Literature update week 04 (2020)

[1] *Kleess LE, Janicic N*. **SEVERE HYPERTRIGLYCERIDEMIA IN PREGNANCY: A CASE REPORT AND REVIEW OF THE LITERATURE**. AACE clinical case reports 2019; 5:e99-e103.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31967011
ABSTRACT
Objective: Severe gestational hypertriglyceridemia is a rare disease, and there are no published guidelines to assist the clinician in management. However, due to the elevations in lipids that occur during pregnancy, this condition is encountered in clinical practice and presents a therapeutic dilemma. We report the successful management and treatment of a patient with severe gestational hypertriglyceridemia and conducted a review of the literature regarding treatment modalities. Methods: We conducted a search in PubMed from 1990 to 2018 for the following terms: "severe hypertriglyceridemia in pregnancy;" "management of hypertriglyceridemia in pregnancy;" "apheresis for severe gestational hypertriglyceridemia;" "TPN for severe gestational hypertriglyceridemia;" "insulin for severe gestational hypertriglyceridemia;" and "heparin for treatment of severe hypertriglyceridemia." We then reviewed the literature. Results: Given the risks to the mother and fetus of severe hypertriglyceridemia, aggressive therapy should be initiated within a multidisciplinary team. There are multiple treatment modalities, including restrictive diet, various medications such as niacin, fibrates, intravenous heparin, insulin, and apheresis. Choice of treatment will depend on the patient's comorbidities, clinical status, and if there are any associated complications. Conclusion: Treatment for severe gestational hypertriglyceridemia should be initiated immediately and aggressively to avoid risk to the mother and infant, including pancreatitis, hyperviscosity syndrome, preeclampsia, fetal death, and preterm labor.

[2] *Burdick DJ, Skelton NJ, Ultsch M et al.* **Design of Organo-Peptides As Bipartite PCSK9 Antagonists**. ACS chemical biology 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31962046
ABSTRACT
Proprotein convertase subtilisin/kexin 9 (PCSK9) has become an important therapeutic target for lipid lowering, since it regulates low-density lipoprotein cholesterol (LDL-c) levels by binding to liver LDL receptors (LDLR) and effecting their intracellular degradation. However, the development of small molecule inhibitors is hampered by the lack of attractive PCSK9 target sites. We recently discovered helical peptides that are able to bind to a cryptic groove site on PCSK9, which is situated in proximity to the main LDLR binding site. Here, we designed potent bipartite PCSK9 inhibitors by appending organic moieties to a helical groove-binding peptide to reach a hydrophobic pocket in the proximal LDLR binding region. The ultimately designed 1-amino-4-phenylcyclohexane-1-carbonyl extension improved the peptide affinity by >100-fold, yielding organo-peptide antagonists that potently inhibited PCSK9 binding to LDLR and preserved cellular LDLR. These new bipartite antagonists have reduced mass and improved potency compared to the first-generation peptide antagonists, further validating the PCSK9 groove as a viable therapeutic target site.

[3] *Choubey AP, Alqahtani A, Verghese C*. **Atorvastatin-Induced Eosinophilia**. American journal of therapeutics 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31977565
ABSTRACT

