**Literature update week 50 (2019)**

[1] *Ji H, Wu G, Li Y et al.* **Self-Albumin Camouflage of Carrier Protein Prevents Nontarget Antibody Production for Enhanced LDL-C Immunotherapy**. Advanced healthcare materials 2019:e1901203.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=31814301
***ABSTRACT***
Elevated low-density lipoprotein cholesterol (LDL-C) increases the risk of atherosclerotic cardiovascular disease. Peptide-based PCSK9 vaccines have shown a promising prospect of reducing LDL-C. In peptide vaccine (pVax) design, the peptide antigens need to conjugate with carrier protein (CP). However, CP incorporation can induce undesirable anti-CP antibodies, which sterically mask peptide epitopes from being recognized by specific B cells and impair subsequent therapeutically antibody production. This epitopic suppression has posed a barrier in clinical translation of conjugate vaccines all along. A model CP (keyhole limpet hemocyanin, KLH) is herein camouflaged with serum albumin (SA) into hybrid nanocarriers (SA@N), with PCSK9 peptide being anchored onto the surface to form nanovaccine (SA@NVax). Such camouflage of KLH via high "self" SA coverage is able to inhibit KLH from extracellular immune recognition and prevent detectable anti-KLH antibody production. Furthermore, the nanovaccine around 70 nm stabilized by intermolecular disulfide network is ideal for internalization and biodegradation by antigen presenting cells as well as better retention in draining lymph nodes and spleen. As expected, the SA@NVax efficiently primes higher anti-PCSK9 IgG antibody titer than PCSK9 pVax.

[2] *Zijlstra LE, Mooijaart SP, Jukema JW*. **PCSK9 inhibition in high-risk patients**. Aging 2019.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=31829977
***ABSTRACT***

[3] *Chen Q, Wu G, Li C et al.* **Safety of Proprotein Convertase Subtilisin/Kexin Type 9 Monoclonal Antibodies in Regard to Diabetes Mellitus: A Systematic Review and Meta-analysis of Randomized Controlled Trials**. American journal of cardiovascular drugs : drugs, devices, and other interventions 2019.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=31823301
***ABSTRACT***
BACKGROUND: Evidence shows a positive association between the use of statins and new-onset diabetes. There is, however, contradictory evidence as to whether a similar association exists for the use of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors. OBJECTIVE: The aim of this study was to investigate the safety of PCSK9 monoclonal antibodies (PCSK9-mAbs) in regard to incident diabetes. METHODS AND RESULTS: Randomized controlled trials that reported data on the incidence of new-onset diabetes mellitus or the worsening of pre-existing diabetes were searched, and risk ratios (RRs) and 95% confidence intervals (CIs) were calculated to compare the endpoints. Twenty-three studies including 65,957 participants were identified. Compared with controls, PCSK9-mAb treatment was not associated with the adverse event of diabetes (RR 0.97, 95% CI 0.91-1.02; p = 0.22). When we analysed the trials in terms of PCSK9-mAb type, alirocumab was associated with a significant reduction in the risk of diabetes (RR 0.91, 95% CI 0.85-0.98; p = 0.01), whereas no significant reduction was observed in participants receiving evolocumab or bococizumab. Interestingly, compared with ezetimibe, which was actively used as lipid-modifying therapy in the control group, PCSK9-mAbs seem to have a lower risk of incident diabetes (RR 0.60, 95% CI 0.37-0.99; p = 0.04). This meta-analysis also revealed a noticeable increase in the risk of incident diabetes in the evolocumab and alirocumab pool

(RR 2.14, 95% CI 1.12-4.07; p = 0.02) when the use of statins was equivalent between the experimental and active comparator arms. CONCLUSION: Compared with placebo or any other comparator, PCSK9-mAb treatment was not associated with the adverse event of diabetes. However, evolocumab and alirocumab show high risk of incident diabetes when there is no interference from unbalanced use of statins. The imbalance in background lipid modifying therapy or different comparators used in the control arms of the studies might have masked the effect of PCSK9-mAb therapy on diabetes.

[4] *Lu Z, Li Y, Syn WK et al.* **Amitriptyline Inhibits Nonalcoholic Steatohepatitis and Atherosclerosis Induced by High-Fat Diet and LPS through Modulation of Sphingolipid Metabolism**. American journal of physiology. Endocrinology and metabolism 2019.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=31821039
***ABSTRACT***
We reported previously that increased acid sphingomyelinase (ASMase)-catalyzed hydrolysis of sphingomyelin, which leads to increases in ceramide and sphingosine 1 phosphate (S1P), played a key role in the synergistic upregulation of proinflammatory cytokines by palmitic acid (PA), a major saturated fatty acid (SFA), and lipopolysaccharide (LPS) in macrophages. Since macrophages are vital players in nonalcoholic steatohepatitis (NASH) and atherosclerosis, we assessed the effect of ASMase inhibition on NASH and atherosclerosis cooperatively induced by high PA-containing high-fat diet (HP-HFD) and LPS in LDL receptor-deficient (LDLR-/-) mice. LDLR-/- mice were fed HP-HFD, injected with low dose of LPS, and treated with or without ASMase inhibitor amitriptyline. Neutral sphingomyelinase inhibitor GW4869 was used as control. Metabolic study showed that both amitriptyline and GW4869 reduced glucose, lipids and insulin resistance. Histological analysis and Oil Red O staining showed that amitriptyline robustly reduced hepatic steatosis while GW4869 had modest effects. Interestingly, immunohistochemical study showed that amitriptyline, but not GW4869, strongly reduced hepatic inflammation. Furthermore, results showed that both amitriptyline and GW4869 attenuated atherosclerosis. To elucidate the underlying mechanisms whereby amitriptyline inhibited both NASH and atherosclerosis, but GW4869 only inhibited atherosclerosis, we found that amitriptyline, but not GW4869, downregulated proinflammatory cytokines in macrophages. Finally, we found that inhibition of S1P production is a potential mechanism whereby amitriptyline inhibited proinflammatory cytokines. Collectively, this study showed that amitriptyline inhibited NASH and atherosclerosis through modulation of sphingolipid metabolism in LDLR-/- Mice and indicated that sphingolipid metabolism in macrophages plays a crucial role in the linkage of NASH and atherosclerosis.

[5] *Hung J, Scanlon JP, Mahmoud AD et al.* **Novel Plaque Enriched Long Noncoding RNA in Atherosclerotic Macrophage Regulation (PELATON)**. Arteriosclerosis, thrombosis, and vascular biology 2019:Atvbaha119313430.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=31826651
***ABSTRACT***
OBJECTIVE: Long noncoding RNAs (lncRNAs) are an emergent class of molecules with diverse functional roles, widely expressed in human physiology and disease. Although some lncRNAs have been identified in cardiovascular disease, their potential as novel targets in the prevention of atherosclerosis is unknown. We set out to discover important lncRNAs in unstable plaque and gain insight into their functional relevance. Approach and Results: Analysis of RNA sequencing previously performed on stable and unstable atherosclerotic plaque identified a panel of 47 differentially regulated lncRNAs. We

focused on LINC01272, a lncRNA upregulated in unstable plaque previously detected in inflammatory bowel disease, which we termed PELATON (plaque enriched lncRNA in atherosclerotic and inflammatory bowel macrophage regulation). Here, we demonstrate that PELATON is highly monocyte- and macrophage-specific across vascular cell types, and almost entirely nuclear by cellular fractionation (90%-98%). In situ hybridization confirmed enrichment of PELATON in areas of plaque inflammation, colocalizing with macrophages around the shoulders and necrotic core of human plaque sections. Consistent with its nuclear localization, and despite containing a predicted open reading frame, PELATON did not demonstrate any protein-coding potential in vitro. Functionally, knockdown of PELATON significantly reduced phagocytosis, lipid uptake and reactive oxygen species production in high-content analysis, with a significant reduction in phagocytosis independently validated. Furthermore, CD36, a key mediator of phagocytic oxLDL (oxidized low-density lipoprotein) uptake was significantly reduced with PELATON knockdown. CONCLUSIONS: PELATON is a nuclear expressed, monocyte- and macrophage-specific lncRNA, upregulated in unstable atherosclerotic plaque. Knockdown of PELATON affects cellular functions associated with plaque progression.

[6] *Berent T, Berent R, Sinzinger H*. **Lipoprotein apheresis - Shortening of treatment intervals reduces cardiovascular events: Case reports**. Atherosclerosis. Supplements 2019; 40:125-130.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=31818444
***ABSTRACT***
BACKGROUND: Lipoprotein (Lp-) apheresis is a life-long therapy, usually performed in weekly intervals. In some cases, however, atherosclerotic disease progresses despite adequate therapy with weekly Lp-apheresis and maximal lipid lowering medication. In an attempt to improve the effectiveness of therapy, we temporarily shortened treatment intervals of Lp-apheresis in patients with elevated lipoprotein(a) (Lp(a)) and further progression of coronary atherosclerosis despite weekly Lp-apheresis and maximal lipid lowering medication. METHODS: We illustrate three case reports of patients with elevated Lp(a), who underwent regular weekly Lp-apheresis treatment for secondary prevention. The intensified treatment protocol contained three therapies in two weeks (alternating 2 per week and 1 per week). RESULTS: The shortening of treatment intervals achieved a stabilization of atherosclerotic disease in case 1. After a total of 68 therapies in 52 weeks (1.31 sessions/week) the elective coronary angiography revealed excellent long-term results. In case 2, the intensified treatment protocol is still ongoing. The patient reported a decrease in angina pectoris and an increase in exercise capacity since the beginning of more frequent therapy sessions. In some cases, as it is shown in case 3, a fast decision for shortening the treatment intervals is necessary. CONCLUSIONS: The intensified treatment regimen resulted in an improvement in clinical symptoms and no further progression of atherosclerosis. In conclusion, shorter therapeutic Lp-apheresis intervals, at least temporarily, should be considered in patients who suffer from clinical and/or angiographic progression of atherosclerosis, despite maximal lipid lowering medication and weekly Lp-apheresis.

[7] *Dlouha D, Prochazkova I, Eretova Z et al.* **Influence of lipoprotein apheresis on circulating plasma levels of miRNAs in patients with high Lp(a)**. Atherosclerosis. Supplements 2019; 40:12-16.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=31818442
***ABSTRACT***
BACKGROUND: Lipoprotein apheresis (LA) is a well-established therapy for lowering lipid levels in serious cases of dyslipidaemia, including high levels of lipoprotein(a) [Lp(a)]. This method lowers both

LDL cholesterol and Lp(a) by more than 60% in most of patients; however, because randomized clinical studies could be extremely difficult, also other markers of the effect of this procedures on vascular health are of importance. Therefore, in addition to changes in plasma lipids and Lp(a) during LA, we also analysed the response of biomarkers associated with vascular integrity: small non-coding microRNAs (miRNAs). MATERIALS AND METHODS: We analysed the changes in miRNAs in two women (age 70 and 72 years) with clinically manifest extensive and progressive atherosclerotic disease and high levels of Lp(a) and with different clinical course who were treated by LA. In both women we analysed changes of 175 circulating plasma miRNAs using pre-defined serum/plasma focus panels at the beginning of and one year after the therapy. RESULTS: In addition to reduced levels of plasma lipids and Lp(a), circulating plasma levels of miR-193a-5p; -215-5p; -328-3p; -130a-3p; -362-3p; -92b-3p decreased, and levels of miR-125a-5p; -185-5p; -106a-5p; -320b; -19a increased (all P<0.05) in both women. Moderate differences were found between both women with regard to the different course of atherosclerotic disease. CONCLUSIONS: Long-term LA substantially changes circulating plasma miRNAs associated with vascular integrity reflected different clinical course in both women. If confirmed, this approach could improve the assessment of the effectiveness of this therapy on an individual basis.

