Literature update week 07 (2020)

[1] *Chen F, Yang M, Wan C et al.* **Efficacy and safety of statin therapy in pulmonary hypertension: a systematic review and meta-analysis**. Annals of translational medicine 2019; 7:786.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32042802
ABSTRACT
Background: Pulmonary hypertension (PH) is a multi-causal disease and no satisfactory therapeutic strategies for it. Statins have been suggested as potential drugs in PH, whose effects in different clinic types of PH have not been conclusive. In this study, we included randomized controlled clinical trials (RCTs) evaluating the efficacy and safety of statins therapy in PH. Methods: We searched databases including Medline, Embase, Cochrane, PubMed and Web of science, with time up to January 1, 2019. With 95% confidence interval (CI), weighted mean difference (WMD) or standardized mean difference (SMD) was pooled and calculated in a random or fixed effect model according to I2 statistic. Results: A total of nine RCTs with 657 patients were included. Four types of statins (atorvastatin, pravastatin, rosuvastatin and simvastatin) were used at different doses (10-80 mg daily) for up to 6 months. In the pooled-data analysis, compared with placebo, there were significant improvements in pulmonary arterial pressure (PAP), in addition to low-density lipoprotein (LDL) in patients treated with statins, but not in 6-minute walking distance (6MWD), cardiac index (CDI). No more adverse events and all-cause mortality were revealed. Subgroup analysis indicated that statins could decrease PAP in the subtype of PH due to chronic obstructive pulmonary disease (COPD), but not pulmonary arterial hypertension (PAH). Conclusions: This study indicates that statins can efficiently and safely reduce PAP in PH, especially in the subtype due to COPD. Further RCTs are needed to focus on the efficacy and safety of statin therapy in different subtypes of PH.

[2] *Momtazi-Borojeni AA, Nik ME, Jaafari MR et al.* **Effects of immunisation against PCSK9 in mice bearing melanoma**. Archives of medical science : AMS 2020; 16:189-199.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32051723
ABSTRACT
Introduction: Inhibition of proprotein convertase subtilisin/kexin 9 (PCSK9) is an established modality for the treatment of hypercholesterolaemia. However, the impact of PCSK9 inhibition in other situations such as cancer remains largely unknown. The current study was conducted to study the effects of PCSK9 inhibition on cancer endpoints in mice bearing melanoma. Material and methods: To generate antiPCSK9 antibody in vivo, a nanoliposomal antiPCSK9 vaccine adsorbed to 0.4% Alum adjuvant was subcutaneously injected in C57BL/6 mice four times with bi-weekly intervals. Two weeks after the last immunisation, mice were subcutaneously inoculated with B16F0 melanoma cells. After a tumour mass was palpable (approximately 10 mm(3)), the mice were randomly divided into four groups and subjected to different treatment protocols: (1) PBS (untreated control), (2) vaccine group, (3) the combination of vaccine and a single dose of liposomal doxorubicin (Doxil((R))), and (4) liposomal doxorubicin (positive control) group. To determine therapeutic efficacy, mouse body weight, tumour size, and survival were monitored every three days for 36 days. Results: The nanoliposomal antiPCSK9 vaccine was found to efficiently induce specific antibodies against PCSK9 in C57BL/6 mice, thereby reducing plasma levels and function of PCSK9. Tumour volumes in the vaccinated group were not significantly different from those in the liposomal doxorubicin, combination, and control groups. The time to reach endpoint (TTE) values of the vaccine (28 +/-5 days), combination (30 +/-6 days), liposomal doxorubicin (34 +/-

2 days), and control (31 +/-2 days) groups were not significantly different, either. Furthermore, the tumour growth delay (TGD) values of the vaccine (-11.5 +/-15.4%), liposomal doxorubicin (7.75 +/-6.5%), combination (-6 +/-20.77%), and control (0 +/-7.5) groups were not significantly different. Finally, there was no significant difference between the median survival time and lifespan of the vaccinated versus other tested groups. Conclusions: The nanoliposomal PCSK9 vaccine did not adversely affect the growth of melanoma tumour nor the survival of tumour-bearing mice.

[3] *Socha M, Pietrzak A, Grywalska E et al.* **The effect of statins on psoriasis severity: a meta-analysis of randomized clinical trials**. Archives of medical science : AMS 2020; 16:1-7.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32051699
ABSTRACT
Introduction: Statins may reduce the severity of psoriasis, but the available evidence is unclear. We conducted a meta-analysis of randomized controlled studies (RCTs) that investigated the effect of statins on psoriasis severity assessed with the Psoriasis Area and Severity Index (PASI). Material and methods: Two investigators searched independently the following databases: Medline, EMBASE, Cochrane Central Register of Controlled Trials and ClinicalTrials.gov from inception to February 2019. Additionally, reference lists from all available articles were searched manually. We included only RCTs carried out among adult (>/= 16 years) patients with psoriasis who received oral statins for >/= 8 weeks and had psoriasis severity assessed with the PASI at baseline and at the end of follow-up. We used random effects meta-analysis to calculate the mean difference (D) in PASI change between patients who received either a statin or a comparator. Results: Of 279 records identified, there were 5 eligible RCTs, with a total of 223 patients, including 128 patients who received a statin (atorvastatin or simvastatin). The improvement in psoriasis severity (PASI) was significantly greater in patients who received statins than in those who received comparators (D = 2.76, 95% CI: 0.49-5.04, p = 0.017). In subgroup analyses, the improvement in PASI values was significant for simvastatin (D = 3.70, 95% CI: 2.52-4.89, p < 0.001) but not for atorvastatin (D = 2.30, 95% CI: -1.28-5.88, p = 0.210). Conclusions: Oral statins may improve psoriasis, particularly in patients with severe disease. This observation should be verified in long-term, well-designed studies that will enable analyses adjusted for clinical variables.

[4] *Arnaboldi L, Ossoli A, Giorgio E et al.* **LIPA gene mutations affect the composition of lipoproteins: Enrichment in ACAT-derived cholesteryl esters**. Atherosclerosis 2020; 297:8-15.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32058863
ABSTRACT
BACKGROUND AND AIMS: Cholesteryl ester storage disease (CESD) due to LIPA gene mutations is characterized by hepatic steatosis, hypercholesterolemia and hypoalphalipoproteinemia, exposing affected patients to an increased cardiovascular risk. Further insights into the impact of LIPA gene mutations on lipid/lipoprotein metabolism are limited. Aim of the study was to investigate the effect of carrying one or two mutant LIPA alleles on lipoprotein composition and function. METHODS: Lipoproteins were isolated from 6 adult CESD patients, 5 relatives carrying one mutant LIPA allele (carriers) and 12 sex/age matched controls. Lipid profile, lipoprotein mass composition and the fatty acid distribution of cholesteryl esters (CEs) were assessed. HDL function was evaluated as the ability to promote nitric oxide release by endothelial cells. RESULTS: Despite the lipid-lowering therapy, total cholesterol, LDL-cholesterol and triglycerides were increased in CESD

patients compared to controls, while HDL-cholesterol was reduced. Carriers also displayed elevated total and LDL-cholesterol. Very low and intermediate density lipoproteins from CESD patients and carriers were enriched in CEs compared to the control ones, with a concomitant reduction of triglycerides. Fatty acid composition of CEs in serum and lipoproteins showed a depletion of linoleate content in CESD patients, due to the reduced LCAT activity. In CESD HDL, fatty acid distribution of CEs was shifted towards saturated ones, if compared to control HDL. The changes in HDL composition did not affect HDL ability to promote nitric oxide release by endothelial cells. CONCLUSIONS: LIPA gene mutations significantly affected plasma levels and lipid composition of lipoproteins, likely contributing to the increased cardiovascular risk of affected patients.

[5] *Wang X, Chen X*. **Clinical Characteristics of 162 Patients with Drug-Induced Liver and/or Kidney Injury**. BioMed research international 2020; 2020:3930921.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32051826
ABSTRACT
Context: Drug-induced liver and kidney injuries are the most common adverse drug reactions in the clinic, and they have similar pathogeneses. Aims: To analyze the clinical characteristics of patients with drug-induced liver and/or kidney injury. Settings and Design: This was a retrospective study. Methods and Materials: We analyzed data from 162 patients with drug-induced liver and/or kidney injury from 2008 to 2018 at the Chinese Rocket Force Characteristic Medical Center. Univariate and multivariate logistic analyses were performed on the drugs used, sex, age, weight, complications, and laboratory test results. Statistical analysis was performed using SPSS 25.0 statistical software. Results: (1) The most common drugs causing organ injury in this study were antineoplastic drugs, antibiotics, traditional Chinese medicine, lipid-lowering drugs, and nonsteroidal anti-inflammatory drugs. (2) Among 22 patients with drug-induced liver and kidney injuries, 68.18% had a hepatocellular pattern, 13.64% had a mixed pattern, and 18.18% had a cholestatic pattern. Among the three groups, the P value for creatinine was 0.002. (3) The P value for urinary protein between the isolated kidney injury group and the liver and kidney injury group was 0.028. (4) Multivariate analysis showed that, among the drug-induced renal injury patients and all injury patients, those with a higher neutrophil percentage had a lower risk of liver injury (OR = 0.574, 95% CI: 0.390-0.846; OR = 0.545, 95% CI: 0.396-0.749). Conclusions: (1) The serum creatinine level was higher in liver injury patients with the cholestatic pattern than in those with the hepatocellular or mixed pattern. (2) There was a significant difference in urinary protein between the isolated kidney and the liver and kidney injury groups. (3) Among patients with drug-induced organ injury, those with a higher neutrophils percentage had a lower risk of liver injury.