[4] *Ding F, Shan C, Li H et al.* **Simvastatin alleviated diabetes mellitus-induced erectile dysfunction in rats by enhancing AMPK pathway-induced autophagy**. Andrology 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31955524
ABSTRACT
BACKGROUND: Diabetes mellitus-induced erectile dysfunction (DMED) is a common diabetic complication, and new therapeutics and the pathogenesis of DMED need to be investigated. OBJECTIVES: The aim was to investigate the pathogenesis of DMED and the pharmacological mechanism of simvastatin treatment in DMED model rats. MATERIALS AND METHODS: A total of 86 male Sprague-Dawley (SD) rats aged 8 weeks old were used in this study. The rats were divided into 3 groups: control (normal), DMED (streptozotocin (STZ) -injected), and DMED+simvastatin (sim). Each group was subdivided into 2 subgroups for in vitro and in vivo analyses. A bioinformatics method was used to detect differences in gene expression in the corpus cavernosum between normal and DMED rats. Erectile function was measured by a cavernous nerve (CN) electrostimulation test. Corpus cavernosum fibrosis was assessed by Masson staining and Western blotting. Immunofluorescence and Western blotting were performed to explore the differential expression of autophagy-related genes and the AMPK-SKP2-CARM1 pathway genes in rat cavernous smooth muscle cells (CSMCs) and the corpus cavernosum. The autophagosomes of the corpus cavernosum tissue were observed by transmission electron microscopy. RESULTS: Autophagy-related genes and pathways (the AMPK and FoxO pathway) were identified by bioinformatics analysis and confirmed at the protein level. Simvastatin, an AMPK agonist, was used to treat DMED rats for 8 weeks, demonstrating that erectile function was improved for 80.5% ($P < 0.05$) of rats. Corpus cavernosum fibrosis was alleviated ($P < 0.05$), and autophagy was further enhanced ($P < 0.05$); these results might be partially caused by AMPK-SKP2-CARM1 pathway activation ($P < 0.05$). DISCUSSION AND CONCLUSION: Simvastatin could enhance protective autophagy by activating the AMPK-SKP2-CARM1 pathway to improve erectile function in DMED rats.

[5] *Ceglarek U, Dittrich J, Leopold J et al.* **Free cholesterol, cholesterol precursor and plant sterol levels in atherosclerotic plaques are independently associated with symptomatic advanced carotid artery stenosis**. Atherosclerosis 2019; 295:18-24.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31981947
ABSTRACT
BACKGROUND AND AIMS: Circulating sterols result either from cholesterol (CH) synthesis or intestinal uptake. They are mainly esterified and can be oxygenated. Sterols accumulate in atherosclerotic plaques whereby their clinical impact is uncertain. Here, we determined associations between circulating and plaque sterol levels in patients with advanced carotid artery stenosis in respect to a prior ischemic event and statin treatment. METHODS: Free and esterified CH, CH precursors and plant sterols as well as oxysterols were quantified by liquid chromatography-tandem mass spectrometry in 63 consecutive patients undergoing carotid endarterectomy. RESULTS: CH, CH precursors, plant sterols and oxysterols accumulated in carotid artery plaques. Absolute circulating sterol levels were not predictive for their corresponding plaque levels. After normalisation to CH, plant sterol but not oxysterol levels correlated between plasma and plaques. Among the circulating sterols, oxysterols occurred proportionally less in plaques. Furthermore, CH and plant sterols were less esterified in plaques than in plasma. Patients who experienced a prior ischemic event (n = 29) and asymptomatic patients had, except for lanosterol, comparable circulating sterol levels. In contrast, the absolute

plaque levels of free CH, CH precursors and plant sterols as well as oxysterols were increased in symptomatic compared to asymptomatic patients. These differences remained significant for free CH, precursors and 3 out of 4 analyzed plant sterols after adjustment to the most influencing covariates - statin treatment, type 2 diabetes and age. CONCLUSIONS: Increased absolute plaque levels of free CH, precursors and plant sterols predict an ischemic event in patients with advanced carotid artery stenosis.