[8] *Giurgea GA, Karkutli E, Granegger S et al.* **One year follow-up of patients with reduced left ventricular ejection fraction (LVEF) on lipoprotein apheresis**. Atherosclerosis. Supplements 2019; 40:44-48.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=31818449
***ABSTRACT***
BACKGROUND: Left ventricular ejection fraction (LVEF) is a valuable measure to assess left ventricular systolic function. Lipid lowering therapy by statins has been shown to have an impact on LVEF already after a 6 months treatment. Higher doses of statins have been claimed to be more effective as compared to a conventional one and even a difference between lipophilic and hydrophilic compounds has been reported. The effect of regular lipoprotein-apheresis (LP-apheresis) on LVEF was previously poorly examined. Patients involved in a regular LP-apheresis program are supposed to undergo a number of follow-up investigations among them myocardial scintigraphy and LVEF, measured by radionuclide ventriculography. METHODS: We examined 18 patients before initiation and after one year of ongoing LP-apheresis. 13 patients (11 males, 2 females, mean age 58.3+/-5.3 years, groups A) were since more than a year on stable, unchanged statin treatment (atorvastatin 40mg, simvastatin 40mg, rosuvastatin 20mg+/-ezetimibe), the other 5 patients (3 males, 2 females, mean age 57.1+/-4.6 years, group B) were intolerant to statins being on micronized fenofibrate+/-resorption inhibitors (cholestyramine). All patients had a Lp(a)<30mg/dl. As part of the usual follow-up monitoring, LVEF was determined by means of radionuclide ventriculography after application of 550 MBq (99m) Tc-pertechnetate. RESULTS: The follow-up LVEF was checked at a mean of 48.7 weeks in group A and 51.2 weeks in group B. Except in 1 patient (LVEF 46.8% before vs. 45.2% after LP-apheresis initiation) in group A we noted a significant increase in LVEF in 12 patients of group A (92%) and in all patients of group B. Mean LVEF increased significantly in both groups (A: 42.7+/-8.1-->46.5+/-7.5% (p<0.001) and B: 41.9+/-8.4-->46.5+/-6.3 %; p<0.001). The relative rise was nearly identical (group A 9.6%, in group B 9.7%). CONCLUSIONS: Our findings indicate that regular long-term LP-apheresis treatment apparently increases LVEF, independently on current statin treatment. This implies a role of lowering of atherogenic lipoproteins as underlying mechanism. A prospective study should clarify the relative extent of LVEF improvement induced by LP-apheresis.

[9] *Heigl F, Pflederer T, Klingel R et al.* **Lipoprotein apheresis in Germany - Still more commonly indicated than implemented. How can patients in need access therapy?** Atherosclerosis. Supplements 2019; 40:23-29.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=31818446

***ABSTRACT***

BACKGROUND: Although lipid-lowering drugs, especially statins, and recently also PCSK9 inhibitors can reduce LDL cholesterol (LDL-C) and decrease the risk for cardiovascular disease (CVD) including coronary artery disease (CAD) events most efficiently, only 5-10% of high-risk cardiovascular patients reach the target values recommended by international guidelines. In patients who cannot be treated adequately by drugs it is possible to reduce increased LDL-C and/or lipoprotein(a) (Lp(a)) values by the use of lipoprotein apheresis (LA) with the potential to decrease severe CVD events in the range of 70%->80%. Even in Germany, a country with well-established reimbursement guidelines for LA, knowledge about this life-saving therapy is unsatisfactory in medical disciplines treating patients with CVD. Starting in 1996 our aim was to offer LA treatment following current guidelines for all patients in the entire region of our clinic as standard of care. METHODS: Based on the experience of our large apheresis competence center overlooking now nearly 80,000 LA treatments in the last two decades, we depict the necessary structure for identification of patients, defining indication, referral, implementation and standardisation of therapy as well as for reimbursement. LA is unfamiliar for most patients and even for many practitioners and consultants. Therefore nephrologists performing more than 90% of LA in Germany have to form a network for referral and ongoing medical education, comprising all regional care-givers, general practitioners as well as the respective specialists and insurances or other cost bearing parties for offering a scientifically approved therapeutic regimen and comprehensive care. The German Lipid Association (Lipid-Liga) has implemented the certification of a lipidological competence center as an appropriate way to realize such a network structure. RESULTS: Working as a lipidological and apheresis competence center in a region of 400,000 to 500,000 inhabitants, today we treat 160 patients in the chronic LA program. In spite of the availability of PCSK9 inhibitors since 2015, LA has remained as an indispensable therapeutic option for targeted lipid lowering treatment. An analysis of nearly 37,000 LA treatments in our own center documented a >80% reduction of cardiovascular events in patients treated by regular LA when comparing with the situation before the start of the LA therapy. We have implemented the concept of an apheresis competence center characterised by ongoing medical education with a focus on lipidological and cardiovascular aspects, interdisciplinary networking and referral. CONCLUSIONS: Incidence and prevalence of LA patients in our region demonstrate that based on our ongoing patient-centered approach the access of patients in need to LA is substantially above the German average, thus contributing to an extraordinary reduction of cardiovascular events in the population we in particular feel responsible for.

[10] *Julius U, Tselmin S, Schatz U et al.* **Actual situation of lipoprotein apheresis in patients with elevated lipoprotein(a) levels**. Atherosclerosis. Supplements 2019; 40:1-7.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=31818437

***ABSTRACT***

An elevation of lipoprotein(a) (Lp(a)) is an internationally recognized atherogenic risk factor, documented in epidemiological studies, in studies with Mendelian randomization and in genome-wide association studies (GWAS). At present, no drug is available to effectively reduce its concentration. In

Germany, an elevation of Lp(a) associated with progressive cardiovascular diseases is officially recognized as an indication for a lipoprotein apheresis (LA). The number of patients who were treated with LA with this abnormality was steadily increasing in the years 2013-2016 - the official data are reported. In all new patients, who started to be treated at our LA center in 2017 (n=20) the increased Lp(a) was a main indication for extracorporeal therapy, though some of them also showed clearly elevated LDL cholesterol (LDL-C) concentrations despite being treated with a maximal tolerated lipid-lowering drug therapy. A diabetes mellitus was seen in 5 patients. The higher was the Lp(a) level before the first LA session, the higher was the cardiovascular risk. Lp(a) concentrations measured before LA sessions were usually about 20% lower than those before the start of the LA therapy. Acutely, Lp(a) levels were reduced by about 70%. Following LA sessions the Lp(a) levels increased and in the majority reach pre-session concentrations after one week. Thus a weekly interval is best for the patients, but a few may need two sessions per week to stop the progress of atherosclerosis. The interval mean values were about 39% lower than previous levels. Several papers had been published showing a higher efficiency of LA therapy on the incidence of cardiovascular events in patients with high Lp(a) values when comparing with hypercholesterolemic patients with normal Lp(a) concentrations. Russian specific anti-Lp(a) columns positively affected coronary atherosclerosis. PCSK9 inhibitors reduce Lp(a) concentrations in many patients and in this way have a positive impact on cardiovascular outcomes. In the future, an antisense oligonucleotide against apolipoprotein(a) may be an alternative therapeutic option, provided a clear-cut reduction of cardiovascular events will be demonstrated.

[11] *Klingel R, Heigl F, Schettler V et al.* **Lipoprotein(a) - Marker for cardiovascular risk and target for lipoprotein apheresis**. Atherosclerosis. Supplements 2019; 40:17-22.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=31818445
***ABSTRACT***
Lipoprotein(a) (Lp(a)) consists of an LDL particle whose apolipoprotein B (apoB) is covalently bound to apolipoprotein(a) (apo[a]). An increased Lp(a) concentration is a causal, independent risk factor for atherosclerotic cardiovascular disease (ASCVD) and a predictor of incident or recurrent cardiovascular events. Although Lp(a) was first described as early as 1963, only the more recent results of epidemiological, molecular, and genetic studies have led to this unequivocal conclusion. More than 20% of Western populations have elevated Lp(a) values. Lp(a) concentrations should be always part of the lipid profile when ASCVD risk is assessed. However, presence of other risk factors, laboratory findings, medical history and family history must be considered to conclude on its clinical relevance in an individual patient. Early or progressive ASCVD or a familial predisposition are key findings which can be associated with elevated Lp(a). The cholesterol portion contained in Lp(a) is also included in the various methods of LDL-C measurement. To assess proximity to the cardiovascular risk related target value for LDL-C, appropriate correction should be applied when high Lp(a) values are obtained to estimate the LDL-C that can actually be treated by lipid lowering drugs. Initial study data show that antisense oligonucleotides, which selectively decrease apolipoprotein(a), are promising as future treatment options. Currently, lipoprotein apheresis, which has a reimbursement guideline in Germany, is the therapy of choice for patients with Lp(a)-associated progressive ASCVD, with the aim of sustained prevention of further cardiovascular events.

[12] *Korneva V, Kuznetsova T, Julius U*. **Efficiency and problems of statin therapy in patients with heterozygous familial hypercholesterolemia**. Atherosclerosis. Supplements 2019; 40:79-87.

**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=31818452

***ABSTRACT***

Familial hypercholesterolemia (FH) is associated with a very high risk of cardiovascular complications and the need for an early aggressive lipid-lowering therapy. The achievement of lipid target levels is often an extremely difficult task in these patients. AIMS: to analyze sex and age structure of ischemic heart disease (IHD) in patients with a definite, possible and probable FH. to assess the degree of achievement of low density lipoprotein cholesterol (LDL-C) target levels in FH patients on statin therapy and complications that occur during therapy; to analyze the adherence of FH patients to statin therapy and reveal the factors which have an influence on it. MATERIALS AND METHODS: The analysis of IHD clinical characteristics was performed in 253 FH patients from Karelian register, mean age 52.5 years (confidence interval, CI 22.0; 78.0). Using Dutch Lipid Clinic Network Criteria (DLCN), we established the diagnosis of FH as "definite" if the total number of points was more than eight, "probable" - if the number of points was 6-8, "possible" if the number of points was 3-5. The diagnosis was considered to be excluded if the score was less than three. A definite FH was diagnosed in 96 patients. For the evaluation of target LDL-C levels achievement on statin therapy we analyzed data from 191 FH patients (75 males). For the evaluation of adherence to statin therapy Morisky-Green questionnaire was used in 93 definite FH patients. RESULTS: In the group with a definite FH the incidence of IHD in the age range from 39 to 60 years was higher in women than in men (50% and 39.4%, p>0.05), in patients older than 60 years IHD was observed in 66.7% of women and 50% of men (p>0.05). In general, in the group with a definite FH, the frequency of IHD was more than three times higher in the age group over 40 years compared with patients under 40 years. 57% of patients with a definite FH were adherent to lipid-lowering therapy, 16% had partial adherence and no adherence to therapy was documented in 27% of patients. The achievement of LDL-C target levels was 19.2%: 22.6% in definite FH group and 12.5% in possible FH. Smoking and gender were not associated with adherence to statin therapy. Associated factors with increased adherence to statin therapy were age (p=0.000003), arterial hypertension (OR=1.90 (1.02; to 3.55), p=0.044), the history of IHD (OR=2.99 (1.50; of 5.97) p=0.002), myocardial infarction (OR=5.26 (2.03; 13.60), p=0.0006), myocardial revascularization (OR=20.3 (2.64; 156.11), p=0.004) and the fact of target LDL-cholesterol levels achievement (OR=19.93 (7.03; 56.50), p<0.0001). The main reason for the non-acceptance of statin therapy for FH patients was the fear of side effects in 87%. The main reasons for stopping current statin intake were myalgia in 12%, an increase in transaminases in 35%, skin rashes in 12%, and high cost in 6%. 29% of patients had made the decision to stop therapy themselves. CONCLUSIONS: the frequency of IHD in FH patients was more than three times higher in the age group over 40 years and was higher in women. In clinical practice statin therapy in FH patients rarely reaches target lipid values, one of the reasons was low adherence to statin therapy.