[6] *Kim MY, Jung M, Noh Y et al.* **Impact of Statin Use on Dementia Incidence in Elderly Men and Women with Ischemic Heart Disease**. Biomedicines 2020; 8.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32050497
ABSTRACT
This study aimed to determine the association between statins and the prevention of dementia according to sex differences in elderly patients with ischemic heart disease (IHD). We performed a nationwide retrospective cohort study using the Korean Health Insurance Review and Assessment Service database (2007-2015). Among the 264,036 eligible patients aged >/=65 years with IHD, statin users were compared with non-users by propensity score matching at a 1:1 ratio (71,587 in

each group). The primary outcome was dementia risk by estimating hazard ratios (HRs) and 95% confidence intervals (CIs). Differential risks of dementia were assessed by sex in the subgroups of statin types, exposure duration, and patient age, implying that sex is an influential factor for the link between statin use and dementia incidence. Among seven commonly prescribed statins, rosuvastatin was associated with the greatest preventive effect on dementia incidence, with an adjusted HR of 0.82 (95% CI = 0.78-0.87). In a subgroup analysis organized by sex, the differential risk of dementia incidence was assessed in each statin group, implying that sex is an influential factor for the link between statin and dementia. This study suggests that appropriate statin use considering sex differences may have beneficial effects on the development of dementia.

[7] *Evison BJ, Palmer JT, Lambert G et al.* **A small molecule inhibitor of PCSK9 that antagonizes LDL receptor binding via interaction with a cryptic PCSK9 binding groove**. Bioorganic & medicinal chemistry 2020; 28:115344.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32051094
ABSTRACT
Proprotein convertase (PC) subtilisin kexin type 9 (PCSK9) inhibits the clearance of low density lipoprotein (LDL) cholesterol from plasma by directly interacting with the LDL receptor (LDLR). As the interaction promotes elevated plasma LDL cholesterol levels and a predisposition to cardiovascular disease (CVD), it has attracted much interest as a therapeutic target. While anti-PCSK9 monoclonal antibodies have been successful in the treatment of hypercholesteremia by decreasing CVD risk, their high cost and a requirement for injection have prohibited widespread use. The advent of an orally bioavailable small molecule inhibitor of the PCSK9-LDLR interaction is an attractive alternative, however efforts have been tempered as the binding interface is unfavourable for binding by small organic molecules. Despite its challenging nature, we report herein the discovery of compound 3f as a small molecule inhibitor of PCSK9. The kinase inhibitor nilotinib emerged from a computational screen that was applied to identify compounds that may bind to a cryptic groove within PCSK9 and proximal to the LDLR-binding interface. A subsequent in vitro PCSK9-LDLR binding assay established that nilotinib was a bona fide but modest inhibitor of the interaction (IC50 = 9.8 microM). Through multiple rounds of medicinal chemistry, 3f emerged as a lead-like molecule by demonstrating disruption of the PCSK9-LDLR interaction at nanomolar levels in vitro (IC50 = 537 nM) with no inhibitory activity (IC50 > 10 microM) against a small panel of kinases. Compound 3f restored LDL uptake by liver cells at sub-micromolar levels and demonstrated excellent bioavailability when delivered subcutaneously in mice. Most significantly, compound 3f lowered total cholesterol levels in the plasma of wild-type mice, thereby providing proof-of-concept that the notion of a small molecule inhibitor against PCSK9 is therapeutically viable.

[8] *Dildar S, Shamsi TS*. **Case report of one month and 15 days old baby with type V hyperlipoproteinemia (HLP)**. BMC endocrine disorders 2020; 20:22.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32046690
ABSTRACT
BACKGROUND: Most of the patients with type 1 and V hyperlipoproteinemia (HLP) present with symptoms and signs of acute pancreatitis due to marked elevation of triglycerides, but this baby presented with a chest infection, which was later diagnosed as type V HLP on laboratory workup.

CASE PRESENTATION: We report a case of a 1 month and 15 days old baby boy, product of 2-nd degree consanguinity admitted to a nearby hospital with complaints of refusal to feed, cough and excessive crying. On examination his heart rate was 102 beats/min, respiratory rate was 55 breaths/min and temperature was within the normal range, provisional diagnosis of Pneumonia was made. His samples were tested at our laboratory, the lipid Profile at age of 1 month 15 days showed total cholesterol (TC) of 1400 mg/dl reference range (RR < 200 mg/dl), triglycerides (TG) of > 885 mg/dl after dilution it was 31,400 mg/dl (RR < 150 mg/dl), High density Cholesterol (HDL) of 35 mg/dl (RR > 40 mg/dl) and low density cholesterol (LDL) of 200 mg/dl (RR < 100 mg/dl). The patient's blood sample was grossly milky and lipemic in appearance. A "Refrigerator test" was performed after overnight storage of the sample in refrigerator at 4 degrees C, which gave a creamy layer at the top and clear infranatant due to caking of the Chylomicrons. Lipoprotein electrophoresis performed 1 month later showed Chylomicrons of 4.7% (RR 0-2%), Pre-beta lipoproteins of 51.5% (RR 5-22%), beta lipoproteins of 16.5% (RR 39-70%) and alpha of 27.3% (RR 23-53%). Initially he was diagnosed as type 1 HLP, but later on he was correctly diagnosed as type V HLP. Cholestyramine (Questran sachet) powder was started at a dose of 100 mg/kg on t.i.d basis with NAN-1 formula Milk at the age of 1 month and 15 days. On follow up, detailed advices regarding the weaning food was given to the mother (using olive oil in cooking, giving proteins and avoiding heavy fatty meals). His lipid profile was repeated at age of 3 months, which showed some improvement, his TGs were 1986 mg/dl and TC 105 mg/dl. CONCLUSION: There is no universal diagnostic criterion for diagnosing Type V HLP, most likely, due to a scanty literature on this disorder. It stimulated us to report this case so that our findings may help for a timely diagnosis of the affected patients.

[9] *Chapman G, Tanner S*. **An unusually impressive atorvastatin-induced elevation of serum alkaline phosphatase**. BMJ case reports 2020; 13.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32047080
ABSTRACT
A 90-year-old woman is referred six months after a transient ischaemic attack (TIA) with asymptomatic cholestatic liver function test (LFT) derangement. Following the TIA, atorvastatin and clopidogrel therapy are initiated. This is added to pre-existent once daily nifedipine for hypertension. Nifedipine (a weak inhibitor of CYP3A4 and competing substrate) and clopidogrel (a competitive inhibitor of CYP3A4) may have affected the metabolism of atorvastatin, resulting in the elevation of serum alkaline phosphatase levels to over six times the upper limit of normal. More often, statin therapy elevates serum alanine aminotransferase levels. Drug-induced liver injury (DILI) was deemed 'probable' as judged by the Roussel Uclaf Causality Assessment Method score. Statin therapy remains overwhelmingly safe, with benefits outweighing risks in the vast majority. The UK recommended LFT monitoring regime facilitates early recognition of DILI. Case reports are examined where similar drug combinations resulted in severe morbidity and mortality.

[10] *Lozano-Cuenca J, Valencia-Hernandez I, Lopez-Canales OA et al.* **Possible mechanisms involved in the effect of the subchronic administration of rosuvastatin on endothelial function in rats with metabolic syndrome**. Brazilian journal of medical and biological research = Revista brasileira de pesquisas medicas e biologicas / Sociedade Brasileira de Biofisica ... [et al.] 2020; 53:e9304.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32049102

ABSTRACT
Metabolic syndrome is a multifaceted condition associated with a greater risk of various disorders (e.g., diabetes and heart disease). In a rat model of metabolic syndrome, an acute in vitro application of rosuvastatin causes relaxation of aortic rings. Since the outcome of a subchronic rosuvastatin treatment is unknown, the present study explored its effect on acetylcholine-induced vasorelaxation of aortic rings from rats with metabolic syndrome. Animals were submitted to a 16-week treatment, including a standard diet, a cafeteria-style diet (CAF-diet), or a CAF-diet with daily rosuvastatin treatment (10 mg/kg). After confirming the development of metabolic syndrome in rats, aortic segments were extracted from these animals (those treated with rosuvastatin and untreated) and the acetylcholine-induced relaxant effect on the corresponding rings was evaluated. Concentration-response curves were constructed for this effect in the presence/absence of L-NAME, ODQ, KT 5823, 4-aminopyridine (4-AP), tetraethylammonium (TEA), apamin plus charybdotoxin, glibenclamide, indomethacin, clotrimazole, and cycloheximide pretreatment. Compared to rings from control rats, acetylcholine-induced vasorelaxation decreased in rings from animals with metabolic syndrome, and was maintained at a normal level in animals with metabolic syndrome plus rosuvastatin treatment. The effect of rosuvastatin was inhibited by L-NAME, ODQ, KT 5823, TEA, apamin plus charybdotoxin, but unaffected by 4-AP, glibenclamide, indomethacin, clotrimazole, or cycloheximide. In conclusion, the subchronic administration of rosuvastatin to rats with metabolic syndrome improved the acetylcholine-induced relaxant response, involving stimulation of the NO/cGMP/PKG/Ca2+-activated K+ channel pathway.