[6] *Kimer N, Gronbaek H, Fred RG et al.* **Atorvastatin for prevention of disease progression and hospitalisation in liver cirrhosis: protocol for a randomised, double-blind, placebo-controlled trial**. BMJ open 2020; 10:e035284.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31980514
ABSTRACT
INTRODUCTION: Patients with liver cirrhosis are often diagnosed late and once complications are present, the 2-year survival is 50%. Increasing evidence supports systemic inflammation and metabolic dysfunction in the hepatic stellate cell as key drivers of progression of cirrhosis. However, there is no registered medication, that targets inflammation and cellular dysfunction in the liver. METHODS AND ANALYSIS: In a randomised double-blind and placebo-controlled trial with atorvastatin for liver cirrhosis, we aim to investigate clinical endpoints of survival, hospitalisations and safety, but also exploratory endpoints of genomics and protein functions in the liver. ETHICS AND DISSEMINATION: There is no registered medication that actively prevents development of complications or systemic inflammation in liver cirrhosis. All patients continue regular clinical management during the trial period. Atorvastatin has been on the market for several years with a safety profile that is acceptable even in patients with liver disease. A beneficial effect of atorvastatin on clinical outcomes in cirrhosis will provide cheap and effective causal treatment for chronic liver disease. The trial is registered by the Danish Data Protection Agency (P-2019-635) and approved by the Danish Medicines Agency (EudraCT 2019-001806-40) and the Scientific Ethics Committee of the Capital Region of Denmark (H-19030643) before initiation. Reporting of the trial will follow the Consolidated Standards of Reporting Trials guidelines for reporting of randomised clinical trials. TRIAL REGISTRATION NUMBER: The trial is registered in clinicaltrials.gov (NCT04072601) and in clinicaltrialsregister.eu (EudraCT 2019-001806-40) (Pre-results).

[7] *Hero C, Karlsson SA, Franzen S et al.* **Adherence to lipid-lowering therapy and risk for cardiovascular disease and death in type 1 diabetes mellitus: a population-based study from the Swedish National Diabetes Register**. BMJ open diabetes research & care 2020; 8.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31958300
ABSTRACT
AIMS/HYPOTHESIS: Dyslipidemia is an important modifiable risk factor and lipid-lowering treatment (LLT) is essential to reduce the risk of cardiovascular disease (CVD). Studies in type 2 diabetes indicate that low adherence to statin therapy is a barrier to reach full protective potential, and less is known in type 1 diabetes (T1D). The aim was to assessrisk of CVD by adherence and nonpersistence to LLT in T1D. METHOD: A population-based study with a retrospective longitudinal design was conducted between 2006 and 2010, with follow-up until December 2013. In total, 6192 adult individuals withT1D, initiatingLLTbetween 2006 and 2010, were included.Information on LLT, socioeconomic characteristics, comorbidities and cardiovascular eventswere collected. After 18 months, refill adherence was

estimated by calculating medication possession ratio (MPR). Nonpersistence was defined as being without medicines on hand for at least 180 days. Individuals were thereafterfollowed untilCVD, deathorend of follow-up in December 2013. Cox regression analyses were performed to assess adherence level and nonpersistence of LLT as predictor ofCVD. Analyses wereadjusted for cardiovascular risk factors andsocioeconomic status. RESULTS: Mean MPRwas 72%, 52% of the participants had an MPR above 80% and 27% discontinued LLT. There were 637nonfataland58 fatal CVDevents, mean follow-up 3.6 and 3.9 years, respectively. MPR above 80% was associated with reduced risk for nonfatal CVD compared with lower MPR, HR 0.78 (95% CI 0.65 to 0.93)). For fatal CVD, results indicated a negative effect of high adherence but the association did not reach statistical significance, HR 1.96 (0.96 to 4.01). Individuals discontinuing LLT had higher risk of nonfatal CVD, HR 1.43 (95% CI 1.18 to 1.73). CONCLUSIONS/INTERPRETATION: In T1D, the risk for nonfatal CVD was lower among individuals with high adherence and higher among those discontinuing LLT within 18 months. It is important to evaluate andemphasize adherence toprescribedLLTat clinical visits to achieve treatment goals and reduce the risk of CVD.