[13] *Tselmin S, Julius U, Weinert N et al.* **Experience with proprotein convertase subtilisin/kexine type 9 inhibitors (PCSK9i) in patients undergoing lipoprotein apheresis**. Atherosclerosis. Supplements 2019; 40:38-43.

**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=31818448

***ABSTRACT***

PURPOSE: We analyzed efficacy and safety of PCSK9i in patients undergoing lipoprotein apheresis (LA) and in patients treated at our outpatient department for metabolic disorders. METHODS: The medical records of 40 LA patients, taking PCSK9i were reviewed with respect to LDL-cholesterol (LDL-C) and

lipoprotein(a) (Lp(a)) lowering as well as occurrence of adverse events. Furthermore, we analyzed the data of 152 patients of our outpatient department, undergoing PCSK9i therapy. RESULTS: Mean pre-apheresis LDL-C value was reduced by PCSK9i from 3.71+/-1.19 to 1.78+/-0.84mmol/l (53+/-12%). The relative lowering of the pre-apheresis Lp(a) was 20+/-12% (from 191+/-63.5 to 152+/-51.9nmol/l). 25% of LA patients could stop LA after reaching LDL-C target after initiation of PCSK9i. 75% of the patients are continuing the regular LA therapy, showing an insufficient LDL-C lowering following PCSK9i injections or/and additionally elevated Lp(a) or/and adverse effects of PCSK9i, leading to the discontinuation of injections. The number of LA patients has grown from 112 in 2016 to 128 nowadays due to an increasing percentage of patients with elevated Lp(a) (79% and 89% respectively). The mean reduction rate of LDL-C under PCSK9i therapy in outpatients was 53.03%. In 34% of patients the target value could not be reached. 43% of persons suffered from adverse effects. CONCLUSIONS: 3/4 of LA patients could not stop extracorporeal treatment after PCSK9i administration. In hypercholesterolemic patients with coexisting elevated Lp(a) and progressive cardiovascular disease the combination of LA and PCSK9i could be beneficial. The total patients' number in LA units increases due to persons with Lp(a)-hyperlipoproteinemia.

[14] *Koskinen JS, Kyto V, Juonala M et al.* **Childhood risk factors and carotid atherosclerotic plaque in adulthood: The Cardiovascular Risk in Young Finns Study**. Atherosclerosis 2019; 293:18-25.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=31830725
***ABSTRACT***
BACKGROUND AND AIMS: Carotid plaque is a specific sign of atherosclerosis and adults with carotid plaque are at increased risk for cardiovascular outcomes. Atherosclerosis has roots in childhood and pediatric guidelines provide cut-off values for cardiovascular risk factors. However, it is unknown whether these cut-offs predict adulthood advanced atherosclerosis. METHODS: The Cardiovascular Risk in Young Finns Study is a follow-up of children that begun in 1980 when 2653 participants with data for the present analyses were aged 3-18 years. In 2001 and 2007 follow-ups, in addition to adulthood cardiovascular risk factors, carotid ultrasound data was collected. Long-term burden, as the area under the curve, was evaluated for childhood (6-18 years) risk factors. To study the associations of guideline-based cut-offs with carotid plaque, both childhood and adult risk factors were classified according to clinical practice guidelines. RESULTS: Carotid plaque, defined as a focal structure of the arterial wall protruding into lumen >50% compared to adjacent intima-media thickness, was present in 88 (3.3%) participants. Relative risk for carotid plaque, when adjusted for age and sex, was 3.03 (95% CI, 1.76-5.21) for childhood dyslipidemia, 1.51 (95% CI, 0.99-2.32) for childhood elevated systolic blood pressure, and 1.93 (95% CI, 1.26-2.94) for childhood smoking. Childhood dyslipidemia and smoking remained independent predictors of carotid plaque in models additionally adjusted for adult risk factors and family history of coronary heart disease. Carotid plaque was present in less than 1% of adults with no childhood risk factors. CONCLUSIONS: Findings reinforce childhood prevention efforts and demonstrate the utility of guideline-based cut-offs in identifying children at increased risk for adulthood atherosclerosis.

[15] *Ramin-Mangata S, Wargny M, Pichelin M et al.* **Circulating PCSK9 levels are not associated with the conversion to type 2 diabetes**. Atherosclerosis 2019; 293:49-56.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=31835041
***ABSTRACT***

BACKGROUND AND AIMS: PCSK9 is an endogenous inhibitor of the LDL receptor pathway. Recently, Mendelian randomization studies have raised a doubt about the diabetogenic risk of PCSK9 inhibitors. Here, we assessed the relationship between plasma PCSK9 levels and the risk of new onset diabetes (NOD). METHODS: Fasting plasma PCSK9 levels were measured at baseline by ELISA in subjects without lipid lowering treatment in IT-DIAB (n = 233 patients with prediabetes, follow-up 5 years) and ELSA-Brasil (n = 1751; 27.5% with prediabetes, follow-up 4 years) prospective cohorts. The primary outcome in both studies was the incidence of NOD. The association of NOD with plasma PCSK9 levels was studied using multivariable Cox models. RESULTS: Plasma PCSK9 levels were not significantly associated with NOD in IT-DIAB (HR (+1SD) 0.96, CI95% [0.76; 1.21]) and ELSA-Brasil (OR (+1SD) 1.13 [0.89; 1.42]). In ELSA-Brasil, a significant positive association between PCSK9 and worsening of glucose homeostasis, including the progression from normoglycemia to prediabetes, was found (OR (+1SD) 1.17 [1.04; 1.30], p = 0.0074). Plasma PCSK9 concentration was also positively associated with the change in fasting plasma glucose between the first and second visit in ELSA-Brasil (beta = 0.053, CI95% [0.006; 0.10], p = 0.026). Plasma PCSK9 levels positively correlated with total cholesterol in IT-DIAB and ELSA-Brasil, but not with glucose homeostasis parameters, except for a positive correlation with HOMA-IR in ELSA-Brasil. CONCLUSIONS: Plasma PCSK9 levels were not significantly associated with NOD risk in longitudinal analyses. These data suggest that inhibition of the PCSK9 extra-cellular pathway should not be deleterious for glucose homeostasis.

[16] *Ghelani H, Razmovski-Naumovski V, Inampudi V et al.* **Atorvastatin Improves Hepatic Lipid Metabolism and Protects Renal Damage in Adenine-Induced Chronic Kidney Disease in Sprague-Dawley Rats**. BioMed research international 2019; 2019:8714363.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=31828139

***ABSTRACT***

Objective: Chronic kidney disease (CKD), including nephrotic syndrome, is a major cause of cardiovascular morbidity and mortality. The literature indicates that CKD is associated with profound lipid disorders largely due to the dysregulation of lipoprotein metabolism which further aggravates the progression of kidney disease. The present study sought to determine the efficacy of atorvastatin treatment on hepatic lipid metabolism and renal tissue damage in CKD rats. Methods: Serum, hepatic and faecal lipid contents and the expression and enzyme activity of molecules involved in cholesterol and triglyceride metabolism, along with kidney function, were determined in untreated adenine-induced CKD, atorvastatin-treated CKD (10 mg/kg/day oral for 24 days) and control rats. Key Findings: CKD resulted in metabolic dyslipidaemia, renal insufficiency, hepatic lipid accumulation, upregulation of 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase, acyl-CoA cholesterol acyltransferase-2 (ACAT2) and the downregulation of LDL receptor protein, VLDL receptor, hepatic lipase, lipoprotein lipase (LPL), lecithin-cholesterol acyltransferase (LCAT) and scavenger receptor class B type 1 (SR-B1). CKD also resulted in increased enzymatic activity of HMG-CoA reductase and ACAT2 together with decreased enzyme activity of lipase and LCAT. Atorvastatin therapy attenuated dyslipidaemia, renal insufficiency, reduced hepatic lipids, HMG-CoA reductase and ACAT2 protein abundance and raised LDL receptor and lipase protein expression. Atorvastatin therapy decreased the enzymatic activity of HMG-CoA reductase and increased enzymatic activity of lipase and LCAT. Conclusions: Atorvastatin improved hepatic tissue lipid metabolism and renal function in adenine-induced CKD rats.

[17] *Momtazi-Borojeni AA, Jaafari MR, Badiee A et al.* **Therapeutic effect of nanoliposomal PCSK9 vaccine in a mouse model of atherosclerosis**. BMC medicine 2019; 17:223.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=31818299

***ABSTRACT***

BACKGROUND: Proprotein convertase subtilisin/kexin 9 (PCSK9) is an important regulator of low-density lipoprotein receptor (LDLR) and plasma levels of LDL cholesterol (LDL-C). PCSK9 inhibition is an efficient therapeutic approach for the treatment of dyslipidemia. We tested the therapeutic effect of a PCSK9 vaccine on dyslipidemia and atherosclerosis. METHODS: Lipid film hydration method was used to prepare negatively charged nanoliposomes as a vaccine delivery system. An immunogenic peptide called immunogenic fused PCSK9-tetanus (IFPT) was incorporated on the surface of nanoliposomes using DSPE-PEG-maleimide lipid (L-IFPT) and adsorbed to Alhydrogel(R) (L-IFPTA(+)). The prepared vaccine formulation (L-IFPTA(+)) and empty liposomes (negative control) were inoculated four times with bi-weekly intervals in C57BL/6 mice on the background of a severe atherogenic diet and poloxamer 407 (thrice weekly) injection. Antibody titers were evaluated 2 weeks after each vaccination and at the end of the study in vaccinated mice. Effects of anti-PCSK9 vaccination on plasma concentrations of PCSK9 and its interaction with LDLR were determined using ELISA. To evaluate the inflammatory response, interferon-gamma (IFN-gamma)- and interleukin (IL)-10-producing splenic cells were assayed using ELISpot analysis. RESULTS: L-IFPTA(+) vaccine induced a high IgG antibody response against PCSK9 peptide in the vaccinated hypercholesterolemic mice. L-IFPTA(+)-induced antibodies specifically targeted PCSK9 and decreased its plasma consecration by up to 58.5% (- 164.7 +/- 9.6 ng/mL, p = 0.0001) compared with the control. PCSK9-LDLR binding assay showed that generated antibodies could inhibit PCSK9-LDLR interaction. The L-IFPTA(+) vaccine reduced total cholesterol, LDL-C, and VLDL-C by up to 44.7%, 51.7%, and 19.2%, respectively, after the fourth vaccination booster, compared with the control group at week 8. Long-term studies of vaccinated hypercholesterolemic mice revealed that the L-IFPTA(+) vaccine was able to induce a long-lasting humoral immune response against PCSK9 peptide, which was paralleled by a significant decrease of LDL-C by up to 42% over 16 weeks post-prime immunization compared to control. Splenocytes isolated from the vaccinated group showed increased IL-10-producing cells and decreased IFN-gamma-producing cells when compared with control and naive mice, suggesting the immune safety of the vaccine. CONCLUSIONS: L-IFPTA(+) vaccine could generate long-lasting, functional, and safe PCSK9-specific antibodies in C57BL/6 mice with severe atherosclerosis, which was accompanied by long-term therapeutic effect against hypercholesterolemia and atherosclerosis.