[11] *Colhoun HM, Leiter LA, Muller-Wieland D et al.* **Effect of alirocumab on individuals with type 2 diabetes, high triglycerides, and low high-density lipoprotein cholesterol**. Cardiovascular diabetology 2020; 19:14.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32035487

ABSTRACT
BACKGROUND: Mixed dyslipidemia [elevated non-high-density lipoprotein cholesterol (non-HDL-C) and triglycerides (TGs), and decreased HDL-C] is common in type 2 diabetes mellitus (T2DM) and is associated with increased cardiovascular risk. Non-HDL-C and apolipoprotein B (ApoB) are the preferred therapeutic targets for mixed dyslipidemia. Alirocumab is a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 (PCSK9) that effectively reduces low-density lipoprotein cholesterol (LDL-C), non-HDL-C, ApoB, and lipoprotein(a) (Lp[a]), and is well-tolerated in individuals with T2DM. METHODS: The previously reported open-label ODYSSEY DM-DYSLIPIDEMIA trial data demonstrated the effects of alirocumab on individuals with non-HDL-C >/= 100 mg/dL and TGs >/= 150 and < 500 mg/dL receiving stable maximally tolerated statin (n = 413). This post hoc subgroup analysis of the primary trial investigated the effects of alirocumab [75 mg every 2 weeks (Q2W) with possible increase to 150 mg Q2W at Week 12] versus usual care [ezetimibe, fenofibrate, or no additional lipid-lowering therapy (LLT)] on non-HDL-C and other lipids in individuals with T2DM and baseline TGs >/= 200 mg/dL and HDL-C < 40 mg/dL (men) or < 50 mg/dL (women). RESULTS: Alirocumab significantly reduced non-HDL-C [LS mean difference (standard error (SE)), - 35.0% (3.9)], ApoB [LS mean difference (SE), - 34.7% (3.6)], LDL-C [LS mean difference (SE), - 47.3% (5.2)], LDL particle number [LS mean difference (SE), - 40.8% (4.1)], and Lp(a) [LS mean difference (SE), - 29.9% (5.4)] versus usual care from baseline to Week 24 (all P < 0.0001). Results were similar for alirocumab versus usual care. TG reductions were similar between alirocumab and

usual care (no significant difference), but greater with fenofibrate versus alirocumab (P = 0.3371). Overall, alirocumab significantly increased HDL-C versus usual care [LS mean difference (SE), 7.9% (3.6); P < 0.05], although differences with alirocumab versus ezetimibe or fenofibrate were non-significant. Most individuals receiving alirocumab achieved ApoB < 80 mg/dL (67.9%) and non-HDL-C < 100 mg/dL (60.9%). Adverse event frequency was similar between alirocumab (67.2%) and usual care (70.7%). Additionally, no clinically relevant effect of alirocumab on change in glycemic parameters or use of antihyperglycemic agents was observed. CONCLUSIONS: Alirocumab is an effective therapeutic option for individuals with T2DM, TGs >/= 200 mg/dL, and HDL-C < 40 mg/dL (men) or < 50 mg/dL (women). Atherogenic lipid (ApoB and non-HDL) reductions were greater with alirocumab than ezetimibe, fenofibrate, or no LLT. Consistent with previous studies, alirocumab was generally well tolerated. Trial registration Clinicaltrials.gov, NCT02642159. Registered December 24, 2015, https://clinicaltrials.gov/ct2/show/NCT02642159.

[12] *Escate R, Padro T, Suades R et al.* **High miR-133a levels in the circulation anticipates presentation of clinical events in familial hypercholesterolemia patients**. Cardiovascular research 2020.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32061123

ABSTRACT

AIMS: Presentation of acute events in patients with atherosclerosis remains unpredictable even after controlling for classical risk factors. MicroRNAs (miRNAs) measured in liquid biopsies could be good candidate biomarkers to improve risk prediction. Here, we hypothesized that miRNAs could predict atherosclerotic plaque progression and clinical event presentation in familial hypercholesterolemia (FH) patients. METHODS AND RESULTS: Circulating miRNAs (plasma, exosomes, microvesicles) were investigated by TaqMan Array and RT-qPCR assays. Patients with genetic diagnosis of FH and healthy relatives from the SAFEHEART cohort were included. A differential signature of 10 miRNA was obtained by comparing two extreme phenotypes consisting of FH-patients suffering a cardiovascular event (CVE) within a 8-year follow-up period (FH-CVE, N=42) and non-FH hypercholesterolemic relatives from the same cohort, matched for age and treatment, without CVE during the same period (nFH-nCVE, N=30). The validation studies included two independent groups of patients with FH-background (Discovery-Group, N=89, Validation-Group N=196), developing a future CVE (FH-CVE) or not (FH-nCVE) within the same time period of follow-up. Of the 10 miRNAs initially selected, miR-133a was significantly higher in FH-CVE than in FH-nCVE patients. ROC-analysis confirmed miR-133a as the best microRNA for predicting CVE in FH-patients (0.76+/-0.054; P<0.001). Furthermore, Kaplan-Meier and COX-analysis showed that high plasma miR-133a levels associated to the higher risk of presenting a CVE within the next 8 years (HR: 3.89 [95%CI: 1.88-8.07], P<0.001). In silico analysis of curate biological interactions related miR-133a with target genes involved in regulation of the cell-membrane lipid-receptor LRP6 and inflammatory cytokines (CXCL8, IL6, TNF). These predictions were experimentally proven in human macrophages and endothelial cells transfected with agomiR-133a. CONCLUSION: Elevated levels of miR-133a in the circulation anticipate those FH-patients that are going to present a clinical CVE within the next 2 years (average). Mechanistically, miR-133a is directly related with lipid- and inflammatory-signalling in key cells for atherosclerosis progression. TRANSLATIONAL PERSPECTIVE: The present study in patients with familial hypercholesterolemia shows that epigenetic markers can allow the identification of those patients that are going to present an acute clinical event

within the next two years (average). There are currently few prognostic biomarkers able to identify subjects at risk of developing major acute cardiovascular events. Here, by using a non-targeted approach of miRNA-discovery, we show for first time that plasma levels of miR-133a have prognostic value to predict incident cardiovascular events in patients with familial hypercholesterolemia treated as per guidelines. Future studies with larger independent cohorts are needed to validate the prognostic value of miR-133a in the general population.

[13] *Climent E, Benaiges D, Pedro-Botet J*. **Lipid-lowering treatment in secondary prevention of ischaemic cerebrovascular disease**. Clinica e investigacion en arteriosclerosis : publicacion oficial de la Sociedad Espanola de Arteriosclerosis 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32035666
ABSTRACT
Stroke is the second cause of death after myocardial infarction, and the main cause of acquired disability. Patients with ischaemic stroke have a higher risk of future vascular events, including recurrent stroke, myocardial infarction, and death by vascular cause. The initial epidemiological studies demonstrated a weak or non-existent relationship between cholesterolaemia and stroke. Subsequently, statin intervention trials showed a reduction in the risk of recurrence of cerebrovascular events. The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL), the first clinical trial designed to assess effects of statin therapy in secondary stroke prevention, highlighted the reduction of stroke recurrence with atorvastatin 80mg/daily in patients with a recent ischaemic established or transient stroke, with a modest increase in the rate of haemorrhagic stroke. Successive studies have also reported the benefits of statin therapy combined with ezetimibe or PCSK9 inhibitors in primary and secondary ischaemic stroke prevention. Since 80% of recurrent cerebrovascular events could be prevented, it is considered of interest to carry out a narrative review of the benefits of lipid-lowering therapy in the secondary prevention of ischaemic cerebrovascular disease.

[14] *Li X, Wang M, Zhang X et al.* **The novel llama-human chimeric antibody has potent effect in lowering LDL-c levels in hPCSK9 transgenic rats**. Clinical and translational medicine 2020; 9:16.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32056048
ABSTRACT
BACKGROUND: The advent of proprotein convertase subtilisin/kexin type 9 (PCSK9)-inhibiting drugs have provided an effective, but extremely expensive treatment for the management of low density lipoprotein (LDL). Our aim was to explore a cost-effective application of camelid anti-PCSK9 single domain antibodies (sdAbs), which are high variable regions of the camelid heavy chain antibodies (VHHs), as a human PCSK9 (hPCSK9) inhibitor. One female llama was immunized with hPCSK9. Screening of high affinity anti-PCSK9 VHHs was carried out based on surface plasmon resonance (SPR) technology. We reported a lysate kinetic analysis method improving the screening efficiency. To increase the serum half-life and targeting properties, the constant region fragment of the human immunoglobulin gamma sub-type 4 (IgG4 Fc) was incorporated to form a novel llama-human chimeric molecule (VHH-hFc). RESULTS: The PCSK9 inhibiting effects of the VHH proteins were analyzed in two human liver hepatocellular cells (HepG2 and Huh7) and in the hPCSK9 transgenic Sprague-Dawley (SD) rat model. The hPCSK9 antagonistic potency of the bivalent VHH-hFc exceeded the monovalent VHH ($P < 0.001$) in hepatocarcinoma cells. Furthermore, the llama-

human chimeric VHH-Fc protein had a similar reduction (~ 40%) of the LDL-c and total cholesterol when compared to the approved evolocumab in transgenic SD rat model, but with low cost. More surprisingly, the chimeric heavy chain antibodies could be persevered for 3 months at room temperature with little loss of the affinity. CONCLUSIONS: Due to the high yield and low cost of Pichia pastoris, lipid-lowering effect and strong stability, the llama-human chimeric antibody (VHH-Fc) offers a potent therapeutic candidate for the control of the serum lipid level.