[8] *Georgakis MK, Malik R, Anderson CD et al.* **Genetic determinants of blood lipids and cerebral small vessel disease: role of high-density lipoprotein cholesterol**. Brain 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31968102

ABSTRACT

Blood lipids are causally involved in the pathogenesis of atherosclerosis, but their role in cerebral small vessel disease remains largely elusive. Here, we explored associations of genetic determinants of blood lipid levels, lipoprotein particle components, and targets for lipid-modifying drugs with small vessel disease phenotypes. We selected genetic instruments for blood levels of high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglycerides, for cholesterol and triglycerides components of size-defined lipoprotein particles, and for lipid-modifying drug targets based on published genome-wide association studies (up to 617 303 individuals). Applying two-sample Mendelian randomization approaches we investigated associations with ischaemic and haemorrhagic manifestations of small vessel disease [small vessel stroke: 11 710 cases, 287 067 controls; white matter hyperintensities (WMH): 10 597 individuals; intracerebral haemorrhage: 1545 cases, 1481 controls]. We applied the inverse-variance weighted method and multivariable Mendelian randomization as our main analytical approaches. Genetic predisposition to higher HDL-C levels was associated with lower risk of small vessel stroke [odds ratio (OR) per standard deviation = 0.85, 95% confidence interval (CI) = 0.78-0.92] and lower WMH volume (beta = -0.07, 95% CI = -0.12 to -0.02), which in multivariable Mendelian randomization remained stable after adjustments for LDL-C and triglycerides. In analyses of lipoprotein particle components by size, we found these effects to be specific for cholesterol concentration in medium-sized high-density lipoprotein, and not large or extra-large high-density lipoprotein particles. Association estimates for intracerebral haemorrhage were negatively correlated with those for small vessel stroke and WMH volume across all lipid traits and lipoprotein particle components. HDL-C raising genetic variants in the gene locus of the target of CETP inhibitors were associated with lower risk of small vessel stroke (OR: 0.82, 95% CI = 0.75-0.89) and lower WMH volume (beta = -0.08, 95% CI = -0.13 to -0.02), but a higher risk of intracerebral haemorrhage (OR: 1.64, 95% CI = 1.26-2.13). Genetic predisposition to higher HDL-C, specifically to cholesterol in medium-sized high-density lipoprotein particles, is associated with both a lower risk of small vessel stroke and lower WMH volume. These analyses indicate that HDL-C raising strategies could

be considered for the prevention of ischaemic small vessel disease but the net benefit of such an approach would need to be tested in a randomized controlled trial.

[9] *Luput L, Sesarman A, Porfire A et al.* **Liposomal simvastatin sensitizes C26 murine colon carcinoma to the antitumor effects of liposomal 5-fluorouracil in vivo**. Cancer science 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31960547
ABSTRACT
5-fluorouracil-based therapy remains the main approach in colorectal cancer, even though there are still some drawbacks, such as chemoresistance. In this study we combined 5-fluorouracil encapsulated in long-circulating liposomes with simvastatin also encapsulated in long-circulating liposomes that was previously proved to exert antitumor actions on the same tumor model. The production of angiogenic/inflammatory proteins was assessed by protein array and the production of markers for tumor aggressiveness (Bcl-2, Bax, and NF-kB) were determined via western blot. Intratumor oxidative stress was evaluated through measurement of malondialdehyde level via HPLC, and through spectrophotometric analysis of catalytic activity of catalase and of total antioxidant capacity. Immunohistochemical analysis of tumors for CD 31 expression was assessed. Intratumor activity of matrix metalloprotease-2 by gelatin zymography was also performed. Our results revealed that combined therapies based on liposomal formulations exerted enhanced antitumor activities compared with combined administration of free drugs, sequential administration of liposomal simvastatin and liposomal 5-fluorouracil showing the strongest antitumor activity in C26 colon carcinoma in vivo mainly, via inhibition of tumor angiogenesis. Important markers for cancer progression (Bcl-2, Bax, NF-kB, and intratumor antioxidants) demonstrated that liposomal simvastatin might sensitize C26 cells to liposomal 5-fluorouracil administration in both regimens tested. The outcome of simultaneous administration of liposomal formulations was superior to sequential administrations of both liposomal types as invasive capacity of C26 tumors was strongly increased after the latest treatment. The antitumor efficacy of combined therapy in C26 colon carcinoma might be linked to the restorative effects on proteins balance involved in tumor angiogenesis.