[18] *Ibrahim AB, Zaki HF, Wadie W et al.* **Simvastatin Evokes An Unpredicted Antagonism For Tamoxifen In MCF-7 Breast Cancer Cells**. Cancer management and research 2019; 11:10011-10028.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=31819634

***ABSTRACT***

Purpose: Tamoxifen (TAM) is a non-steroidal antiestrogen drug, used in the prevention and treatment of all stages of hormone-responsive breast cancer. Simvastatin (SIM) is a lipid-lowering agent and has been shown to inhibit cancer cell growth. The study aimed to investigate the effect of the combination of TAM and SIM in the treatment of estrogen receptor positive (ER+) breast cancer cell line, MCF-7, and in mice-bearing Ehrlich solid tumors. Methods: MCF-7 cells were treated with different concentrations of TAM or/and SIM for 72 hours and the effects of the combination treatment on cytotoxicity, oxidative stress markers, apoptosis, angiogenesis, and metastasis were investigated using

different techniques. In addition, tumor volume, oxidative markers, and inflammatory markers of the combined therapy were explored in mice bearing solid EAC tumors. Results: The results showed that treatment of MCF-7 cells with the combination of 10 microM TAM, and 2 microM SIM significantly inhibited the increase in oxidative stress markers, LDH, and NF-kB induced by TAM. In addition, there was a significant decrease in the total apoptotic ratio, caspase-3 activity, and glucose uptake, while there was a non-significant change in Bax/bcl-2 ratio compared to the TAM-treated group. Using the isobologram equation, the drug interaction was antagonistic with combination index, CI=1.18. On the other hand, the combination regimen decreased VEGF, and matrix metalloproteinases, MMP 2&9 compared to TAM-treated cells. Additionally, in vivo, the combination regimen resulted in a non-significant decrease in the tumor volume, decreased oxidative markers, and the protein expression of TNF-alpha, and NF-kappaB compared to the TAM treated group. Conclusion: Although the combination regimen of TAM and SIM showed an antagonistic drug interaction in MCF-7 breast cancer, it displayed favorable antiangiogenic, anti-metastatic, and anti-inflammatory effects.

[19] *Heuvelman VD, Van Raalte DH, Smits MM*. **Cardiovascular effects of GLP-1 receptor agonists: from mechanistic studies in humans to clinical outcomes**. Cardiovascular research 2019.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=31825468
***ABSTRACT***
Type 2 diabetes mellitus (T2DM) is currently one of the most prevalent diseases, with as many as 415 million patients worldwide. T2DM is characterised by elevated blood glucose levels and is often accompanied by several comorbidities, such as cardiovascular disease (CVD). Treatment of T2DM is focused on reducing glucose levels by either lifestyle changes or medical treatment. One treatment option for T2DM is based on the gut-derived hormone glucagon-like peptide 1 (GLP-1). GLP-1 reduces blood glucose levels by stimulating insulin secretion, however, it is rapidly degraded, and thereby losing its glycaemic effect. GLP-1 receptor agonists (GLP-1RAs) are immune to degradation, prolonging the glycaemic effect. Lately, GLP-1RAs have spiked the interest of researchers and clinicians due to their beneficial effects on CVD. Preclinical and clinical data have demonstrated that GLP-1 receptors are abundantly present in the heart and that stimulation of these receptors by GLP-1 has several effects. In this review, we will discuss the effects of GLP-1RA on heart rate, blood pressure, microvascular function, lipids and inflammation, as measured in human mechanistic studies, and suggest how these effects may translate into the improved CV outcomes as demonstrated in several trials.

[20] *Gutierrez JA, Aday AW, Patel MR, Jones WS*. **Polyvascular Disease: Reappraisal of the Current Clinical Landscape**. Circulation. Cardiovascular interventions 2019; 12:e007385.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=31833412
***ABSTRACT***
Atherosclerosis within 2 or more arterial beds has been termed polyvascular disease. Although polyvascular disease has long been associated with heightened cardiovascular risk, much is still unknown regarding its pathophysiology and management. In this past decade, the field of cardiovascular disease has experienced exponential growth in terms of antithrombotic and lipid-lowering therapies aimed at mitigating ischemic events. This review describes the inherent risk associated with polyvascular disease in contemporary observational and clinical trial populations and summarizes novel therapies in this high-risk population.

[21] *Page MM, Bell DA, Watts GF*. **Widening the spectrum of genetic testing in familial hypercholesterolaemia: Will it translate into better patient and population outcomes?** Clinical genetics 2019.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=31833051
***ABSTRACT***
Familial hypercholesterolaemia (FH) is caused by pathogenic variants in LDLR, APOB or PCSK9. Impaired low-density lipoprotein (LDL) receptor function leads to decreased LDL catabolism and premature atherosclerotic cardiovascular disease (ASCVD). Thousands of LDLR variants are known, but assignation of pathogenicity requires accurate phenotyping, family studies and assessment of LDL receptor function. Precise, genetic diagnosis of FH using targeted next generation sequencing allows for optimal treatment, distinguishing FH from pathogenically distinct disorders requiring different treatment. Polygenic hypercholesterolaemia resulting from an accumulation of LDL cholesterol-raising single nucleotide polymorphisms (SNPs) could also be suspected by this approach. Similarly, ASCVD risk could be estimated by broader sequencing of cholesterol and non-cholesterol related genes. Both of these areas require further research. The clinical management of FH, focusing on the primary or secondary prevention of ASCVD, has been boosted by PCSK9 inhibitor therapy. The efficacy of PCSK9 inhibitors in homozygous FH may be partly predicted by the LDLR variants. While expanded genetic testing in FH is clinically useful in providing an accurate diagnosis and enabling cost-effective testing of relatives, further research is needed to establish its value in improving clinical outcomes. This article is protected by copyright. All rights reserved.

[22] *Diaz Rodriguez A, Mantilla Morato T*. **LDL as a therapeutic objective**. Clinica e investigacion en arteriosclerosis : publicacion oficial de la Sociedad Espanola de Arteriosclerosis 2019; 31 Suppl 2:1-15.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=31813617
***ABSTRACT***
The incidence of atherosclerotic cardiovascular disease has increased in the developed countries. Dyslipidemia is a primary major risk factor for atherosclerotic cardiovascular disease and LDL lowering is one of the main objectives. Although treatment goals for dyslipidemias should be personalized in every patient, statins are cost-effective in primary and secondary prevention of atherosclerotic cardiovascular disease. New treatments with higher power and greater decreases in LDL, PSCK9 inhibitors, have made a new breakthrough in atherosclerotic cardiovascular disease treatment. The 2019 guidelines for de management of dyslipidemias: lipid modification to reduce cardiovascular risk (European Society of Cardiology/European Atherosclerosis Society) with the level of evidence and the strength of the recommendations can facilitate the best decisions and benefits to our patients in clinical practice.

[23] *Pedro-Botet J, Pinto X*. **LDL-cholesterol: The lower the better**. Clinica e investigacion en arteriosclerosis : publicacion oficial de la Sociedad Espanola de Arteriosclerosis 2019; 31 Suppl 2:16-27.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=31813618
***ABSTRACT***
The reduction of low density lipoprotein-cholesterol (LDL-chol) has been associated with a decrease in cardiovascular morbidity and mortality. It has been demonstrated that there is no value of LDL-chol below which there ceases to be a preventive benefit with its reduction, and neither has it been

observed that there is a higher incidence of secondary effects associated with lower concentrations of LDL-chol. Although there is a wide range of lipid-lowering drugs available, a high percentage of patients do not achieve the desired LDL-chol levels. The high-potency statins reduce the LDL-chol by 15-30%, and can double the percentage of patients that reach their desired level. This combination has shown to be safe and effective in the primary and secondary prevention of cardiovascular disease. Another option is the combination of statins with exchange resins, although this requires a more complex management. The inhibition of PCSK9 protein with monoclonal antibodies reduces the LDL-chol by more than 60%, and is effective in the prevention of cardiovascular disease. However, due to its cost, its use is restricted to patients with ischaemia or familial hypercholesterolaemia that do not achieve the desired levels with conventional drugs. The evidence base as regards the benefit and safety of achieving the desired levels of LDL-chol is very wide and is still increasing. In the next few years, it may be necessary to adjust the intensity of the hypercholesterolaemia treatment to the level of vascular risk of the patients, and to the level of reduction necessary to achieve the therapeutic targets. This will result in a more effective cardiovascular prevention and in a better quality of life, particularly in the large group of patients at higher vascular risk.

[24] *Almourani R, Chinnakotla B, Patel R et al.* **Diabetes and Cardiovascular Disease: an Update**. Current diabetes reports 2019; 19:161.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=31828525
***ABSTRACT***
PURPOSE OF REVIEW: Cardiovascular disease (CVD) is the leading cause of mortality in people with diabetes. Our aim was to review the pathophysiology of CVD in diabetes, review related landmark trials, and discuss the cardiovascular benefit of glucose-lowering agents. We have also discussed the role of controversial anti-platelet therapy. RECENT FINDINGS: Recent studies have shown the impact of glucose-lowering agents on CVD in people with diabetes. Statins are now recommended for all patients with diabetes over the age of 40 regardless of the LDL level given the cardiovascular benefit of these drugs. Current recommendations suggest a blood pressure < 130/80 for individuals with high cardiovascular risk. Cardiovascular risk reduction should be an important part of the management of diabetes. Focusing solely on glycemic control may not be the best therapeutic strategy. Multifactorial risk reduction should be taken into account. Lipid-lowering agents and anti-hypertensives should be a corner stone of treatment of diabetes. With currently available data, glucose-lowering agents with cardiovascular benefit should be started early in the disease process.

[25] *Vyas HS, Upadhyay KK, Devkar RV*. **miRNAs Signatures In Patients With Acute Liver Injury: Clinical Concerns and Correlations**. Current molecular medicine 2019.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=31823701
***ABSTRACT***
Non-coding RNAs can be highly exploited for their biological significance in living systems. miRNAs are in upstream position of cellular regulation cascade and holds merit in its state. A wealth of information is available on wide variety of miRNAs that undergo alterations in experimentally induced models of liver injuries. The underlying mechanisms governed by these miRNAs have been inferred through cell-based experiments but the scientific knowledge on miRNA signatures in patients with liver injury are primordial and lack scientific clarity. Hence, it is crucial to get insight into the status and synergy of miRNAs in patients, with varying degree of acute toxic manifestations in liver. Though, some miRNAs

are being investigated in clinical trials, a major research lacunae exist with regard to the functional role of other miRNAs in liver diseases. This review article is a meticulous compile of disease based or drug/alcohol based acute liver injuries in patients and resultant alteration in their miRNA profile. Investigative reports on underlying miRNA-liver crosstalk in cell based or murine models is also discussed herein to draw correlation with clinical findings.

[26] *Hansen M, Kuhlman ACB, Sahl RE et al.* **Corrigendum to "Inflammatory biomarkers in patients in simvastatin treatment: No effect of co-enzyme Q10 supplementation" [Cytokine 113 (2019) 393-399]**. Cytokine 2019:154941.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=31818692
***ABSTRACT***

[27] *Farmakis I, Zafeiropoulos S, Pagiantza A et al.* **Low-density lipoprotein cholesterol target value attainment based on 2019 ESC/EAS guidelines and lipid-lowering therapy titration for patients with acute coronary syndrome**. European journal of preventive cardiology 2019:2047487319891780.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=31818140
***ABSTRACT***

[28] *Takada I, Makishima M*. **Peroxisome proliferator-activated receptor agonists and antagonists: a patent review (2014-present)**. Expert Opin Ther Pat 2019:1-13.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=31825687
***ABSTRACT***
Introduction: Peroxisome proliferator-activated receptors (PPARs), PPARalpha, PPARdelta, and PPARgamma, play an important role in the regulation of various physiological processes, specifically lipid and energy metabolism and immunity. PPARalpha agonists (fibrates) and PPARgamma agonists (thiazolidinediones) are used for the treatment of hypertriglyceridemia and type 2 diabetes, respectively. PPARdelta activation enhances mitochondrial and energy metabolism but PPARdelta-acting drugs are not yet available. Many synthetic ligands for PPARs have been developed to expand their therapeutic applications.Areas covered: The authors searched recent patent activity regarding PPAR ligands. Novel PPARalpha agonists, PPARdelta agonists, PPARgamma agonists, PPARalpha/gamma dual agonists, and PPARgamma antagonists have been claimed for the treatment of metabolic disease and inflammatory disease. Methods for the combination of PPAR ligands with other drugs and expanded application of PPAR agonists for bone and neurological disease have been also claimed.Expert opinion: Novel PPAR ligands and the combination of PPAR ligands with other drugs have been claimed for the treatment of mitochondrial disease, inflammatory/autoimmune disease, neurological disease, and cancer in addition to metabolic diseases including dyslipidemia and type 2 diabetes. Selective therapeutic actions of PPAR ligands should be exploited to avoid adverse effects. More basic studies are needed to elucidate the molecular mechanisms of selective actions.