[15] *Grover A, Oberoi M, Rehan HS et al.* **Self-reported Morisky Eight-item Medication Adherence Scale for Statins Concords with the Pill Count Method and Correlates with Serum Lipid Profile Parameters and Serum HMGCoA Reductase Levels**. Cureus 2020; 12:e6542.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32042518
ABSTRACT
Background It is imperative that non-compliance with statins be identified and addressed to maximize their clinical benefits. Patient self-reporting methods are convenient to apply in clinical practice but need to be validated. Objective We studied the concordance of a patient self-report method, Morisky eight-item medication adherence scale (MMAS)), with the pill count method in measuring adherence with statins and their correlation with extended lipid profile parameters and serum hydroxyl-methylglutaryl coenzyme A reductase (HMGCoA-R) enzyme levels. Methods MMAS and the pill count method were used to measure the adherence with statins in patients on statins for any duration. Patients were subjected to an estimation of extended lipid profile and serum HMGCoA-R levels at the end of three months follow-up. Results Out of a total of 200 patients included in the study, 117 patients had a low adherence (score less than 6 on MMAS) whereas 65 and 18 patients had medium (score 6 or 7) and high adherence (score of 8), respectively. The majority of patients who had low adherence to statins by MMAS were nonadherent by the pill count method yielding a concordance of 96.5%. Medium or high adherence to statins by the MMAS method had a concordance of 89.1% with the pill count method. The levels of total cholesterol, low-density lipoprotein-cholesterol, apolipoprotein B, and HMGCoA-R were negatively correlated with compliance measured by pill count and MMAS in a statistically significant way and with similar correlation coefficients. HMGCoA-R levels demonstrated a plateau phenomenon, with levels being 9-10 ng/ml when compliance with statin therapy was greater than 60% by pill count and greater than 6 on the Morisky scale. Conclusion In conclusion, MMAS and the pill count method showed concordance in measuring adherence to statins. These methods need to be explored further for their interchangeability as surrogates for biomarker levels.

[16] *Ma'ayeh M, Rood KM, Kniss D, Costantine MM*. **Novel Interventions for the Prevention of Preeclampsia**. Curr Hypertens Rep 2020; 22:17.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32052203
ABSTRACT
PURPOSE OF REVIEW: To review the rationale and biological plausibility and discuss the current research on novel interventions for the prevention of preeclampsia. RECENT FINDINGS: Preeclampsia affects up to 8% of pregnancies worldwide and remains a major cause of maternal and neonatal morbidity and mortality. Multiple medications have been investigated or repurposed as potential effective interventions for preeclampsia prevention. Aspirin is currently the only drug for which there is some evidence of benefit for preeclampsia prevention, and its use is

recommended by professional societies for pregnancies at risk. Statins have shown promise for prevention of preeclampsia in animal models and human pilot studies, without any trend or concerns for safety signals or teratogenicity. The use of metformin has also gained popularity in experimental studies, but observations from randomized clinical trials were not consistent on its utility as a possible intervention for preeclampsia prevention. While initial studies evaluating esomeprazole were promising, randomized trials failed to show benefit. Contemporary research shows exciting new opportunities for prophylactic treatment for preeclampsia, to prevent this debilitating and life-threatening disease.

[17] *Welty FK*. **Hypobetalipoproteinemia and abetalipoproteinemia: liver disease and cardiovascular disease**. Current opinion in lipidology 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32039990
ABSTRACT
PURPOSE OF REVIEW: Several mutations in the apolipoprotein (apo) B, proprotein convertase subtilisin kexin 9 (PCSK9) and microsomal triglyceride transfer protein genes result in low or absent levels of apoB and LDL cholesterol (LDL-C) in plasma which cause familial hypobetalipoproteinemia (FHBL) and abetalipoproteinemia (ABL). Mutations in the angiopoietin-like protein 3 ANGPTL3 gene cause familial combined hypolipidemia (FHBL2). Clinical manifestations range from none-to-severe, debilitating and life-threatening disorders. This review summarizes recent genetic, metabolic and clinical findings and management strategies. RECENT FINDINGS: Fatty liver, cirrhosis and hepatocellular carcinoma have been reported in FHBL and ABL probably due to decreased triglyceride export from the liver. Loss of function mutations in PCSK-9 and ANGPTL3 cause FHBL but not hepatic steatosis. In 12 case-control studies with 57 973 individuals, an apoB truncation was associated with a 72% reduction in coronary heart disease (odds ratio, 0.28; 95% confidence interval, 0.12-0.64; P = 0.002). PCSK9 inhibitors lowered risk of cardiovascular events in large, randomized trials without apparent adverse sequelae. SUMMARY: Mutations causing low LDL-C and apoB have provided insight into lipid metabolism, disease associations and the basis for drug development to lower LDL-C in disorders causing high levels of cholesterol. Early diagnosis and treatment is necessary to prevent adverse sequelae from FHBL and ABL.

[18] *Wang X, Chen X, Zhang X et al.* **A small-molecule inhibitor of PCSK9 transcription ameliorates atherosclerosis through the modulation of FoxO1/3 and HNF1alpha**. EBioMedicine 2020; 52:102650.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32058941
ABSTRACT
BACKGROUND: Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a secreted protein that down-regulates hepatic low-density lipoprotein receptor (LDLR) by binding and shuttling LDLR to lysosomes for degradation. The development of therapy that inhibits PCSK9 has attracted considerable attention for the management of cardiovascular disease risk. However, only monoclonal antibodies of PCSK9 have reached the clinic use. Oral administration of small-molecule transcriptional inhibitors has the potential to become a therapeutic option. METHODS: Here, we developed a cell-based small molecule screening platform to identify transcriptional inhibitors of PCSK9. Through high-throughput screening and a series of evaluation, we found several active compounds. After detailed investigation on the pharmacological effect and molecular mechanistic

characterization, 7030B-C5 was identified as a potential small-molecule PCSK9 inhibitor. FINDINGS: Our data showed that 7030B-C5 down-regulated PCSK9 expression and increased the total cellular LDLR protein and its mediated LDL-C uptake by HepG2 cells. In both C57BL/6 J and ApoE KO mice, oral administration of 7030B-C5 reduced hepatic and plasma PCSK9 level and increased hepatic LDLR expression. Most importantly, 7030B-C5 inhibited lesions in en face aortas and aortic root in ApoE KO mice with a slight amelioration of lipid profiles. We further provide evidences suggesting that transcriptional regulation of PCSK9 by 7030B-C5 mostly depend on the transcriptional factor HNF1alpha and FoxO3. Furthermore, FoxO1 was found to play an important role in 7030B-C5 mediated integration of hepatic glucose and lipid metabolism. INTERPRETATION: 7030B-C5 with potential suppressive effect of PCSK9 expression may serve as a promising lead compound for drug development of cholesterol/glucose homeostasis and cardiovascular disease therapy. FUND: This work was supported by grants from the National Natural Science Foundation of China (81473214, 81402929, and 81621064), the Drug Innovation Major Project of China (2018ZX09711001-003-006, 2018ZX09711001-007 and 2018ZX09735001-002), CAMS Innovation Fund for Medical Sciences (2016-I2M-2-002, 2016-I2M-1-011 and 2017-I2M-1-008), Beijing Natural Science Foundation (7162129).

[19] *Raal FJ, Chilton R, Ranjith N et al.* **PCSK9 Inhibitors: From Nature's Lessons to Clinical Utility**. Endocrine, metabolic & immune disorders drug targets 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32053090
ABSTRACT
BACKGROUND: Proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors are a novel class of non-statin lipid lowering therapy that reduce LDL-cholesterol by 50 - 60%. PCSK9 inhibitors decrease LDL-cholesterol by preventing intracellular degradation of LDL receptors; subsequently, a greater number of LDL-receptors are available on the cell surface to extract circulating LDL. OBJECTIVE: To describe the origins of PCSK9 inhibitors and their current use in clinical practice. METHODS: We performed a narrative review of the PCSK9 inhibitor class of drugs Results: Current data indicates that PCSK9 inhibitors effectively reduce LDL-cholesterol and are well tolerated and safe. PCSK9 inhibitors have also been shown to reduce cardiovascular event rates in patients with stable atherosclerotic cardiovascular disease and in patients with a recent (up to one year) acute coronary syndrome. Given the costs, chronicity of the treatment and the potential budget impact, PCSK9 inhibitors are often limited to patients with the highest absolute risk for major adverse cardiovascular events despite optimal treatment with high-intensity statin and ezetimibe. CONCLUSION: PCSK9 inhibitors have a favorable safety, efficacy and tolerability profile. Post-marketing safety surveillance and real-world studies are needed to further support the long-term safety profile of this class of medicine.

[20] *Strilchuk L, Tocci G, Fogacci F, Cicero AFG*. **An overview of rosuvastatin/ezetimibe association for the treatment of hypercholesterolemia and mixed dyslipidemia**. Expert opinion on pharmacotherapy 2020:1-9.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32036729
ABSTRACT
Introduction: Although statin therapy is a powerful lipid-lowering strategy, only one-fifth of statin users currently reach their lipid goals. In addition, statin treatment alone has relatively low efficacy

in reducing other lipid fractions than low-density lipoprotein-cholesterol (LDL-C). In such cases, most guidelines recommend adding the cholesterol absorption inhibitor ezetimibe.Areas covered: This paper summarizes the main pharmacological characteristics of rosuvastatin and ezetimibe (mechanism of action, metabolism), their lipid-lowering and pleiotropic effects, with particular attention to the clinical effects of the combined drugs in hypercholesterolemia and mixed dyslipidemia patients (such as the ones affected by diabetes mellitus and Acquired Immune Deficiency Syndrome (AIDS)).Expert opinion: The additive effect of rosuvastatin and ezetimibe helps to reach lipid goals in a large number of high-risk patients, while avoiding some safety issues related to high dosages of intensive statin therapy. Patients with diabetes receive additional benefits from ezetimibe as they seem to absorb cholesterol more effectively than non-diabetic ones, because of increased NPC1L1 gene expression. Ezetimibe augments rosuvastatin triglyceride-lowering and anti-inflammatory effects, as well. Taking into account its excellent safety profile and lack of clinically relevant drug-drug interactions, the rosuvastatin/ezetimibe association is a valuable alternative to statin dose uptitration.