[10] *Colivicchi F, Massimo Gulizia M, Arca M et al.* **Lipid Lowering Treatment and Eligibility for PCSK9 Inhibition in Post-Myocardial Infarction Patients in Italy: Insights from Two Contemporary Nationwide Registries**. Cardiovascular therapeutics 2020; 2020:3856242.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31969932
ABSTRACT
Introduction: The current use of lipid lowering therapies and the eligibility for proprotein convertase subtilisin/kexin-9 (PCSK9) inhibitors of patients surviving a myocardial infarction (MI) is poorly known. Methods: Using the data from two contemporary, nationwide, prospective, real-world registries of patients with stable coronary artery disease, we sought to describe the lipid lowering therapies prescribed by cardiologists in patients with a prior MI and the resulting eligibility for PCSK9 inhibitors according to the European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) and the Italian regulatory agency (Agenzia Italiana del Farmaco; AIFA) criteria. The study cohort was stratified according to the following low-density lipoprotein cholesterol (LDL-C) levels at the time of enrolment: <70 mg/dl; 70-99 mg/dl and >/=100 mg/dl. Results: Among the 3074 post-MI patients with LDL-C levels available, a target level of LDL-C < 70 mg/dl was present in 1186 (38.6%), while 1150 (37.4%) had LDL-C levels ranging from 70 to 99 mg/dl and the remaining 738 (24.0%) an LDL-C >/= 100 mg/dl. A statin was

prescribed more frequently in post-MI patients with LDL-C levels <70 mg/dl (97.1%) compared to the other LDL-C groups (p < 0.0001). A low dose of statin was prescribed in 9.3%, while a high dose in 61.4% of patients. Statin plus ezetimibe association therapy was used in less than 18% of cases. In the overall cohort, 293 (9.8%) and 450 (22.2%) resulted eligible for PCSK9 inhibitors, according to ESC/EAS and AIFA criteria, respectively. Conclusions: Post-MI patients are undertreated with conventional lipid lowering therapies. A minority of post-MI patients would be eligible to PCSK9 inhibitors according to ESC/EAS guidelines and Italian regulatory agency criteria.

[11] *Brandts J, Ray KK*. **LDL-Cholesterol Lowering Strategies and Population Health - Time to Move to a Cumulative Exposure Model**. Circulation 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31955599
ABSTRACT
Lifetime medication burden from current approaches to LDL-cholesterol (LDL-C) lowering is reliant on small molecules requiring daily dosing with the burden of responsibility placed upon patients. Patient-related factors (risk perception, health literacy) impact adherence and persistence. Adherence to statins and ezetimibe correlate with LDL-C reduction and risk, potentially accounting for approximately 12 000 avoidable cardiovascular events per 500 000 patients annually (1). Attempts to improve adherence have had mixed results with only textmessaging reminders, community health worker-based reinforcement and fixed-dose combination pills shown to be effective at improving adherence and clinical events (2). Patienttailored strategies combining multiple approaches including in-person consultations may yield better outcomes, but implementation is complex, consuming both time and resource. Obesity and smoking cessation have been tackled with monetary compensation. Technology offers scalable low-cost options for pill and refill reminders through the use of telephone calls, text-messages, and mobile apps. Finally, a crucial barrier to long-term adherence is the asymptomatic nature of cardiovascular risk factors which may impact medication adherence. This could be facilitated by simplifying access to prescriptions and refills, through electronic healthcare solutions that connect pharmacies to electronic patient records and enable automated prescriptions. Here we draw on population studies and therapeutic developments to potentially address the issue of adherence and lifetime exposure to LDL-C.