[29] *Liu B, Wang C, Qu Y*. **Treatment of Arachnoid Cyst With Spontaneous Hemorrhage With Atorvastatin**. Frontiers in pharmacology 2019; 10:1343.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=31824309
***ABSTRACT***

As one of the common neurological diseases, pediatric middle fossa arachnoid cysts(MFACs) can develop intracystic hemorrhage and subdural hematoma. Risk factors for pediatric arachnoid cyst rupture/hemorrhage is very complicated in mechanism. Although surgery is the first choice for children with MFACs and subdural hematoma, the rate of recurrence of the subdural hematoma is very high after 1 or more surgeries. Atorvastatin has proven to be a bold and safe choice in the management of subdural hematoma with mild symptoms. The present study has described a 7-year-old child with a recurrent rupture of arachnoid cyst develops into a subdural hematoma. We demonstrate that atorvastatin is safe and effective in pediatric patient who has failed surgical treatment of middle fossa arachnoid cyst and subdural hematoma. The patient received atorvastatin monotherapy, once daily for the first week, with an initial dose of 5 mg, followed by 10 mg once daily for 7 weeks. In the third month after the initial treatment, the neurological function recovered, and the hematoma completely resolved. This case report supports the concept that atorvastatin can promote the absorption of subdural hematoma.

[30] *Cosin-Sales J, Freixa R, Bravo M et al.* **Impact of different models of improvement of continuity of care on lipid control and the delay of visits to cardiology**. Future cardiology 2019.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=31820660
***ABSTRACT***
Aims: To analyze the impact of implementing three different models of continuity of care on the delay of first visits to the cardiologist (management end point) and on LDL-cholesterol control rates among patients with atherosclerotic vascular disease (clinical end point). Methods: Observational, longitudinal and retrospective study of patients with cardiovascular disease and LDL-cholesterol >/=70 mg/dl attended in three hospitals (H1/H2/H3). In H1 and H2, a virtual system (telecardiology) was developed (in H1, internal audits and specific medical education were also performed). In H3 a cardiologist was integrated into the primary care center. Results: The delay of visits to cardiologist significantly improved from 66.5 +/- 29.1 days to 34.1 +/- 14.1 days ($p < 0.001$), as well as the intensification of lipid-lowering treatment and the achievement of lipid goals. LDL-cholesterol control rates were higher in H1 and the reduction of the delay of visits in H3. Conclusion: Continuity of care is associated with improvements in management and clinical end points.

[31] *Azari S, Rezapour A, Omidi N et al.* **Cost-effectiveness analysis of PCSK9 inhibitors in cardiovascular diseases: a systematic review**. Heart failure reviews 2019.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=31832834
***ABSTRACT***
AIMS: To assess the cost-effectiveness of pro-protein convertase subtilisin/kexin type 9 (PCSK9) inhibitors in cardiovascular disease. METHODS AND RESULTS: We performed a comprehensive search strategy in electronic databases from January 2015 to January 2019. Out of 475 articles, 16 were entered into the study. Quality-adjusted life year, life years gained (LYG), annual cost, and the incremental cost-effectiveness ratio (ICER) regarding the use of PCSK9 inhibitors were considered as the key outcomes. The cost-effectiveness threshold varied from $45,000 in Spain to $150,000 in the USA. The annual cost of PCSK9 inhibitors for studies undertaken in the USA was in the range of $14,000 to $15,000, while it was about $7000 for other developed countries. The results showed that reduction in the price of PCSK9 inhibitors changed from 20 to 88%. The means of QALY were 0.65 and 0.67 in the Markov and Cardiovascular Disease Policy Modeling (CVDPM) models; also, the ICER means were

$197,707 and $625,555 for the Markov and CVDPM model, respectively. CONCLUSION: According to the current study, the effectiveness of PCSK9 inhibitors is well documented, although all studies pointed out a higher cost of these inhibitors. TRIAL REGISTRATION: This study was registered within the International Prospective Register of Systematic Reviews (PROSPERO) database of the University of York (CRD42018088472).

[32] *Muhleck F, Laufs U*. **[Primary prevention of coronary heart disease : Evidence-based drug treatment]**. Herz 2019.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=31822926
***ABSTRACT***
Coronary artery disease (CAD) is the most frequent cause of morbidity and mortality worldwide. Lifestyle modifications and drug treatment of cardiovascular risk factors are able to effectively prevent CAD. The basis of prevention is the assessment of the individual cardiovascular risk, e.g. by using a validated risk score. Documented evidence for prevention of CAD is available for the control of hypertension using angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB) and calcium antagonists, for the treatment of hypercholesterolemia using statins, ezetimibe and proprotein convertase subtilisin-kexin type 9 (PCSK-9) inhibitors and for the treatment of type 2 diabetes mellitus with metformin, sodium-glucose transporter 2 (SGLT-2) inhibitors and glucagon-like peptide 1 (GLP-1) agonists. There is no positive benefit-risk ratio for people with a low risk in the use of acetylsalicylic acid in primary prevention, in contrast to the positive recommendations for secondary prevention. There is no evidence for the efficacy of primary prevention with beta blockers, dipeptidyl peptidase 4 (DPP-4) inhibitors, glitazones, sulfonylureas or insulin. Similarly, there is no evidence for drug treatment of obesity, any supplementation with vitamins or hormone preparations or omega3 fatty acids.

[33] *Guler S, Nakus E, Utku U*. **Risk factors for ischemic stroke and stroke subtypes in patients with chronic kidney disease**. Ideggyogyaszati szemle 2019; 72:389-396.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=31834682
***ABSTRACT***
Background and purpose: The aim of this study was to compare ischemic stroke subtypes with the effects of risk factors, the relationship between grades of kidney disease and the severity of stroke subtypes. Methods: The current study was designed retrospectively and performed with data of patients who were hospitalised due to ischemic stroke. We included 198 subjects who were diagnosed with ischemic stroke of Grade 3 and above with chronic kidney disease. Results: In our study were reported advanced age, coronary artery disease, moderate kidney disease as the most frequent risk factors for cardioembolic etiology. Hypertension, hyperlipidemia, smoking and alcohol consumption were the most frequent risk factors for large-artery disease. Female sex and anaemia were the most frequent risk factors for small-vessel disease. Dialysis and severe kidney disease were the most frequent risk factors in unknown etiologies, while male sex, diabetes mellitus, prior stroke and mild kidney disease were the most frequent risk factors for other etiologies. National Institute of Health Stroke Scale (NIHSS) scores were lower for small-vessel disease compared with other etiologies. This relation was statistically significant (p=0.002). Conclusion: In order to improve the prognosis in ischemic stroke with chronic kidney disease, the risk factors have to be recognised and the treatment options must be modified according to those risk factors.

[34] *Xu SM, Yan J, Li D et al.* **Implementation of a reference-scaled average bioequivalence approach for highly variable generic drug products of atorvastatin in Chinese subjects**. International journal of clinical pharmacology and therapeutics 2019.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=31829925
***ABSTRACT***
OBJECTIVE: The purpose of this study was to evaluate the bioequivalence of two formulations of atorvastatin using the reference-scaled average bioequivalence (RSABE) method and to study the pharmacokinetics of atorvastatin in healthy Chinese subjects under fed conditions. MATERIALS AND METHODS: A single-dose, randomized, open-label, four-way crossover study was conducted in healthy Chinese subjects after informed consent was obtained. Healthy subjects were randomly assigned to receive 20 mg of either the test or reference formulation, following a 7-day washout period. The formulations were considered bioequivalent if 90% confidence intervals (CIs) for the ln-transformed ratios and ratio of geometric means (GMR) of AUC and Cmax of atorvastatin were within the bioequivalence range (80 - 125%). Plasma atorvastatin, ortho-hydroxy atorvastatin and para-hydroxy atorvastatin concentrations were analyzed by liquid chromatography-tandem mass spectrometry. Tolerability was assessed during the entire study period. RESULTS: ANOVA indicated that the period, sequence, and formulation had no significant effect on the pharmacokinetic parameters ($p > 0.05$). The test formulation was bioequivalent to the marketed formulation as the 90% CIs for natural log-transformed ratios of atorvastatin of Cmax (88.45 - 103.57%), AUC0-t (98.08 - 104.89%) and AUC0-infinity (98.15 - 104.87%) were within equivalence limits (80 - 125%). No serious adverse events were found among the subjects. CONCLUSION: The RSABE approach was successful in evaluating the bioequivalence of these two formulations. This study confirmed that test and reference atorvastatin calcium tablets were bioequivalent under fed condition..

[35] *Arzani A*. **Coronary artery plaque growth: A two-way coupled shear stress-driven model**. International journal for numerical methods in biomedical engineering 2019:e3293.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=31820589
***ABSTRACT***
Atherosclerosis in coronary arteries can lead to plaque growth, stenosis formation, and blockage of the blood flow supplying the heart tissue. Several studies have shown that hemodynamics play an important role in the growth of coronary artery plaques. Specifically, low wall shear stress (WSS) appears to be the leading hemodynamic parameter promoting atherosclerotic plaque growth, which in turn influences the blood flow and WSS distribution. Therefore, a two-way coupled interaction exists between WSS and atherosclerosis growth. In this work, a computational framework was developed to study the coupling between WSS and plaque growth in coronary arteries. Computational fluid dynamics (CFD) was used to quantify WSS distribution. Surface mesh nodes were moved in the inward normal direction according to a growth model based on WSS. After each growth stage, the geometry was updated and the CFD simulation repeated to find updated WSS values for the next growth stage. One hundred twenty growth stages were simulated in an idealized tube and an image-based left anterior descending artery. An automated framework was developed using open-source software to couple CFD simulations with growth. Changes in plaque morphology and hemodynamic patterns during different growth stages are presented. The results show larger plaque growth towards the downstream segment of the plaque, agreeing with the reported clinical observations. The developed

framework could be used to establish hemodynamic-driven growth models and study the interaction between these processes.

[36] *Knight-Greenfield A, Quitlong Nario JJ, Vora A et al.* **Associations Between Features of Nonstenosing Carotid Plaque on Computed Tomographic Angiography and Ischemic Stroke Subtypes**. Journal of the American Heart Association 2019; 8:e014818.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=31818209
***ABSTRACT***
Background Thromboembolism from nonstenosing carotid plaques may be an underrecognized cause of embolic strokes of undetermined source (ESUS). We evaluated the association between features of nonstenosing atherosclerotic plaque on computed tomographic angiography and ESUS. Methods and Results We identified consecutive acute ischemic stroke patients from 2011 to 2015 who had unilateral anterior territory infarction on brain magnetic resonance imaging and a neck computed tomographic angiography. We included ESUS cases and as controls, cardioembolic strokes. Patients with >/=50% internal carotid artery atherosclerotic stenosis ipsilateral to the stroke were excluded from this analysis. Reviewers blinded to infarct location and stroke cause retrospectively evaluated computed tomographic angiography studies for specific plaque features including thickness of the total, soft, and calcified plaque; presence of ulceration; and perivascular fat attenuation. Paired t tests and McNemar's test for paired data were used to compare plaque features ipsilateral versus contralateral to the side of infarction. Ninety-one patients with ESUS or cardioembolic stroke were included in this study. Total plaque thickness was greater on the infarcted side (2.1+/-2.0 mm) than the contralateral side (1.2+/-1.5 mm) (P=0.006) among ESUS cases, but not among cardioembolic cases (1.9+/-1.6 mm versus 1.8+/-1.6 mm) (P=0.32). Conclusions Among ESUS cases, total plaque thickness was greater ipsilateral to the side of infarction than on the contralateral, stroke-free side. No such side-to-side differences were apparent in cardioembolic strokes. Our findings suggest that nonstenosing large-artery atherosclerotic plaques represent one underlying mechanism of ESUS.