[21] *Yang B, Ren XL, Li ZH et al.* **Lowering effects of fish oil supplementation on proinflammatory markers in hypertension: results from a randomized controlled trial**. Food & function 2020; 11:1779-1789.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32044905
ABSTRACT
Reduced inflammation is one of the potential mechanisms underlying the cardioprotective efficacy of fish oil enriched with eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Supplementation with fish oil has favorable effects on cardiometabolic profiles in Inner Mongolia patients with hypertension, but whether the cardiovascular benefits can be ascribed to reduced subclinical inflammation is unclear among this population. Seventy-seven middle-aged/elderly hypertensive volunteers were randomly assigned to receive either fish oil (FO, n = 38, 2 g day-1 EPA + DHA) or control corn oil (CO, n = 39) for 90 days. FA compositions in erythrocytes and C-reactive protein (CRP, mg L-1), interleukin-6 (IL-6, pg mL-1) and tumor necrosis factor-alpha (TNF-alpha, pg mL-1) concentrations in the plasma were measured before and after the 90-day supplementation, and the cardiometabolic risk was expressed as continuously distributed z-scores calculated by standardizing and then summing the individual cardiovascular risk factors. Significant reductions in the TNF-alpha (-1.87 +/- 2.71 vs. -0.64 +/- 2.62, p = 0.02) and CRP levels (-0.85 +/- 2.49 vs. 0.56 +/- 2.14, p = 0.01) were found in the FO group compared with the CO group, but not in the IL-6 levels (-0.66 +/- 1.05 vs. -0.25 +/- 0.94, p = 0.10). The decreases in the changes of TNF-alpha levels were positively correlated with the reductions in the cardiometabolic risk scores in the subjects supplemented with FO (r = 0.35, p = 0.02), but not in the control subjects supplemented with CO (r = 0.09, p = 0.54). FO supplementation increased the levels of EPA (p = 0.013), DHA (p = 0.040) and total n-3 FA (p = 0.035), and decreased the levels of 20:4n-6 (p = 0.041) and total n-6 FA (p = 0.011) and the ratio of n-6 to n-3 FA (p = 0.001), compared with the changes related to the CO group. The increases in the changes of erythrocyte total n-3 FA levels were inversely correlated with the concentrations of TNF-alpha (r = -0.34, p = 0.001) and CRP (r = -0.29, p = 0.020). The present findings suggest that fish oil supplementation may attenuate the proinflammatory reactions in hypertension, which might help promote the cardiometabolic benefits in this Inner Mongolia population.

[22] *Capoulade R, Torzewski M, Mayr M et al.* **ApoCIII-Lp(a) complexes in conjunction with Lp(a)-OxPL predict rapid progression of aortic stenosis**. Heart 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32054669
ABSTRACT
OBJECTIVE: This study assessed whether apolipoprotein CIII-lipoprotein(a) complexes (ApoCIII-Lp(a)) associate with progression of calcific aortic valve stenosis (AS). METHODS: Immunostaining for ApoC-III was performed in explanted aortic valve leaflets in 68 patients with leaflet pathological grades of 1-4. Assays measuring circulating levels of ApoCIII-Lp(a) complexes were measured in 218 patients with mild-moderate AS from the AS Progression Observation: Measuring Effects of Rosuvastatin (ASTRONOMER) trial. The progression rate of AS, measured as annualised changes in peak aortic jet velocity (Vpeak), and combined rates of aortic valve replacement (AVR) and cardiac death were determined. For further confirmation of the assay data, a proteomic analysis of purified Lp(a) was performed to confirm the presence of apoC-III on Lp(a). RESULTS: Immunohistochemically detected ApoC-III was prominent in all grades of leaflet lesion severity. Significant interactions were present between ApoCIII-Lp(a) and Lp(a), oxidised phospholipids on apolipoprotein B-100 (OxPL-apoB) or on apolipoprotein (a) (OxPL-apo(a)) with annualised Vpeak (all $p<0.05$). After multivariable adjustment, patients in the top tertile of both apoCIII-Lp(a) and Lp(a) had significantly higher annualised Vpeak ($p<0.001$) and risk of AVR/cardiac death ($p=0.03$). Similar results were noted with OxPL-apoB and OxPL-apo(a). There was no association between autotaxin (ATX) on ApoB and ATX on Lp(a) with faster progression of AS. Proteomic analysis of purified Lp(a) showed that apoC-III was prominently present on Lp(a). CONCLUSION: ApoC-III is present on Lp(a) and in aortic valve leaflets. Elevated levels of ApoCIII-Lp(a) complexes in conjunction with Lp(a), OxPL-apoB or OxPL-apo(a) identify patients with pre-existing mild-moderate AS who display rapid progression of AS and higher rates of AVR/cardiac death. TRIAL REGISTRATION: NCT00800800.

[23] *London E, Tatsi C, Soldin SJ et al.* **Acute Statin Administration Reduces Levels of Steroid Hormone Precursors**. Hormone and metabolic research = Hormon- und Stoffwechselforschung = Hormones et metabolisme 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32040961
ABSTRACT
Cholesterol-lowering statin drugs are used by approximately 25% of US adults 45 years of age and older and frequency of use is even higher among the elderly. Cholesterol provides the substrate for steroid hormone synthesis and its intracellular concentrations are tightly regulated. Our aim was to evaluate whether statin use acutely changes the circulating levels of cortisol, other glucocorticoid precursor molecules and their metabolites. Fourteen subjects not taking statins were administered a single oral dose (2 mg) of pitavastatin. Blood samples collected at baseline and 24 h post-treatment were analyzed for plasma cholesterol and steroid hormone profile. A parallel study in mice entailed the administration of atorvastatin (10 mg/kg) via orogastric delivery for three consecutive days. Cholesterol and corticosterone levels were quantified at baseline and at 1-day and 1-week post-treatment. Several precursor molecules in the steroidogenic pathway (corticosterone, cortisone, and 11-deoxycortisol) were significantly decreased 24 h after administration of a single dose of pitavastatin in human study subjects. Their circulating cholesterol concentrations were unchanged. In mice, there were no significant differences in serum cholesterol

or corticosterone at 1-day or 1-week post-treatment compared to both pre-treatment baseline levels and control group levels. We conclude that acute dysregulation of the production of certain glucocorticoid precursor molecules was observed after a single treatment with a lipophilic statin drug. This may be of clinical relevance for individuals with underlying or subclinical adrenal insufficiency.

[24] *Song X, Zhao X, Liebeskind DS et al.* **Associations between systemic blood pressure parameters and intraplaque hemorrhage in symptomatic intracranial atherosclerosis: a high-resolution MRI-based study**. Hypertension research : official journal of the Japanese Society of Hypertension 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32037397
ABSTRACT
The associations between blood pressure parameters and intracranial vulnerable plaques have not been fully elucidated. The purpose of this study was to investigate the associations between systemic blood pressure parameters, as well as their variability, and intraplaque hemorrhage (IPH) in stroke patients with intracranial atherosclerosis. We retrospectively analyzed the high-resolution MRI data set of intracranial atherosclerosis from a comprehensive stroke center. The atherosclerotic plaque burden and presence of IPH in each vessel were obtained from vessel wall imaging. Blood pressure parameters in the first week of admission were used. The systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse pressure (PP), and their variability (standard deviation [SD] and coefficient of variation [CV]) were compared between the IPH (+) and IPH (-) groups. Logistic regression analysis was used to demonstrate the correlations between different blood pressure parameters and IPH. The results indicated that SBP and PP were associated with multiple plaques and severe luminal stenosis after adjusting for confounders, with OR = 1.071, 95% CI: (1.044-1.098) and OR = 1.039, 95% CI: (1.019-1.060) for SBP and OR = 1.058, 95% CI: (1.027-1.089) and OR = 1.044, 95% CI: (1.019-1.070) for PP, respectively. SBP was associated with IPH after adjusting for cardiovascular risk factors, with OR = 1.021, 95% CI: (1.003-1.038), but not after correcting for plaque burden, with OR = 1.014, 95% CI: (0.996-1.032). No associations between blood pressure variability and atherosclerotic plaque burden or IPH were detected in this study. In conclusion, SBP is associated with IPH after adjusting for cardiovascular risk factors but not after further correction for atherosclerotic plaque burden. The association between blood pressure variability and intracranial atherosclerosis requires further study.

[25] *de Oliveira PSS, da Paixao ABF, da Rocha Junior LF et al.* **Atorvastatin inhibits IL-17A, TNF, IL-6, and IL-10 in PBMC cultures from patients with severe rheumatoid arthritis**. Immunobiology 2020:151908.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32051095
ABSTRACT
BACKGROUND: Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by joint damage, and it may present with comorbidities at the systemic level. The Th1/Th2/Th17 CD4(+) lymphocyte imbalance produces inflammatory cytokines, which begin to act, injuring joint tissue. Atorvastatin is a cholesterol- lowering drug with a range of biological effects including anti-inflammatory potential. Patients with rheumatoid arthritis who used statins exhibited clinical improvement. However, the mechanism is not fully understood. Therefore, we aimed to evaluate

the RA immunomodulatory activity of atorvastatin. METHODS: Peripheral blood mononuclear cells (PBMCs) of RA patients and healthy donors were exposed to atorvastatin in different concentrations following a cytotoxicity assay. Th1, Th2, and Th17 cytokines profiles were evaluated in the culture supernatant by cytometric bead array (CBA). Data were analyzed using the Wilcoxon test, and differences were considered significant when $p < 0.05$. RESULTS: Atorvastatin showed no toxicity at the tested doses in RA PBMC cultures, and at 10muM, it showed the most significant results, reducing IL-17A ($p = 0.002$), TNF ($p = 0.002$), and IL-6 ($p = 0.008$) supernatant levels. The outcomes also revealed that only patients with more severe disease activity and those sensitive to corticoid treatments were responders to atorvastatin in vitro. CONCLUSION: These findings suggest the potential immunomodulatory action of atorvastatin as a mechanism in rheumatoid arthritis treatment.

