMI) was defined as having a MAR below

0.75. Micronutrient inadequacy was defined as the proportion of individuals whose nutrient intake was less than the estimated average requirement. After adjustment confounders, DDS and FVSs were positively associated with MAR and NAR of most nutrients except sodium ($p < 0.05$). A higher DDS was negatively associated with the prevalence of inadequate intake of vitamin A, riboflavin, vitamin C, iron, zinc, selenium, niacin, phosphorus, magnesium and OMI. Similar results were found for FVSs. In conclusion, this study indicates that poor dietary diversity and food variety in Chinese children are directly associated with inadequate micronutrient intake.

[31] *Rinninella E, Mele MC, Merendino N et al.* **The Role of Diet, Micronutrients and the Gut Microbiota in Age-Related Macular Degeneration: New Perspectives from the Gut(-)Retina Axis**. Nutrients 2018; 10.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30400586
ABSTRACT
Age-related macular degeneration (AMD) is a complex multifactorial disease and the primary cause of legal and irreversible blindness among individuals aged >/=65 years in developed countries. Globally, it affects 30(-)50 million individuals, with an estimated increase of approximately 200 million by 2020 and approximately 300 million by 2040. Currently, the neovascular form may be able to be treated with the use of anti-VEGF drugs, while no effective treatments are available for the dry form. Many studies, such as the randomized controlled trials (RCTs) Age-Related Eye Disease Study (AREDS) and AREDS 2, have shown a potential role of micronutrient supplementation in lowering the risk of progression of the early stages of AMD. Recently, low-grade inflammation, sustained by dysbiosis and a leaky gut, has been shown to contribute to the development of AMD. Given the ascertained influence of the gut microbiota in systemic low-grade inflammation and its potential modulation by macro- and micro-nutrients, a potential role of diet in AMD has been proposed. This review discusses the role of the gut microbiota in the development of AMD. Using PubMed, Web of Science and Scopus, we searched for recent scientific evidence discussing the impact of dietary habits (high-fat and high-glucose or -fructose diets), micronutrients (vitamins C, E, and D, zinc, beta-carotene, lutein and zeaxanthin) and omega-3 fatty acids on the modulation of the gut microbiota and their relationship with AMD risk and progression.

[32] *Soko ND, Masimirembwa C, Dandara C*. **Rosuvastatin pharmacogenetics in African populations**. Pharmacogenomics 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30398065
ABSTRACT

[33] *Chen TH, Wang JJ*. **Niacin Pretreatment Attenuates Ischemia and Reperfusion of Pancreas-induced Acute Pancreatitis and Remote Lung Injury Through Suppressing Oxidative Stress and Inflammation and Activation of SIRT1**. Transplantation proceedings 2018; 50:2860-2863.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30401412
ABSTRACT

BACKGROUND: Lung injury subsequent to pancreatic ischemia and reperfusion (PIR) due to shock, revascularization, and pancreas transplantation is a major clinical problem. In addition to proteases, massive production and release of reactive oxygen species (ROS) and induction of inflammatory cytokines have been implicated in remote lung injury. Niacin, also known as vitamin B3, is both antioxidative and anti-inflammatory. In this study, we examined the protective effectiveness of niacin pretreatment against PIR-induced pancreatic and remote lung injury. METHODS: Male Sprague-Dawley rats were divided into a sham-operated group, a PIR group, and a PIR group pretreated with niacin; the niacin (300 mg/kg per day) was given on 4 consecutive days before the study. Pancreatic ischemia was established by occluding both the gastroduodenal and splenic arteries for 120 minutes, followed by 240 minutes of reperfusion. Lung injury was assessed by pulmonary barrier function via pulmonary filtration coefficient, Kfc, using an isolated-perfused rat lung preparation. Alveolar protein leakage was assessed by protein concentration in the bronchoalveolar lavage fluid (PCBAL). Lung water content was assessed by both wet-weight/dry-weight ratio (W/D) and lung-weight/body-weight ratio (LW/BW). Lung inflammation was evaluated by the lavage differential neutrophil cell count and tissue tumor necrosis-alpha (TNF-alpha) level. Oxidative stress was assessed by tissue malondialdehyde (MDA) level. Serum lactate dehydrogenase (LDH) and amylase were examined for lung and pancreas injury. We also evaluated lung tissue SIRT1 mRNA expression. RESULTS: Compared with the sham group, the PIR group had increased serum amylase and LDH, and impaired the pulmonary barrier dysfunction with marked increases in Kfc, PCBAL, W/D, and LW/BW, and augumented oxidative stress and inflammation with elevated tissue MDA and TNF-alpha and lavage neutrophil count, which correlated with decreased SIRT1 mRNA expression. Conversely, niacin pretreatment reduced pancreatic and remote lung injury and attenuated pulmonary oxidative stress and inflammation, and also protected against PIR-induced pulmonary barrier dysfunction while restoring SIRT1 mRNA expression. CONCLUSION: Niacin pretreatment reduced PIR-induced pancreatic and lung injury and protected against pulmonary barrier function impairment, which was associated with niacin's antioxidative and anti-inflammatory activity and its capacity to increase SIRT1 mRNA expression.