[37] *Riggs KA, Joshi PH, Khera A et al.* **Impaired HDL Metabolism Links GlycA, A Novel Inflammatory Marker, with Incident Cardiovascular Events**. Journal of clinical medicine 2019; 8.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=31817053
***ABSTRACT***
High-density lipoproteins (HDL) exert anti-atherosclerotic effects via reverse cholesterol transport, yet this salutary property is impaired in the setting of inflammation. GlycA, a novel integrated glycosylation marker of five acute phase reactants, is linked to cardiovascular (CV) events. We assessed the hypothesis that GlycA is associated with measures of impaired HDL function and that dysfunctional HDL may contribute to the association between GlycA and incident CV events. Baseline measurements of HDL cholesterol (HDL-C), HDL particle concentration (HDL-P), apoliprotein A1 (Apo A1), cholesterol efflux capacity, GlycA and high-sensitivity C-reactive protein (hs-CRP) were obtained from the Dallas Heart Study, a multi-ethnic cohort of 2643 adults (median 43 years old; 56% women, 50% black) without cardiovascular disease (CVD). GlycA was derived from nuclear magnetic resonance imaging. Participants were followed for first nonfatal MI, nonfatal stroke, coronary revascularization, or CV death over a median of 12.4 years (n = 197). The correlation between GlycA and hs-CRP was 0.58 ($p < 0.0001$). In multivariate models with HDL-C, GlycA was directly associated with HDL-P and Apo A1 and inversely associated with cholesterol efflux (standardized beta estimates: 0.08, 0.29, -0.06,

respectively; all p </= 0.0004) GlycA was directly associated with incident CV events (adjusted hazard ratio (HR) for Q4 vs. Q1: 3.33, 95% confidence interval (CI) 1.99, 5.57). Adjustment for cholesterol efflux mildly attenuated this association (HR for Q4 vs. Q1: 3.00, 95% CI 1.75 to 5.13). In a multi-ethnic cohort, worsening inflammation, as reflected by higher GlycA levels, is associated with higher HDL-P and lower cholesterol efflux. Impaired cholesterol efflux likely explains some of the association between GlycA and incident CV events. Further studies are warranted to investigate the impact of inflammation on HDL function and CV disease.

[38] *Nelson AJ, Stephenson DJ, Cardona CL et al.* **Macrophage Polarization is Linked to Ca2+-Independent Phospholipase A2beta-Derived Lipids and Cross-Cell Signaling in Mice**. Journal of lipid research 2019.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=31818877
***ABSTRACT***
Phospholipases A2 (PLA2s) catalyze hydrolysis of the sn-2 substituent from glycerophospholipids to yield a free fatty acid (i.e., arachidonic acid), which can be metabolized to pro- or anti-inflammatory eicosanoids. Macrophages modulate inflammatory responses and are affected by Ca(2+)-independent PLA2beta (iPLA2beta). Here, we assessed the link between iPLA2beta-derived lipids (iDLs) and macrophage polarization. Macrophages from wild-type (WT) and knockout (iPLA2beta(-/-)) mice were classically (M1 pro-inflammatory phenotype) or alternatively (M2 anti-inflammatory phenotype) activated, and eicosanoid production was determined by ultra-performance liquid chromatography electrospray ionization MS/MS. As a genotypic control, we performed similar analyses on macrophages from RIP.iPLA2beta.Tg mice with selective iPLA2beta overexpression in beta-cells. Compared with WT, generation of select pro-inflammatory prostaglandins was lower in iPLA2beta(-/-) knockouts, and that of a specialized pro-resolving lipid mediator (SPM), resolvin D2, was higher; both changes are consistent with the M2 phenotype. Conversely, macrophages from RIP.iiPLA2beta.Tg mice exhibited an opposite landscape, one associated with the M1 phenotype: namely, increased production of proinflammatory eicosanoids (6-keto PGF1alpha, PGE2, LTB4) and decreased ability to generate resolvin D2. These changes were not linked with secretory PLA2 or cytosolic PLA2alpha or with leakage of the transgene. Thus, we report previously unidentified links between select iPLA2beta-derived eicosanoids, an SPM, and macrophage polarization. Importantly, our findings reveal for the first time that beta-cell iPLA2beta-derived signaling can predispose macrophage responses. These findings suggest that iDLs play critical roles in macrophage polarization, and we posit that they could be targeted therapeutically to counter inflammation-based disorders.

[39] *Jiayu Y, Botta A, Simtchouk S et al.* **Egg white consumption increases GSH and lowers oxidative damage in 110-week-old geriatric mice hearts**. The Journal of nutritional biochemistry 2019; 76:108252.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=31816560
***ABSTRACT***
The number of geriatrics with an advanced age is rising worldwide, with attendant cardiovascular disorders, characterized by elevated oxidative stress. Such oxidative stress is accelerated by an age-related loss of critical antioxidants like glutathione (GSH) and dietary solutions to combat this loss does not exist. While egg white is rich in sulphur amino acids (AAs), precursors for GSH biosynthesis, whether they can increase sulphur AA in vivo and augment GSH in the aged myocardium remain

unclear. We hypothesized that egg white consumption increases GSH and reduces oxidative damage and inflammation in the geriatric heart. To this end, 101-102 week-old mice were given a AIN 76A diet supplemented with either 9% w/w egg white powder or casein for 8 weeks. Subsequent analysis revealed that egg white increased serum sulphur AA and cardiac GSH, while reducing the cysteine carrying transporter SNAT-2 and elevating glutamine transporter ASCT2 in the heart. Increased GSH was accompanied by elevated expression of GSH biosynthesis enzyme glutathione synthase as well as mitochondrial antioxidants like superoxide dismutase 2 and glutathione peroxidase 1 in egg white-fed hearts. These hearts also demonstrated lower oxidative damage of lipids (4-hydroxynonenal) and proteins [nitrotyrosine] with elevated anti-inflammatory IL-10 gene expression. These data demonstrate that even at the end of lifespan, egg whites remain effective in promoting serum sulphur AAs and preserve cardiac GSH with potent anti-oxidant and mild anti-inflammatory effects in the geriatric myocardium. We conclude that egg white intake may be an effective dietary strategy to attenuate oxidative damage in the senescent heart.

[40] *Solomando JC, Antequera T, Gonzalez-Mohino A, Perez-Palacios T*. **Fish oil/lycopene microcapsules as a source of EPA and DHA: a case study on spreads**. Journal of the science of food and agriculture 2019.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=31821560
***ABSTRACT***
BACKGROUND: The consumption of Omega-3 fatty acids has many beneficial effects for human health but the intake of foods rich in these fatty acids are not enough to achieve the recommended quantity per person and day and their direct addition in foods cause oxidation and unacceptable rancidity and off-flavor. Taking account all these aspects, the present study was firstly aimed to develop stables microcapsules of fish oil (omega-3 PUFA) and lycopene (antioxidant), and investigate their effect on different spreads. RESULTS: The inclusion of different proportions of lycopene in fish oil did not show great benefits in the quality characteristics of emulsions and microcapsules. After the addition of fish oil and fish oil + lycopene microcapsules to dry-cured ham and cheese spread, no significant differences were found in the proximal composition and oxidative stability, while fatty acids composition and sensory analysis were influenced. The EPA and DHA content increased with the fish oil content in both products, but decreased significantly after storage in the cheese spreads. Addition of microcapsules did not significantly influence on quantitative-descriptive and acceptability sensory analyses in dry-cured spreads, but it negatively affected the flavor of cheese spreading creams. CONCLUSION: There is no need of adding antioxidant to improve the stability of the fish oil microcapsules of the present study, which are appropriate as EPA and DHA vehicles to enrich meat derived spreading creams. 

[41] *Han T, Lv Y, Wang S et al.* **Pioglitazone prevents cholesterol gallstone formation through the regulation of cholesterol homeostasis in guinea pigs with a lithogenic diet**. Lipids in health and disease 2019; 18:218.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=31829191
***ABSTRACT***
BACKGROUND: The cholesterol gallstones diseases (CGD) is highly correlated with metabolic syndrome and type 2 diabetes. The present study aimed to investigate preventive effects of pioglitazone (PIO), an antidiabetic drug, on the CGD in guinea pigs fed with a lithogenic diet (LD). METHODS: The guinea pigs

were fed with the LD for 8 weeks. All guinea pigs were grouped as follows: low fat diet; LD; LD plus PIO (4 mg/kg); LD plus PIO (8 mg/kg); LD plus ezetimibe (EZE) (2 mg/kg). Gallbladder stones were observed using microscopy. The profile of biliary composition, and blood glucose, insulin and lipid were analyzed. The liver or ileum was harvested for determinations of hydroxyl-methyl-glutaryl-CoA reductase (HMGCR), sterol regulatory element-binding proteins 2 (SREBP2), 7alpha-hydroxylase (CYP7A1), adenosine triphosphate-binding cassette (ABC) sterol transporters G5 and G8 (ABCG5, ABCG8), bile salt export pump (BSEP), Niemann-Pick C1-Like 1 (NPC1L1) and acetyl-coenzyme A cholesterol acyltransferase (ACAT2) by Western blot. The gallbladders were used for histological examination. RESULTS: The LD successfully induced gallstone. Both pioglitazone and ezetimibe prevented gallstone formation, as well as hepatic and cholecystic damages. Pioglitazone significantly decreased HMGCR and SREBP2, but increased CYP7A1, ABCG5, ABCG8, and BSEP in the liver. Pioglitazone also remarkably decreased NPC1L1 and ACAT2, while increased ABCG5/8 in the intestine. The beneficial alterations of cholesterol and bile acids in the bile, as well as profile of glucose, insulin and lipid in the blood were found in the guinea pigs treated with pioglitazone. CONCLUSION: Pioglitazone has a noticeable benefit towards the CGD, which is involved in changes of synthesis, transformation, absorption, and transportation of cholesterol.

[42] *Perez-Calahorra S, Laclaustra M, Marco-Benedi V et al.* **Comparative efficacy between atorvastatin and rosuvastatin in the prevention of cardiovascular disease recurrence**. Lipids in health and disease 2019; 18:216.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=31829197
***ABSTRACT***
BACKGROUND: There is no randomized clinical trials with recurrence of atherosclerotic cardiovascular disease (ASCVD) as a major outcome with rosuvastatin. In order to analyze potential differences in the clinical response to atorvastatin and rosuvastatin in secondary ASCVD prevention, we have analyzed the clinical evolution of those subjects of the Dyslipemia Registry of the Spanish Society of Arteriosclerosis (SEA) who at the time of inclusion in the Registry had already suffered an ASCVD. METHODS: This observational, retrospective, multicenter, national study was designed to determine potential differences between the use of atorvastatin and rosuvastatin in the ASCVD recurrence. Three different follow-up start-times were performed: time of inclusion in the registry; time of first event if this occurred after 2005, and time of first event without date restriction. RESULTS: Baseline characteristics were similar between treatment groups. Among atorvastatin or rosuvastatin users, 89 recurrences of ASCVD were recorded (21.9%), of which 85.4% were coronary. At the inclusion of the subject in the registry, 345 participants had not suffered a recurrence yet. These 345 subjects accumulated 1050 person-years in a mean follow-up of 3 years. Event rates were 2.73 (95% CI: 1.63, 4.25) cases/100 person-years and 2.34 (95% CI: 1.17, 4.10) cases/100 person-years in the atorvastatin and rosuvastatin groups, respectively. There were no statistically significant differences between the two groups independently of the follow-up start-time. CONCLUSIONS: This study does not find differences between high doses of rosuvastatin and atorvastatin in the recurrence of ASCVD, and supports their use as clinically equivalent in secondary prevention of ASCVD.