[26] *Duell PB, Fazio S*. **Aggressive Treatment for Severe Forms of Familial Hypercholesterolemia**. Journal of the American College of Cardiology 2020; 75:575-577.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32057370
ABSTRACT

[27] *Santos RD, Stein EA, Hovingh GK et al.* **Long-Term Evolocumab in Patients With Familial Hypercholesterolemia**. Journal of the American College of Cardiology 2020; 75:565-574.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32057369
ABSTRACT
BACKGROUND: Proprotein convertase subtilisin/kexin type 9 inhibitor therapy is a treatment option for patients with familial hypercholesterolemia (FH) who are unable to reach low-density lipoprotein cholesterol (LDL-C) goals. OBJECTIVES: The aim of this study was to provide long-term safety and efficacy data for evolocumab in patients with homozygous FH (HoFH) and severe heterozygous FH (HeFH). METHODS: In this open-label, single-arm study, patients with HoFH or severe HeFH >/=12 years of age and on stable lipid-lowering therapy began subcutaneous evolocumab 420 mg monthly or 420 mg every 2 weeks if on lipoprotein apheresis. After 12 weeks, those not on apheresis could be up-titrated to 420 mg every 2 weeks. The primary endpoint was the incidence of treatment-emergent adverse events; secondary endpoints were changes in LDL-C and other lipids. RESULTS: In total, 300 patients (106 with HoFH, including 14 <18 years of age at enrollment) received evolocumab for a median of 4.1 years. Adverse events occurred in 89.3% of patients, the most common of which were nasopharyngitis, influenza, upper respiratory tract infection, and headache. Mean change in LDL-C from baseline to week 12 was -21.2% (-59.8 mg/dl) in patients with HoFH and -54.9% (-104.4 mg/dl) in those with severe HeFH and was sustained over time. Of 48 patients with HoFH who were up-titrated, mean change in LDL-C improved from -19.6% at week 12 to -29.7% after 12 weeks of 420 mg every 2 weeks. The adjudicated cardiovascular event rate was 2.7% per year. Of 61 patients receiving apheresis at enrollment, 16 discontinued apheresis. CONCLUSIONS: Evolocumab was well tolerated and effectively reduced plasma LDL-C levels in patients with HoFH and severe HeFH over a median of 4.1 years.

[28] *Abd-Rabo MM, Wahman LF, El Hosary R, Ahmed IS*. **High-fat diet induced alteration in lipid enzymes and inflammation in cardiac and brain tissues: Assessment of the effects of Atorvastatin-loaded nanoparticles**. Journal of biochemical and molecular toxicology 2020:e22465.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32048413

ABSTRACT

Treatment with Lipitor is associated with several adverse impacts. Here we investigated the effects of low Lipitor nanoparticles (atorvastatin calcium nanopartilcle [AC-NP]), with size less than 100 , on enzymes of lipid metabolism and inflammation in cardiac, hepatic, and brain tissues of hypercholestremic adult male rats. Adult male rats were divided into five experimental groups. In group 1, the intact control (normal pellet diet), animals were fed a normal control diet; the other four groups were fed a high-fat diet (HFD) for 6 weeks. After 6 weeks, groups from 2 to 5 were assigned as a positive control (HFD), HFD + Lipitor, HFD + AC-NP-R1, or HFD + AC-NP-R2. Different treatments were administrated orally for two regimen periods (R1 daily and R2 once every 3 days). The treatment was conducted for two consecutive weeks. The HFD group faced a significant elevation in 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA), associated with a significant reduction in low-density lipoprotein receptor (LDL-R) along with cholesterol 7 alpha-hydroxylase enzyme in hepatic tissues, compared with the control group. Also, the HFD group induced hepatic, cardiac, and brain inflammation, evidenced by increased hepatic oxidative stress markers and cardiac homocysteine, together with elevated proinflammatory cytokines interleukin-1beta (IL-1beta) and IL-6 levels in brain tissue, compared with the control group. Different AC-NP treatments significantly augmented both mRNA LDL-R and mRNA 7alpha-hydroxylase expression in hepatic tissues, associated with significant depletion in mRNA HMG-CoA expression, compared with HFD + Lipitor. The inflammation symptoms were ameliorated by the AC-NP treatments, compared to HFD + Lipitor. Lipitor encapsulation in NP formulation results in increased efficiency and reduced dose-related adverse effects known to be associated with the Lipitor chronic administration.

[29] *Setia N, Movva S, Balakrishnan P et al.* **Genetic analysis of familial hypercholesterolemia in Asian Indians: A single-center study**. Journal of clinical lipidology 2020.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32044282

ABSTRACT

BACKGROUND: Familial hypercholesterolemia (FH), an autosomal codominant disorder characterized by very high low-density lipoprotein cholesterol, is strongly associated with premature coronary artery disease. OBJECTIVES: Molecular landscape of FH in Asian Indians is not well studied, although this ethnic group comprises a large proportion of the world population. Knowledge of mutations in these groups is useful for identifying persons affected with FH, saving their lives, and cascade screening in their relatives. METHODS: Potential cases of FH (n = 100) were identified by criteria adapted for the Indian population from Dutch Lipid Clinic Network criteria. Pathogenic variants were analyzed in LDLR, APOB 100 (exons 26 and 29), PCSK9, and APOE genes using Sanger sequencing and multiplex ligation-dependent probe amplification technique. Cases in whom there were no pathogenic variants were tested by next-generation sequencing using a targeted panel of genes. RESULTS: Thirty-eight pathogenic variants were identified in 47 of 100 unrelated probands. Of these variants, 33 were identified in LDLR, 3 in APOB, and 2 in PCSK9 genes. Ten pathogenic variants were novel. Mutations were detected in 91.4% of those subjects classified as definite, 40% as probable, and in 18.8% as possible FH cases based on modified Dutch Lipid Clinic Network criteria. A likely founder mutation in intron 10 (c.1587-1G>A) of LDLR gene was observed in 6 North Indian families. The conventional pathogenic variants in APOB and PCSK9 genes and those previously reported in LDLR gene among Asian Indians were not detected in this cohort.

CONCLUSION: This study demonstrates genetic heterogeneity of FH in India. The variants observed were different from those described in Western populations. Next-generation sequencing technology helped identify new mutations in APOB gene, suggesting that in less-studied populations, it is better to sequence the whole gene rather than test for specific mutations.

[30] *Werner RA, Thackeray JT, Bengel FM*. **Does lipid-lowering medication improve cardiac sympathetic nerve integrity?** Journal of nuclear cardiology : official publication of the American Society of Nuclear Cardiology 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32043241
ABSTRACT

[31] *Seyedi SHS, Mottaghi A, Mirmiran P et al.* **The relationship between dietary patterns and lipoprotein-associated phospholipase A2 levels in adults with cardiovascular risk factors: Tehran Lipid and Glucose Study**. Journal of research in medical sciences : the official journal of Isfahan University of Medical Sciences 2020; 25:3.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32055243
ABSTRACT
Background: Pathogenesis of cardiovascular diseases (CVDs) may be indicated by lipoprotein-associated phospholipase A2 (Lp-PLA2), serving as an inflammatory biomarker. However, the general dietary predictors of Lp-PLA2 have not been investigated so far. The aim of the present study is to investigate the relationship between the serum levels of Lp-PLA2 and dietary patterns in adults with cardiovascular risk factors. Materials and Methods: Dietary patterns extracted using factor analysis and serum levels of Lp-PAL2 in 470 adults aged 40-70 years who participated in the 5(th) phase of the Tehran Lipid and Glucose Study (2011-2014) were determined. Associations between the dietary patterns and serum levels of Lp-PAL2 considering some confounder factors were evaluated. Results: The results showed that Western and semi-Mediterranean dietary patterns had significant effects on changes in Lp-PLA2 levels in univariate analyses. In multivariate analyses, after adjusting for age, sex, total cholesterol, low-density lipoprotein cholesterol, body mass index and physical activity, energy intake, hormone therapy for women, and taking blood lipid-lowering drugs as potential confounders, the Western dietary pattern remained a significant factor influencing the Lp-PLA2 level (beta value: 1.65, 95% confidence interval: 1.12, 1.89; $P < 0.05$). Moreover, after adjustment for the mentioned confounder factors, the effect of the semi-Mediterranean dietary pattern on Lp-PLA2 disappeared. Conclusion: It can be concluded that the Western dietary pattern is associated with higher Lp-PLA2 levels. We recommend that adults eat less carbonated drinks, fast foods, salty snacks, mayonnaise, and organ meat to counteract increased serum Lp-PLA2 levels, which are directly associated with vascular inflammation and CVDs.