[12] *Paquette M, Gauthier D, Chamberland A et al.* **Circulating PCSK9 is associated with liver biomarkers and hepatic steatosis**. Clinical biochemistry 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31972148
ABSTRACT
BACKGROUND: In parallel to the increasing prevalence of metabolic syndrome, the prevalence of hepatic steatosis has also increased dramatically worldwide. Hepatic steatosis is a major risk factor of hepatic cirrhosis, cardiovascular disease and type 2 diabetes. Circulating levels of proprotein convertase subtilisin/kexin type 9 (PCSK9) have been positively associated with the metabolic syndrome. However, the association between PCSK9 and the liver function is still controversial. OBJECTIVE: The objective of this study is to investigate the association between circulating PCSK9 levels and the presence of hepatic steatosis, as well as with liver biomarkers in a cohort of healthy individuals. METHODS: Total PCSK9 levels were measured by an in-house ELISA using a polyclonal antibody. Plasma albumin, alkaline phosphatase, ALT, AST, total bilirubin and GGT were measured in 698 individuals using the COBAS system. The presence of hepatic steatosis was assessed using

ultrasound liver scans. RESULTS: In a multiple regression model adjusted for age, sex, insulin resistance, body mass index and alcohol use, circulating PCSK9 level was positively associated with albumin (beta=0.102, P=0.008), alkaline phosphatase (beta=0.201, P<0.0001), ALT (beta=0.238, P<0.0001), AST (beta=0.120, P=0.003) and GGT (beta=0.103, P=0.007) and negatively associated with total bilirubin (beta= -0.150, P<0.0001). Tertile of circulating PCSK9 was also associated with hepatic steatosis (OR 1.48, 95% CI 1.05-2.08, P=0.02). CONCLUSION: Our data suggest a strong association between PCSK9 and liver biomarkers as well as hepatic steatosis. Further studies are needed to explore the role of PCSK9 on hepatic function.

[13] *Raju S, Fish JE, Howe KL*. **MicroRNAs as sentinels and protagonists of carotid artery thromboembolism**. Clinical science (London, England : 1979) 2020; 134:169-192.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31971230
ABSTRACT
Stroke is the leading cause of serious disability in the world and a large number of ischemic strokes are due to thromboembolism from unstable carotid artery atherosclerotic plaque. As it is difficult to predict plaque rupture and surgical treatment of asymptomatic disease carries a risk of stroke, carotid disease continues to present major challenges with regard to clinical decision-making and revascularization. There is therefore an imminent need to better understand the molecular mechanisms governing plaque instability and rupture, as this would allow for the development of biomarkers to identify at-risk asymptomatic carotid plaque prior to disease progression and stroke. Further, it would aid in creation of therapeutics to stabilize carotid plaque. MicroRNAs (miRNAs) have been implicated as key protagonists in various stages of atherosclerotic plaque initiation, development and rupture. Notably, they appear to play a crucial role in carotid artery thromboembolism. As the molecular pathways governing the role of miRNAs are being uncovered, we are learning that their involvement is complex, tissue- and stage-specific, and highly selective. Notably, miRNAs can be packaged and secreted in extracellular vesicles (EVs), where they participate in cell-cell communication. The measurement of EV-encapsulated miRNAs in the circulation may inform disease mechanisms occurring in the plaque itself, and therefore may serve as sentinels of unstable plaque as well as therapeutic targets.

[14] *Milajerdi A, Sadeghi A, Mousavi SM et al.* **Influence of Statins on Circulating Inflammatory Cytokines in Patients with Abnormal Glucose Homeostasis: A Meta-Analysis of Data From Randomized Controlled Trials**. Clinical therapeutics 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31955966
ABSTRACT
PURPOSE: Chronic inflammation increases the risks for cardiovascular disease, type 2 diabetes, and cancer. Recently, the antiinflammatory effects of statins, as cholesterol-lowering medications, have been considered. This study systematically reviewed and summarized earlier findings from randomized clinical trials about the effects of statins on serum concentrations of C-reactive protein (CRP) and interleukin (IL)-6 in patients with abnormal glucose homeostasis. METHODS: Relevant articles published through October 2019 were searched using suitable key words on the PubMed/MEDLINE, SCOPUS, EMBASE, and Google Scholar databases. RCTs were included if they compared the effects of statins on serum concentrations of CRP and IL-6 in adults with abnormal glucose homeostasis. The effect sizes were represented as weighted mean differences (WMDs) and 95% CI s using a random-