[43] *Sun L, Liu X, Li W, Jia D*. **HDL-C to hsCRP ratio is associated with left ventricular diastolic function in absence of significant coronary atherosclerosis**. Lipids in health and disease 2019; 18:219.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=31831002

***ABSTRACT***
BACKGROUND: High-density lipoprotein cholesterol (HDL-C) is considered as a protective marker of coronary atherosclerotic disease (CAD). It is still not clear if HDL-C is associated with left ventricular (LV) diastolic function in an inflammation-related manner in absence of significant coronary atherosclerosis. METHODS: 392 patients who complained of chest pain and were suspected of CAD without heart failure were enrolled in this study. Coronary angiography or coronary artery CT scan was performed to detect coronary atherosclerosis. Transthoracic echocardiography was performed to evaluate cardiac function. Plasma level of HDL-C and high-sensitive C-reactive protein (hsCRP) were determined in each subject. Relationship between HDL-C/hsCRP ratio and LV diastolic function in subjects without significant coronary atherosclerosis was investigated. RESULTS: 204 subjects without significant coronary plaques were analyzed finally, including 84 males and 120 females whose ages ranged from 30 to 84 years old. When divided into HDL-C/hsCRP quartiles, those in the fourth quartile demonstrated the best diastolic function (E/e' 10.14 +/- 2.87, P = 0.02 ). HDL-C/hsCRP was the most significant factor correlated with E/e' in univariate regression analysis (r = - 0.232, P < 0.001) and multiple regression analysis adjusted by other factors (standardized beta = - 0.258 , P < 0.0005 ). In logistic regression, HDL-C/hsCRP was proved to be a protective factor of LV diastolic dysfunction E/e' > 14 (OR = 0.649, 95%CI 0.444-0.948,P = 0.025 ). The sensitivity and specificity of using HDL-C/hsCRP < 0.98 to predict LV diastolic dysfunction were 64.3% and 56.2%, respectively. HDL-C/hsCRP ratio presented a reduced trend as increasing rate of CV risk factors. CONCLUSIONS: HDL-C/hsCRP ratio strongly correlates with LV diastolic function in absence of significant coronary atherosclerosis. Low HDL-C/hsCRP ratio tends to relate with LV diastolic dysfunction.

[44] *Zanetti HR, Goncalves A, Teixeira Paranhos Lopes L et al.* **Effects of Exercise Training and Statin Use in People Living with Human Immunodeficiency Virus with Dyslipidemia**. Med Sci Sports Exerc 2020; 52:16-24.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=31834252

***ABSTRACT***
PURPOSE: To evaluate the effects of the combination of exercise training (ET) and statins in people living with human immunodeficiency virus. METHODS: This was a randomized, double-blind, placebo-controlled clinical trial. Eighty-three people living with human immunodeficiency virus were assigned to either placebo (PL), statins (STA), PL + ET (PLET) or STA + ET (STAET) groups. Volunteers assigned to STA and STAET groups were administered 10 mg of rosuvastatin, whereas the PL and PLET groups were administered a placebo. The PLET and STAET groups performed ET three times a week. Before and after the 12-wk follow-up, the volunteers underwent to anthropometric assessment and blood collection to evaluate lipid profile, cardiovascular markers, inflammatory profile; a Doppler ultrasound examination, muscle strength (MS) and cardiorespiratory fitness (CF) tests were performed. RESULTS: There was a decrease in total cholesterol, triglycerides, low-density lipoprotein, C-reactive protein, fibrinogen, interleukin (IL)-1beta and right carotid intima-media thickness in the STA, PLET, and STAET groups compared with PL group (P < 0.001). Furthermore, there was a decrease in total cholesterol, triglycerides, low-density lipoprotein, IL-1beta, IL-6, and IL-8 levels and in left and right carotid intima-media thickness and an increase in HDL-c levels in the STAET groups compared with the STA (P </= 0.001) and PLET groups (P </= 0.001). There was an increase in IL-10 levels, peak-systolic velocity, end-diastolic velocity, wall shear rate in the PLET and STAET groups compared with the PL (P </= 0.001) and STA groups (P </= 0.001). The PLET and STAET groups reduced body fat mass, body fat percentage and

increased lean body mass, MS and CF compared with PL (P </= 0.001) and STA (P </= 0.001) groups. CONCLUSIONS: The combination of ET and statins is useful to enhance lipid and inflammatory profiles, reduce cardiovascular disease markers, and improve Doppler ultrasound findings, MS and CF in people living with HIV.

[45] *Hsu YH, Sung FC, Muo CH et al.* **Increased risk of developing peripheral artery disease in hemodialysis patients receiving statin treatments: a population-based cohort study in Taiwan**. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association 2019.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=31821490
***ABSTRACT***
BACKGROUND: Few investigations have evaluated the influences on peripheral arterial disease (PAD) risk of statin treatment in hemodialysis (HD) subjects with hyperlipidemia (HL). METHODS: From the National Health Insurance Research Dataset, we identified 3658 HD patients with statin therapy for HL as the statin cohort, and then selected, by 1:1 propensity score matching, 3658 HD patients with HL but without statin use as the nonstatin cohort in 2000-07. The cohorts were followed through until the end of 2011. We used Cox proportional hazards regression analysis to assess the hazard ratio (HR) of PAD development. RESULTS: The average follow-up period was 4.18 years; the incident PAD risk was 1.35-fold greater in statin users than in nonusers (16.87 versus 12.46/1000 person-years), with an adjusted HR (aHR) of 1.34 for PAD [95% confidence interval (CI) 1.12-1.62]. The PAD risk increases were significant for patients receiving fluvastatin (aHR 1.88; 95% CI 1.12-3.14) and atorvastatin (aHR 1.60; 95% CI 1.24-2.08). The risk increased with higher annual average statin dosage (P for trend <0.0001); the risk was higher for those receiving moderate-intensity statin treatment. The sensitivity test revealed similar findings. CONCLUSIONS: HD patients with HL on statin medication were at increased PAD risk, which increased with cumulative statin dosage. Thorough considerations are needed before prescribing statins to HD patients.

[46] *Bullon-Vela V, Abete I, Tur JA et al.* **Influence of lifestyle factors and staple foods from the Mediterranean diet on non-alcoholic fatty liver disease among older individuals with metabolic syndrome features**. Nutrition 2019; 71:110620.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=31838461
***ABSTRACT***
OBJECTIVE: Non-alcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver morbidity. This condition often is accompanied by obesity, diabetes, and metabolic syndrome (MetS). The aim of this study was to evaluate the connection between lifestyle factors and NAFLD in individuals with MetS. METHODS: A cross-sectional study with 328 participants (55-75 y of age) diagnosed with MetS participating in the PREDIMED-Plus trial was conducted. NAFLD status was evaluated using the non-invasive hepatic steatosis index (HSI). Sociodemographic, clinical, and dietary data were collected. Adherence to the Mediterranean diet (mainly assessed by the consumption of olive oil, nuts, legumes, whole grain foods, fish, vegetables, fruits, and red wine) and physical activity were assessed using validated questionnaires. RESULTS: Linear regression analyses revealed that HSI values tended to be lower with increasing physical activity tertiles (T2, beta = -1.47; 95% confidence interval [CI], -2.73 to -0.20; T3, beta = -1.93; 95% CI, -3.22 to -0.65 versus T1, Ptrend = 0.001) and adherence to the Mediterranean diet was inversely associated with HSI values: (moderate adherence beta = -0.70; 95%

CI, -1.92 to 0.53; high adherence beta = -1.57; 95% CI, -3.01 to -0.13 versus lower, Ptrend = 0.041). Higher tertiles of legume consumption were inversely associated with the highest tertile of HSI (T2, relative risk ratio [RRR], 0.45; 95% CI, 0.22-0.92; P = 0.028; T3, RRR, 0.48; 95% CI, 0.24-0.97; P = 0.041 versus T1). CONCLUSION: Physical activity, adherence to the Mediterranean diet, and consumption of legumes were inversely associated with a non-invasive marker of NAFLD in individuals with MetS. This data can be useful in implementing precision strategies aimed at the prevention, monitoring, and management of NAFLD.

[47] *Golubev AG, Anisimov VN*. **Aging and cancer: Is glucose a mediator between them?** Oncotarget 2019; 10:6758-6767.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=31827719
***ABSTRACT***
Aging can increase cancer incidence because of accumulated mutations that initiate cancer and via compromised body control of premalignant lesions development into cancer. Relative contributions of these two factors are debated. Recent evidence suggests that the latter is rate limiting. In particular, hyperglycemia caused by compromised body control of blood glucose may be a factor of selection of somatic mutation-bearing cells for the ability to use glucose for proliferation. High glucose utilization in aerobic glycolysis is a long known characteristic of cancer. The new evidence adds to the concepts that have been being developed starting from mid-1970ies to suggest that age-related shifts in glucose and lipid metabolism increase the risk of cancer and compromise prognoses for cancer patients and to propose antidiabetic biguanides, including metformin, for cancer prevention and as an adjuvant means of cancer treatment aimed at the metabolic rehabilitation of patients. The new evidence is consistent with several effects of glucose contributing to aging and acting synergistically to enhance carcinogenesis. Glucose can affect (i) separate cells (via promoting somatic mutagenesis and epigenetic instability), (ii) cell populations (via being a factor of selection of phenotypic variants in cell populations for higher glucose consumption and, ultimately, for high aerobic glycolysis); (iii) cell microenvironment (via modification of extracellular matrix proteins), and (iv) the systemic levels (via shifting the endocrine regulation of metabolism toward increasing blood lipids and body fat, which compromise immunological surveillance and promote inflammation). Thus, maintenance of youthful metabolic characteristics must be important for cancer prevention and treatment.

[48] *Johns DG, Wang SP, Rosa R et al.* **Impact of drug distribution into adipose on tissue function: The cholesteryl ester transfer protein (CETP) inhibitor anacetrapib as a test case**. Pharmacol Res Perspect 2019; 7:e00543.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=31832204
***ABSTRACT***
Anacetrapib is an inhibitor of cholesteryl ester transfer protein (CETP) previously under development as a lipid-modifying agent that reduces LDL-cholesterol and increases HDL-cholesterol in hypercholesterolemic patients. Anacetrapib demonstrates a long terminal half-life and accumulates in adipose tissue, which contributes to a long residence time of anacetrapib. Given our previous report that anacetrapib distributes into the lipid droplet of adipose tissue, we sought to understand whether anacetrapib affected adipose function, using a diet-induced obese (DIO) mouse model. Following 20 weeks of treatment with anacetrapib (100 mg/kg/day), levels of the drug increased to approximately 0.6 mmol/L in white adipose tissue. This level of anacetrapib was not associated with any impairment

in adipose functionality as evidenced by a lack of any reduction in biomarkers of adipose functionality (plasma adiponectin, leptin, insulin; adipose adiponectin, leptin mRNA). In DIO wild-type (WT) mice treated with anacetrapib for 2 weeks and then subjected to 30% food restriction during washout to induce weight loss (18%) and fat mass loss (7%), levels of anacetrapib in adipose and plasma were not different between food restricted and ad lib-fed mice. These data indicate that despite deposition and long-term residence of ~0.6 mmol/L levels of anacetrapib in adipose tissue, adipose tissue function appears to be unaffected in mice. In addition, these data also indicate that even with severe caloric restriction and acute loss of fat mass, anacetrapib does not appear to be mobilized from the fat depot, thereby solidifying the role of adipose as a long-term storage site of anacetrapib.