[32] *Moore JL, McFarland GE, Novak Z et al.* **Effects of statin and antiplatelet therapy noncompliance and intolerance on patient outcomes following vascular surgery**. Journal of vascular surgery 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32035776
ABSTRACT

OBJECTIVE: Prior studies have evaluated the effects of statin and antiplatelet agent (APA) medications on patients with peripheral arterial disease. Although the benefits of statin and APA use are well-described, there is a paucity of research into the specific outcomes of patients who are not compliant or those who are unable to take the medication owing to intolerance. Here we examine the outcomes of patients intolerant to statin and APA and compare them with patients who are compliant or noncompliant with these therapies. METHODS: Patients treated from 2005 to 2018 in the Vascular Quality Initiative registry were included. Patients with missing data or deaths within 30 days of procedure were removed. Patients were considered noncompliant if they were previously prescribed a medication at discharge but were not taking it at 1-year follow-up or if the patient was reported to be noncompliant in the registry. Medication intolerance was defined if listed as "no, for medical reasons," and mortality data were ascertained using the Social Security Death Index, which is regularly cross-referenced to the Vascular Quality Initiative registry. RESULTS: We identified 105,628 patients who met our inclusion criteria. Statin intolerance was noted in 2.3% at discharge and 2.1% at the 1-year follow-up, with 0.7% listed as intolerant at all stages. Factors associated with increased risk of intolerance to statins included female gender (P = .001), discharge APA intolerance (P = .004), insurance status (non-U.S. insurance) (P < .001), discharge APA noncompliance (P = .019), and discharge angiotensin converting enzyme inhibitor noncompliance (P = .005). Patients who were compliant with statins showed a 91% survival at 5 years vs 87% survival in noncompliant patients and 87% in intolerant patients at 5 years (P < .001). Patients with statin intolerance have a similar survival curve as noncompliant patients across all registry cohorts. Noncompliance with statins was correlated with noncompliance with APA medications (R = 0.16, P < .001). Factors associated with increased risk of statin noncompliance included preoperative ambulatory status (requiring assistance) (P = .039), female sex (P < .001), peripheral vascular intervention (P < .001) or infrainguinal open bypass procedure surgery (P = .001), discharge status (to nursing home) (P = .006) and insurance (self-pay) (P < .001). CONCLUSIONS: Patients not taking statin and APA medications have a substantially decreased 5-year survival irrespective of the reason for not taking. Importantly, patients noted to be intolerant have a similar survival curve as noncompliant patients across all registry cohorts. Intolerant patients may benefit from attempts to alter statin dose, type (hydrophilic vs lipophilic), or from newer agents such as PCSK9 inhibitors.

[33] *Trinder M, Francis GA, Brunham LR*. **Association of Monogenic vs Polygenic Hypercholesterolemia With Risk of Atherosclerotic Cardiovascular Disease**. JAMA cardiology 2020.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32049305

ABSTRACT

Importance: Monogenic familial hypercholesterolemia (FH) is associated with lifelong elevations in low-density lipoprotein cholesterol (LDL-C) levels and increased risk of atherosclerotic cardiovascular disease (CVD). However, many individuals with hypercholesterolemia have a polygenic rather than a monogenic cause for their condition. It is unclear if a genetic variant for hypercholesterolemia alters the risk of CVD. Objectives: To assess whether a genetic variant for hypercholesterolemia alters the risk of atherosclerotic CVD and to evaluate how this risk compares with that of nongenetic hypercholesterolemia. Design, Setting, and Participants: In this genetic-association, case-control, cohort study, individuals aged 40 to 69 years were recruited by the UK Biobank from across the United Kingdom between March 13, 2006, and October 1, 2010, and

followed up until March 31, 2017. Genotyping array and exome sequencing data from the UK Biobank cohort were used to identify individuals with monogenic (LDLR, APOB, and PCSK9) or polygenic hypercholesterolemia (LDL-C polygenic score >95th percentile based on 223 single-nucleotide variants in the entire cohort). The data were analyzed from July 1, 2019, to December 30, 2019. Main Outcomes and Measures: The study investigated the association of genotype with the risk of coronary and carotid revascularization, myocardial infarction, ischemic stroke, and all-cause mortality among the overall study population and among participants with monogenic FH (n = 277), polygenic hypercholesterolemia (n = 2379), or hypercholesterolemia with undetermined cause (n = 2232) at comparable levels of LDL-C measured at study enrollment. Results: For the 48741 individuals with genotyping array and exome sequencing data, the mean (SD) age was 56.6 (8.0) years, and 54.5% were female (n = 26541 of 48741). A monogenic FH variant for hypercholesterolemia was found in 277 individuals (0.57%, 1 in 176 individuals). Participants with monogenic FH were significantly more likely than those without monogenic FH to experience an atherosclerotic CVD event at 55 years or younger (17 of 277 [6.1%] vs 988 of 48464 [2.0%]; P < .001). Compared with the general population, both monogenic and polygenic hypercholesterolemia were associated with an increased risk of CVD events. Moreover, among individuals with comparable levels of LDL-C, both monogenic (hazard ratio, 1.93; 95% CI, 1.34-2.77; P < .001) and polygenic hypercholesterolemia (hazard ratio, 1.26; 95% CI, 1.03-1.55; P = .03) were significantly associated with an increased risk of CVD events compared with the risk of such events in individuals with hypercholesterolemia without an identified genetic cause. Conclusions and Relevance: The findings of this study suggest that among individuals with hypercholesterolemia, genetic determinants of LDL-C levels may impose additional risk of CVD. Thus, understanding the possible genetic cause of hypercholesterolemia may provide important prognostic information to treat patients.

[34] *Corpechot C, Poupon R, Chazouilleres O*. **New treatments/targets for primary biliary cholangitis**. JHEP reports (Online) 2019; 1:203-213.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32039371
ABSTRACT
Primary biliary cholangitis (PBC) is an autoimmune, cholestatic, chronic liver disease that ultimately progresses towards cirrhosis and liver failure if untreated. While ursodeoxycholic acid has been established as standard of care for PBC in the last few decades, significant advances in second-line treatment options have recently been made and new therapeutic developments are currently under evaluation. The purpose of this article is to provide the clinician with an overview of the current treatment options and future opportunities for patients with PBC.

[35] *Lebeau PF, Byun JH, Platko K et al.* **Pcsk9 knockout exacerbates diet-induced non-alcoholic steatohepatitis, fibrosis and liver injury in mice**. JHEP reports (Online) 2019; 1:418-429.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32039393
ABSTRACT
The fatty acid translocase, also known as CD36, is a well-established scavenger receptor for fatty acid (FA) uptake and is abundantly expressed in many metabolically active tissues. In the liver, CD36 is known to contribute to the progression of non-alcoholic fatty liver disease and to the more severe non-alcoholic steatohepatitis, by promoting triglyceride accumulation and subsequent lipid-

induced endoplasmic reticulum (ER) stress. Given the recent discovery that the hepatocyte-secreted proprotein convertase subtilisin/kexin type 9 (PCSK9) blocks CD36 expression, we sought to investigate the role of PCSK9 in liver fat accumulation and injury in response to saturated FAs and in a mouse model of diet-induced hepatic steatosis. Methods: In this study, we investigated the role of PCSK9 on the uptake and accumulation of FAs, as well as FA-induced toxicity, in a variety of cultured hepatocytes. Diet-induced hepatic steatosis and liver injury were also assessed in Pcsk9 (-/-) mice. Results: Our results indicate that PCSK9 deficiency in cultured hepatocytes increased the uptake and accumulation of saturated and unsaturated FAs. In the presence of saturated FAs, PCSK9 also protected cultured hepatocytes from ER stress and cytotoxicity. In line with these findings, a metabolic challenge using a high-fat diet caused severe hepatic steatosis, ER stress inflammation and fibrosis in the livers of Pcsk9 (-/-) mice compared to controls. Given that inhibition of CD36 ablated the observed accumulation of lipid in vitro and in vivo, our findings also highlight CD36 as a strong contributor to steatosis and liver injury in the context of PCSK9 deficiency. Conclusions: Collectively, our findings demonstrate that PCSK9 regulates hepatic triglyceride content in a manner dependent on CD36. In the presence of excess dietary fats, PCSK9 can also protect against hepatic steatosis and liver injury. Lay summary: The proprotein convertase subtilisin/kexin type 9 (PCSK9) is a circulating protein known to reduce the abundance of receptors on the surface of liver cells charged with the task of lipid uptake from the circulation. Although PCSK9 deficiency is known to cause lipid accumulation in mice and in cultured cells, the toxicological implications of this observation have not yet been reported. In this study, we demonstrate that PCSK9 can protect against cytotoxicity in cultured liver cells treated with a saturated fatty acid and we also show that Pcsk9 knockout mice develop increased liver injury in response to a high-fat diet.

[36] *Xia B, Lin P, Ji Y et al.* **Ezetimibe promotes CYP7A1 and modulates PPARs as a compensatory mechanism in LDL receptor-deficient hamsters**. Lipids in health and disease 2020; 19:24.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32035489

ABSTRACT

BACKGROUND: The LDL-C lowering effect of ezetimibe has been attributed primarily to increased catabolism of LDL-C via up-regulation of LDL receptor (LDLR) and decreased cholesterol absorption. Recently, ezetimibe has been demonstrated to have reverse cholesterol transport (RCT) promoting effects in mice, hamsters and humans. However, the underlying mechanisms are still not clear. The aim of this study is to investigate whether ezetimibe improves RCT-related protein expression in LDLR(-/-) hamsters. METHODS: A high-fat diet was used to induce a human-like hyperlipidemia in LDLR(-/-) hamsters. Lipid profiles were assayed by commercially available kits, and the effects of ezetimibe on lipid metabolism-related protein expression were carried out via western blot. RESULTS: Our data demonstrated that ezetimibe administration significantly reduced plasma total cholesterol (~ 51.6% reduction, $P < 0.01$) and triglyceride (from ~ 884.1 mg/dL to ~ 277.3 mg/dL) levels in LDLR(-/-) hamsters fed a high-fat diet. Ezetimibe administration (25 mg/kg/d) significantly promoted the protein expression of cholesterol 7 alpha-hydroxylase A1 (CYP7A1), LXRbeta and peroxisome proliferator-activated receptor (PPAR) gamma; and down-regulated the protein expression of PPARalpha and PPARbeta. However, it showed no significant effect on sterol regulatory element-binding protein (SREBP)-1c, SREBP-2, proprotein convertase subtilisin/kexin type 9 (PCSK9), Niemann-Pick C1-like 1 (NPC1L1), and ATP-biding cassette (ABC) G5/G8.