effects model. Subgroup analysis was performed to find possible sources of heterogeneity. FINDINGS: Overall, 17 publications with 21 effect sizes and which enrolled 3766 subjects (1895 participants in intervention and 1871 in control groups) were included. Combining 13 effect sizes from 10 studies, a significant reduction in serum CRP concentration following the administration of atorvastatin was found (WMD, -0.35; 95% CI, -0.54 to -0.17; I(2) = 90.6%). Based on 5 effect sizes from 4 studies, we found a statistically significant reduction in serum IL-6 concentration after atorvastatin therapy (WMD, -0.44; 95% CI, -0.65 to -0.22; I(2) = 93.9%). Pooling 6 effect sizes from 5 studies revealed a significantly reduced serum concentration of CRP after simvastatin therapy (WMD, -0.66; 95% CI, -0.79 to -0.54; I(2) = 97.6%). IMPLICATIONS: The administration of atorvastatin or simvastatin in patients with abnormal glucose hemostasis was associated with a reduced serum CRP concentration. Atorvastatin therapy might also help to decrease serum IL-6 concentration in these patients.

[15] *Wagner JB, Abdel-Rahman S, Gaedigk A et al.* **Impact of SLCO1B1 genetic variation on rosuvastatin systemic exposure in pediatric hypercholesterolemia**. Clinical and translational science 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31981411
ABSTRACT
This study investigated the impact of SLCO1B1 genotype on rosuvastatin systemic exposure in hypercholesterolemic children and adolescents. Participants (8-21 years) with at least one allelic variant of SLCO1B1 c.521T>C (521TC, n=13; 521CC, n=2) and wild type controls (521TT, n=13) completed a single oral dose pharmacokinetic study. The variability contributed by SLCO1B1 c.521 sequence variation to rosuvastatin (RVA) systemic exposure amongst our pediatric cohort was comparable to previous studies in adults. Rosuvastatin concentration-time curve from 0 to 24h (AUC0-24) was 1.4- and 2.2-fold higher in participants with c.521TC and c.521CC genotype compared 521TT participants, respectively. Inter-individual variability of RVA exposure within SLCO1B1 genotype groups exceeded the ~1.5- to 2-fold difference in mean RVA exposure observed between SLCO1B1 genotype groups, suggesting that other factors also contribute to inter-individual variability in the rosuvastatin dose-exposure relationship. A multivariate model performed confirmed SLCO1B1 c.521T>C genotype as the primary factor contributing to RVA systemic exposure in this pediatric cohort, accounting for ~30% of the variability RVA AUC0-24 . However, of the statin investigated to date in the pediatric population, rosuvastatin has the lowest magnitude of variability in systemic exposure.

[16] *Adams SP, Tiellet N, Alaeiilkhchi N, Wright JM*. **Cerivastatin for lowering lipids**. The Cochrane database of systematic reviews 2020; 1:Cd012501.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31981471
ABSTRACT
BACKGROUND: Cerivastatin was the most potent statin until it was withdrawn from the market due to a number of fatalities due to rhabdomyolysis, however, the dose-related magnitude of effect of cerivastatin on blood lipids is not known. OBJECTIVES: Primary objective To quantify the effects of various doses of cerivastatin on the surrogate markers: LDL cholesterol, total cholesterol, HDL cholesterol and triglycerides in children and adults with and without cardiovascular disease. The aim of this review is to examine the pharmacology of cerivastatin by characterizing the dose-related effect and variability of the effect of cerivastatin on surrogate markers. Secondary objectives To quantify the effect of various doses of cerivastatin compared to placebo on withdrawals due to adverse effects. To