[34] *Wu NC, Wang JJ*. **Niacin Pretreatment Attenuates Lung Ischemia and Reperfusion-Induced Pulmonary Barrier Function Impairment by Reducing Oxidative Stress and Activating SIRT1 in an Isolated-Perfused Rat Lung Model**. Transplantation proceedings 2018; 50:2834-2838.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30401407

ABSTRACT

PURPOSE: Alveolar-capillary barrier dysfunction, characterized by alveolar protein leak and lung edema, is a common scenario following cardiopulmonary surgery and thoracic organ transplantation. Reactive oxygen species generated through lung ischemia and reperfusion (I/R) injury during surgery plays a crucial role. Niacin, also known as vitamin B3, has been demonstrated to possess antioxidative and anti-inflammatory capacity. In this study, we examine the pulmonary barrier function via capillary filtration coefficient (Kfc) following lung I/R injury with and without niacin treatment. METHODS: Studies were conducted on male Sprague-Dawley rats in 3 groups: sham-operated, lung I/R injury, and niacin-pretreated lung I/R injury group. Rats were subjected to isolated perfused lung preparation. Lung ischemia was

established by continuous perfusion and stopping ventilation for 60 minutes, followed by 60 minutes of ventilation. We assessed the Kfc, lung water content, and protein concentration in the lung lavage; pulmonary oxidative stress and lung inflammation were assessed by leukocyte counts, tissue level of tumor nercrosis factor alpha (TNF-alpha), and tissue content of malondialdehyde (MDA), respectively. We also assessed the tissue protein level of sirtuin (silent mating type information regulation 2 homolog) 1 (SIRT1). RESULTS: Lungs subjected to I/R injury significantly increased Kfc, pulmonary oxidative stress, lung water content, and lavage leukocyte count and protein concentration ($P < .05$). Rats treated with niacin of 100 mg/kg/day for 4 days increased lung SIRT1 ($P < .05$) and attenuated lung I/R injury-induced pulmonary oxidative stress and inflammation and also improved Kfc. CONCLUSIONS: Niacin pretreatment protects lungs against I/R injury-induced barrier function impairment through the activation of SIRT1 and reduced pulmonary oxidative stress and lung inflammation.

[35] *Yin E, Hara M, Uchiyama M, Niimi M*. **Graft Protective Effect of HMG-CoA Reductase Inhibitor Pravastatin in Murine Cardiac Allograft Transplantation**. Transplantation proceedings 2018; 50:2804-2806.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30401401
ABSTRACT
The HMG-CoA reductase inhibitor (statin), which reduces serum cholesterol, has been demonstrated in the control of immune responses and may potentially play an important role in the regulation of acute and chronic rejection in organ transplantations. We investigated the graft-protective effect of a kind of statin, pravastatin, in the survival of fully major histocompatibility complex--mismatched murine cardiac allograft transplantation. Fully vascularized heterotopic hearts from C57BL/6 donors were transplanted into CBA recipients through microsurgical techniques. CBA recipients transplanted with a C57BL/6 heart received oral administration of 40, 120, or 400 mug/kg/day of pravastatin from the day of transplantation to 7 days afterward. Immunohistochemical staining studies were performed to determine whether intimal formation of coronary arteries in the transplanted cardiac allografts was preserved and also to conduct morphometric analysis. Untreated CBA recipients rejected C57BL/6 cardiac grafts acutely (median survival time [MST] 7 days). CBA recipients exposed with 40 and 120 mug/kg/day of pravastatin had a small prolonged allograft survival (MSTs of 10 and 9 days, respectively). However, the MST of CBA recipients exposed to 400 mug/kg/day of pravastatin was significantly effective for allograft survival (MST 50 days). Immunohistochemical staining assessments on 4 weeks after grafting showed suppression of intimal hyperplasia in allograft coronary arteries. Pravastatin could induce the prolongation of fully major histocompatibility complex--mismatched cardiac allograft through the protection of the coronary artery.

[36] *Di Nora C, Sponga S, Livi U*. **Safety and efficacy of PCSK9 inhibitor treatment in heart transplant patients**. Transplantation 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30399127
ABSTRACT

[37] *Oguz A, Telci Caklili O, Tumerdem Calik B*. **The Prospective Urban Rural Epidemiology (PURE) study: PURE Turkey**. Turk Kardiyoloji Dernegi arsivi : Turk Kardiyoloji Derneginin yayin organidir 2018; 46:613-623.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30391990

ABSTRACT

OBJECTIVE: The Prospective Urban Rural Epidemiology (PURE) study is a prospective cohort study that collects data on social, environmental, and individual risk factors and chronic diseases among residents of 25 countries in the range of 35 to 70 years of age, living in rural and urban areas. The PURE study is directed by the Population Health Research Institute of McMaster University in Canada. In Turkey, the study is conducted by the Metabolic Syndrome Society. METHODS: In Turkey, the study is being conducted in 8 cities. The initial fieldwork began in 2008. Questionnaires were completed, and anthropometric measurements, blood and urine samples, handgrip strength evaluations, electrocardiogram readings, and spirometer and body composition measurements were obtained. Each year, participants were followed up via telephone. Every third year, questionnaires, field measurements, and biological data sampling were repeated. RESULTS: PURE Turkey has 4056 participants (female: 60.7%, male: 39.3%; mean age: 50+/-9.1 years). Among them, 43.9% had metabolic syndrome and 52.8% were obese. The prevalence of hypertension was 41.1% and proportion of controlled hypertension was 34%. A total of 2098 (51.7%) of the participants had a total cholesterol of >/=200 mg/dL or were using a lipid lowering agent. In patients with diabetes, 79.8% had low-density lipoprotein cholesterol levels >/=100 mg/dL. Although a dramatic change was not observed in those parameters in the follow-up years, the prevalence of diabetes mellitus increased from 13.7% in 2008 to 21% in 2015. The baseline and follow-up data of the PURE study were analyzed with the other countries participating in the study and reported for international publication. CONCLUSION: The PURE study is a large, ongoing, prospective epidemiological study that is investigating the "causes of the causes" of noncommunicable diseases in the world. In addition to revealing the health status of nations, the study also has the potential to affect health politics.