CONCLUSION: Ezetimibe may accelerate the transformation from cholesterol to bile acid via promoting CYP7A1 and thereby enhance RCT. As a compensatory mechanism of TG lowering, ezetimibe promoted the protein expression of PPARgamma and decreased PPARalpha and beta. These results are helpful in explaining the lipid-lowering effects of ezetimibe and the potential compensatory mechanisms.

[37] *Yao YS, Li TD, Zeng ZH*. **Mechanisms underlying direct actions of hyperlipidemia on myocardium: an updated review**. Lipids in health and disease 2020; 19:23.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32035485
ABSTRACT
Hyperlipidemia is a common metabolic disorder and one of risk factors for cardiovascular disease. Clinical studies have shown that hyperlipidemia increases the risk of non-ischemic heart failure, while decreasing serum lipids can reverse heart dysfunction. Apart from indirectly affecting the function of the heart by promoting the development of atherosclerosis, hyperlipidemia also affects the systolic function and cardiac electrophysiological response of the heart directly, which may be related to gradual accumulation of cardiac lipids and consequent systemic oxidative stress, proinflammatory state and mitochondrial dysfunction. However, the mechanism underlying direct effects of hyperlipidemia on the heart are not fully understood. In this review, we provide an updated summary of recent experimental and clinical studies that focus on elucidating the mechanisms of the action of hyperlipidemia on cardiac function, the relationship between heart failure and serum lipids, and protective effects of lipid-lowering drugs on the heart. The exciting progress in this field supports the prospect of guiding early protection of the heart to benefit the patients with chronic hyperlipidemia and familial hyperlipidemia.

[38] *Cho EB, Cho HJ, Choi M et al.* **Low high-density lipoprotein cholesterol and high triglycerides lipid profile in neuromyelitis optica spectrum disorder: Associations with disease activity and disability**. Multiple sclerosis and related disorders 2020; 40:101981.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32045867
ABSTRACT
BACKGROUND: Altered lipid metabolism is a feature of systemic autoimmune diseases. Dyslipidemia is associated with the disease activity and progression in patients with multiple sclerosis. However, in neuromyelitis optica spectrum disorder (NMOSD), changes in the lipid profile and the associations between specific lipid levels and disease activity/disability are unknown. METHODS: Serum samples (N = 148) were collected from 53 patients with aquaporin-4 (AQP4)-positive NMOSD when they were not treated with lipid lowering agents. Fasting lipid (total cholesterol, triglyceride [TG], high-density lipoprotein cholesterol [HDL-C], low-density lipoprotein cholesterol) levels were compared between 39 patients with NMOSD, not taking steroids, and 142 age-, sex-, and body mass index-matched healthy controls. In addition, we analyzed the differences in the lipid profile between attack and remission samples and the associations between lipid profiles and clinical outcome in all 148 samples from 53 patients. The generalized estimating equation was used. RESULTS: Patients with NMOSD showed lower HDL-C and higher TG levels compared to healthy controls ($p = 0.017$ and $p < 0.001$, respectively). HDL-C level was significantly lower during attack than remission (beta = -7.851; $p = 0.035$), and TG level had positive correlation with EDSS scores (beta = 0.014; $p = 0.002$) regardless of disease activity status. However, enhanced

lesions on magnetic resonance imaging were not associated with lipid profiles. CONCLUSION: Dyslipidemia with low HDL-C and high TG correlated disease activity and disability in AQP4-positive NMOSD. It remains to be elucidated whether altered lipid metabolism contributes to deleterious immune response, possibly through inflammation, or is secondary to neurological disability in NMOSD.

[39] *Morino J, Hirai K, Kaneko S et al.* **Successful treatment of cholesterol crystal embolism with anti-proprotein convertase subtilisin/kexin type 9 (PCSK9) antibody: a case report**. Renal failure 2020; 42:173-178.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32046605
ABSTRACT
Background: We report a unique case of renal cholesterol crystal embolism (CCE) induced by carotid artery stenting that was successfully treated with evolocumab, a fully human monoclonal antibody against proprotein convertase subtilisin kexin type 9 (PCSK9).Case presentation: A 77-year-old man with hypertension, hyperlipidemia, and chronic kidney disease was referred to our department for decreased estimated glomerular filtration rate (eGFR)-from 32.0 to 13.9 mL/min/1.73 m(2)-5 weeks after carotid artery stenting. Further examination revealed livedo reticularis in the bilateral toes and eosinophilia (723/muL). Skin biopsy from livedo reticularis tissue in the bilateral toes showed cholesterol clefts in the small arteries. The patient was therefore diagnosed with CCE. After 25 weeks' administration of evolocumab at a dose of 140 mg subcutaneously administered every 2 weeks, his eGFR had improved from 10.7 to 18.1 mL/min/1.73 m(2).Conclusion: Evolocumab may have a beneficial effect on renal involvement in patients with CCE.

[40] *Sahebkar A, Simental-Mendia LE, Pirro M et al.* **Author Correction: Impact of ezetimibe on plasma lipoprotein(a) concentrations as monotherapy or in combination with statins: a systematic review and meta-analysis of randomized controlled trials**. Scientific reports 2020; 10:2999.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32060362
ABSTRACT
An amendment to this paper has been published and can be accessed via a link at the top of the paper.

[41] *Bakouei F, Delavar MA, Mashayekh-Amiri S et al.* **Efficacy of n-3 fatty acids supplementation on the prevention of pregnancy induced-hypertension or preeclampsia: A systematic review and meta-analysis**. Taiwanese journal of obstetrics & gynecology 2020; 59:8-15.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32039806
ABSTRACT
The efficacy of n-3 fatty acids supplementation on the prevention of pregnancy-induced hypertension or preeclampsia remains unclear. The aim of study was to examine the effect of supplementation with EPA, and/or DHA, and/or ALA during pregnancy on the pregnancy-induced hypertension or preeclampsia. A systematic search was performed on Scopus, PubMed, Web of Science (WoS), Cochrane Library, and Google scholar, which covered the period between 1991 and 2018. The clinical trials with any control groups (i.e. placebo or other supplementation) were

selected. The whole process of meta-analysis and data analysis was done using Comprehensive Meta-Analysis (Version 2.0, Biostat). The searched keywords were: "Fatty Acids, Omega-3", "n-3 Polyunsaturated Fatty Acid" "Eicosapentaenoic Acid", "Docosahexaenoic Acids", "n-3 Polyunsaturated Fatty Acid", "n-3 PUFAs", "alpha-Linolenic Acid", "fish oil", "Nuts", "nutrient", or their synonyms "pregnancy induced hypertension" and preeclampsia. In addition, some key journals, according to Scopus report and the references of the original and review articles, were manually searched for possible related studies. The meta-analysis of the 14 comparisons demonstrated that n-3 fatty acids supplementation played a protective role against the risk of preeclampsia (RR, 0.82; 95% CI, 0.70-0.97; p = 0.024; I2 = 19.0%). The analysis of the 10 comparisons revealed that n-3 fatty acid supplements for pregnant women did not mitigate the risk of pregnancy-induced hypertension (RR, 0.98; 95% CI, 0.90-1.07; p = 0.652; I2 = 0%). The n-3 fatty acid supplements are an effective strategy to prevent the incidence of preeclampsia in women with low-risk pregnancies.

[42] *Hwang I, Park SI, Lee S et al.* **Pharmacokinetics of fixed-dose combination of rosuvastatin 20 mg and ezetimibe 10 mg compared to concurrent administration of individual tablets in healthy Korean subjects**. Translational and clinical pharmacology 2018; 26:16-24.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32055543

ABSTRACT

This study aimed to compare the pharmacokinetics of fixed-dose combination (FDC) tablet of rosuvastatin 20 mg/ezetimibe 10 mg with that of concurrent administration of individual rosuvastatin 20 mg tablet and ezetimibe 10 mg tablet in healthy subjects. A randomized, open label, single-dose, two-way crossover study was conducted. Subjects randomly received test formulation (FDC tablet of rosuvastatin 20 mg/ezetimibe 10 mg) or reference formulation (co-administration of rosuvastatin 20 mg tablet and ezetimibe 10 mg tablet). After 2 weeks of washout, subjects received the other treatment. Blood samples were collected up to 72 hours post-dose in each period. Plasma concentrations of rosuvastatin, ezetimibe and total ezetimibe (ezetimibe + ezetimibe glucuronide) were analyzed by liquid chromatography-tandem mass spectrometry (LC/MS/MS). The geometric mean ratio (GMR) of Cmax and AUClast (90% confidence interval, CI) for rosuvastatin was 1.036 (0.979-1.096) and 1.024 (0.981-1.070), respectively. The corresponding values for ezetimibe were 0.963 (0.888-1.043) and 1.021 (0.969-1.074), respectively. The corresponding values for total ezetimibe were 0.886 (0.835-0.940) and 0.983 (0.946-1.022), respectively. FDC tablet containing rosuvastatin 20 mg and ezetimibe 10 mg is bioequivalent to the co-administration of commercially available individual tablets of rosuvastatin and ezetimibe as GMR with 90% CI of Cmax and AUClast of rosuvastatin, ezetimibe and total ezetimibe were contained within conventionally accepted bioequivalence criteria.