[49] *Jiang B, Yang YJ, Dang WZ et al.* **Astragaloside IV reverses simvastatin-induced skeletal muscle injury by activating the AMPK-PGC-1alpha signalling pathway**. Phytotherapy research : PTR 2019.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=31823428
***ABSTRACT***
In this study, we investigated the effect of astragaloside IV on skeletal muscle energy metabolism disorder caused by statins and explored the possible mechanisms. High-fat diet-fed apolipoprotein E knockout (ApoE(-/-) ) mice performed aerobic exercise and were administered simvastatin, simvastatin + trimetazidine, or simvastatin + astragaloside IV by gavage. At the end of treatment, exercise performance was assessed by the hanging grid test, forelimb grip test, and running tolerance test. Moreover, plasma lipid and creatine kinase concentrations were measured. After sacrifice, the gastrocnemius muscle was used to assess muscle morphology, and energy metabolism was evaluated by determining the concentration of lactic acid and the storage capacity of adenosine triphosphate and glycogen. Mitochondrial function was assessed by measuring mitochondrial complex III and citrate synthase activity and membrane potential. In addition, oxidative stress was assessed by determining the level of hydrogen peroxide. Finally, using western blotting and reverse transcription polymerase chain reaction, we explored the mechanism of astragaloside IV in alleviating simvastatin-induced muscle injury. Our results demonstrated that astragaloside IV reversed simvastatin-induced muscle injury without affecting the lipid-lowering effect of simvastatin. Moreover, astragaloside IV promoted the phosphorylation of AMPK and activated PGC-1alpha, which upregulated the expression of NRF1 to enhance energy metabolism and inhibit skeletal muscle cell apoptosis.

[50] *Bassols J, Martinez-Calcerrada JM, Osiniri I et al.* **Effects of metformin administration on endocrine-metabolic parameters, visceral adiposity and cardiovascular risk factors in children with obesity and risk markers for metabolic syndrome: A pilot study**. PloS one 2019; 14:e0226303.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=31821361
***ABSTRACT***
BACKGROUND: Metformin treatment (1000-2000 mg/day) over 6 months in pubertal children and/or adolescents with obesity and hyperinsulinism is associated with a reduction in body mass index (BMI) and the insulin resistance index (HOMA-IR). We aimed to ascertain if long-term treatment (24 months) with lower doses of metformin (850 mg/day) normalizes the endocrine-metabolic abnormalities, improves body composition, and reduces the carotid intima-media thickness (cIMT) in pre-puberal and early pubertal children with obesity. METHODS: A pilot double-blind, placebo-controlled trial was conducted on 18 pre-puberal and early pubertal (Tanner stage I-II) children with obesity and risk markers for metabolic syndrome. Patients were randomly assigned (1:1) to receive metformin (850

mg/day) or placebo for 24 months. Clinical, biochemical (insulin, lipids, leptin, and high-sensitivity C-reactive protein [hsCRP]), and imaging (body composition [dual-energy X-ray absorptiometry and magnetic resonance imaging]) parameters as well as cIMT (ultrasonography) were assessed at baseline and at 6, 12, and 24 months. RESULTS: The 12-month treatment tend to cause a reduction in weight standard deviation scores (SDS), BMI-SDS, leptin, leptin-to-high-molecular-weight (HMW) adiponectin ratio, hsCRP, cIMT, fat mass, and liver fat in metformin-treated children compared with placebo. The effect of metformin on the reduction of BMI-SDS, leptin, leptin-to-HMW adiponectin ratio, hsCRP, and liver fat seemed to be maintained after completing the 24 months of treatment. No changes in insulin sensitivity (HOMA-IR) or adverse effects were detected. CONCLUSION: In this pilot study, metformin treatment in pre-puberal and early pubertal children with obesity seemed to improve body composition and inflammation markers. Our data encourage the development of future fully powered trials using 850 mg/day metformin in young children, highlighting its excellent tolerance and potential long-term benefits.

[51] *Haslacher H, Fallmann H, Waldhausl C et al.* **Type 2 diabetes care: Improvement by standardization at a diabetes rehabilitation clinic. An observational report**. PloS one 2019; 14:e0226132.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=31830073
***ABSTRACT***
BACKGROUND: Outcome of type 2 diabetes care depends on the acceptance of self-responsibility by informed patients, as treatment goals will otherwise be missed. AIMS AND METHODS: This pre/post-observational report describes the clinical outcome of type 2 diabetes care in patients with type 2 diabetes (N =930) admitted consecutively to a diabetes rehabilitation clinic (DRC) between June 2013, and June 2016, where they were exposed to standardized lifestyle modification with meals low in salt and rich in vegetables and fruits, totaling 1,200 to 1,600 kcal/d, and an add-on exercise load equivalent to 400-600 kcal/d. RESULTS: At admission, patients presented with multiple treatment modes, elevated HbA1c levels (7.6+/-1.5%, 60+/-16 mmol/mol), a high prevalence of co-morbidities dominated by obesity (79%), a low rate of influenza and pneumococcal immunization (<9%) and underuse of lipid-lowering drugs (-29%). Analysis of clinical and metabolic outcome after 3 weeks shows that simple standardization of and better adherence to treatment recommendations improved (p<0.0001) glucose (HbA1c -0.4+/-0.4%) and lipid metabolism (LDL/HDL ratio, -0.58+/-0.03), permitting a 39% reduction in insulin dosage, omission of insulin in 36/232 patients and omission of oral antidiabetic drugs (OADs) other than metformin and DPP4-inhibitors, while the use of GLP-1 analogs doubled to 5.2%. Improved outcome was independent of treatment strategy and more marked at initially high HbA1c at costs less than 25% of those encountered at a standard hospital. CONCLUSIONS: Our observations support the clinical notion that adherence to basic treatment recommendations is indispensable in type 2 diabetes care if metabolic and clinical treatment goals are to be met, and if inappropriate add-on over-medicalization with OADs and/or insulin is to be avoided. To this end, 'imprinting' patients at a DRC could be of considerable help.

[52] *Svanteson M, Rollefstad S, Klow NE et al.* **Effects of long-term statin-treatment on coronary atherosclerosis in patients with inflammatory joint diseases**. PloS one 2019; 14:e0226479.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=31830762
***ABSTRACT***

BACKGROUND: The effect of statins over time on coronary atherosclerosis in patients with inflammatory joint diseases (IJD) is unknown. Our aim was to evaluate the change in coronary plaque morphology and volume in long-term statin-treated patients with IJD. METHODS: Sixty-eight patients with IJD and carotid artery plaque(s) underwent coronary computed tomography angiography before and after a mean of 4.7 (range 4.0-6.0) years of statin treatment. The treatment target for low density lipoprotein cholesterol (LDL-c) was </=1.8 mmol/L. Changes in plaque volume (calcified, mixed/soft and total) and coronary artery calcification (CAC) from baseline to follow-up were assessed using the 17-segment American Heart Association-model. RESULTS: Median (IQR) increase in CAC after statin treatment was 38 (5-236) Agatston units (p<0.001). Calcified and total plaque volume increased with 5.6 (0.0-49.1) and 2.9 (0.0-23.5) mm3, respectively (p<0.001 for both). The median (IQR) change in soft/mixed plaque volume was -10 (-7.1-0.0), p = <0.001. Patients who had obtained the LDL-c treatment target at follow-up, experienced reduced progression of both CAC and total plaque volume compared to patients with LDL-c >1.8mmol/L (21 [2-143] vs. 69 [16-423], p = 0.006 and 0.65 [-1.0-13.9] vs. 13.0 [0.0-60.8] mm3, p = 0.019, respectively). CONCLUSIONS: A progression of total atherosclerotic plaque volume in statin-treated patients with IJD was observed. However, soft/mixed plaque volume was reduced, suggesting an alteration in plaque composition. Patients with recommended LDL-c levels at follow-up had reduced atherosclerotic progression compared to patients with LDL-c levels above the treatment target, suggesting a beneficial effect of treatment to guideline-recommended lipid targets in IJD patients.

[53] *Xu JY, Qian HY, Huang PS et al.* **Transplantation efficacy of autologous bone marrow mesenchymal stem cells combined with atorvastatin for acute myocardial infarction (TEAM-AMI): rationale and design of a randomized, double-blind, placebo-controlled, multi-center, Phase II TEAM-AMI trial**. Regenerative medicine 2019.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=31829095
***ABSTRACT***
Aim: To determine the efficacy and safety of intracoronary infusion of autologous bone marrow mesenchymal stem cells (MSC(INJ)) in combination with intensive atorvastatin (ATV) treatment for patients with anterior ST-segment elevation myocardial infarction-elevation myocardial infarction. Patients & methods: The trial enrolls a total of 100 patients with anterior ST-elevation myocardial infarction. The subjects are randomly assigned (1:1:1:1) to receive routine ATV (20 mg/d) with placebo or MSCs(INJ) and intensive ATV (80 mg/d) with placebo or MSCs(INJ). The primary end point is the absolute change of left ventricular ejection fraction within 12 months. The secondary end points include parameters in cardiac function, remodeling and regeneration, quality of life, biomarkers and clinical outcomes. Results & conclusion: The trial will implicate the essential of cardiac micro-environment improvement ('fertilizing') for cell-based therapy. Clinical Trial Registration: NCT03047772.

[54] *Escobar C, Anguita M, Arrarte V et al.* **Recommendations to improve lipid control. Consensus document of the Spanish Society of Cardiology**. Revista espanola de cardiologia (English ed.) 2019.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=31818706
***ABSTRACT***
T***he current control of low-density lipoprotein cholesterol among patients with atherosclerotic cardiovascular disease is very low and this is associated with an increase of cardiovascular outcomes. In

addition, the latter this happens, the risk will be greater. This is mainly due to an insufficient use of the lipid-lowering therapy currently available. In fact, with current treatments (statins, ezetimibe and PCSK9 inhibitors), the majority of patients in secondary prevention should achieve low-density lipoprotein cholesterol goals. For these reasons, in this manuscript promoted by the Spanish Society of Cardiology we propose three simple and feasible decision-making algorithms that include the majority of clinical scenarios among patients with ischemic heart disease, with the double aim of attaining therapeutic goals in the majority of patients as soon as possible; in secondary prevention the magnitude of the benefit is risk- and time-dependent.

[55] *Bello-Chavolla OY, Aguilar-Salinas CA*. **FACTORS INFLUENCING ACHIEVEMENT OF LOW-DENSITY LIPOPROTEIN CHOLESTEROL GOALS IN MEXICO: THE INTERNATIONAL CHOLESTEROL MANAGEMENT PRACTICE STUDY**. Revista de investigacion clinica; organo del Hospital de Enfermedades de la Nutricion 2019; 71:408-416.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=31823964
***ABSTRACT***
Background: The International Cholesterol Management Practice Study is a multinational collaborative effort to describe the effectiveness of the lipid-lowering therapy (LLT) as well as the main barriers to achieve the low-density lipoprotein cholesterol (LDL-C) goals. Objective: The objective of the study was to investigate factors associated with the achievement of LDL-C goals in Mexico using real-life data. Methods: This was a cross-sectional observational study from 18 physicians across different health facilities in Mexico, who provided information about their practices between August 2015 and August 2016. We included patients treated for >/=3 months with any LLT in whom LDL-C measurement on stable LLT was available for the previous 12 months. Results: We included 623 patients with a mean age of 59.3 +/- 12.7 years; 55.6% were women. The mean LDL-C value on LLT was 141.8 +/- 56.1 mg/dL. At enrollment, 97.4% of patients were receiving statin therapy (11.3% on high-intensity treatment). Only 24.8% of the very-high cardiovascular (CV) risk patients versus 26.4% of the high risk and 52.4% of the moderate risk patients achieved their LDL-C goals. Independent factors associated with non-achievement of LDL-C goal were statin intolerance, overweight and obesity, abdominal obesity, female sex, high CV risk, use of public health-care service, metabolic syndrome, type 2 diabetes, and hypertriglyceridemia. Higher-level of education was associated with a lower risk of not achieving LDL-C goals. Conclusions: Achievement of LDL-C goals is suboptimal in Mexico, especially in patients with the highest CV risk. The main barriers to achieve the goal are easily detectable. Implementation of LLT should be adapted to the patient's needs and profile.