compare the relative potency of cerivastatin with respect to fluvastatin, atorvastatin and rosuvastatin for LDL cholesterol, total cholesterol, HDL cholesterol and triglycerides. SEARCH METHODS: The Cochrane Hypertension Information Specialist searched the following databases for RCTs up to March 2019: CENTRAL (2019, Issue 3), Ovid MEDLINE, Ovid Embase, the WHO International Clinical Trials Registry Platform, and ClinicalTrials.gov.We also searched the European Patent Office, FDA.gov, and ProQuest Dissertations & Theses, and contacted authors of relevant papers regarding further published and unpublished work. The searches had no language restrictions. SELECTION CRITERIA: RCTs and controlled before-and-after studies evaluating the dose response of different fixed doses of cerivastatin on blood lipids over a duration of three to 12 weeks in participants of any age with and without cardiovascular disease. DATA COLLECTION AND ANALYSIS: Two review authors independently assessed eligibility criteria for trials to be included and extracted data. We entered data from RCTs and controlled before-and-after studies into Review Manager 5 as continuous and generic inverse variance data respectively. We collected information on withdrawals due to adverse effects from the RCTs. We assessed all trials using the 'Risk of bias' tool under the categories of sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting, and other potential biases. MAIN RESULTS: Fifty trials (19 RCTs and 31 before-and-after studies) evaluated the dose-related efficacy of cerivastatin in 12,877 participants who had their LDL cholesterol measured. The participants were of any age with and without cardiovascular disease and the trials studied cerivastatin effects within a treatment period of three to 12 weeks. Cerivastatin 0.025 mg/day to 0.8 mg/day caused LDL cholesterol decreases of 11.0% to 40.8%, total cholesterol decreases of 8.0% to 28.8% and triglyceride decreases of 9.0% to 21.4%. We judged the certainty of evidence for these effects to be high. Log dose-response data over doses of 2.5 mg to 80 mg revealed strong linear dose-related effects on LDL cholesterol, total cholesterol and triglycerides. When compared to fluvastatin, atorvastatin and rosuvastatin, cerivastatin was about 250-fold more potent than fluvastatin, 20-fold more potent than atorvastatin and 5.5-fold more potent than rosuvastatin at reducing LDL cholesterol; 233-fold more potent than fluvastatin, 18-fold more potent than atorvastatin and six-fold more potent than rosuvastatin at reducing total cholesterol; and 125-fold more potent than fluvastatin, 11-fold more potent than atorvastatin and 13-fold more potent than rosuvastatin at reducing triglycerides. There was no dose-related effect of cerivastatin on HDL cholesterol, but overall cerivastatin increased HDL cholesterol by 5%. There was a high risk of bias for the outcome withdrawals due to adverse effects, but a low risk of bias for the lipid measurements. Withdrawals due to adverse effects were not different between cerivastatin and placebo in 11 of 19 of these short-term trials (risk ratio 1.09, 95% confidence interval 0.68 to 1.74). AUTHORS' CONCLUSIONS: The LDL cholesterol, total cholesterol, and triglyceride lowering effect of cerivastatin was linearly dependent on dose. Cerivastatin log dose-response data were linear over the commonly prescribed dose range. Based on an informal comparison with fluvastatin, atorvastatin and rosuvastatin, cerivastatin was about 250-fold more potent than fluvastatin, 20-fold more potent than atorvastatin and 5.5-fold more potent than rosuvastatin in reducing LDL cholesterol, and 233-fold greater potency than fluvastatin, 18-fold greater potency than atorvastatin and six-fold greater potency than rosuvastatin at reducing total cholesterol. This review did not provide a good estimate of the incidence of harms associated with cerivastatin because of the short duration of the trials and the lack of reporting of adverse effects in 42% of the RCTs.

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[17] *Yamashita S, Masuda D, Matsuzawa Y*. **Pemafibrate, a New Selective PPARalpha Modulator: Drug Concept and Its Clinical Applications for Dyslipidemia and Metabolic Diseases**. Current atherosclerosis reports 2020; 22:5.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31974794
ABSTRACT
PURPOSE OF REVIEW: Reduction of serum low-density lipoprotein cholesterol (LDL-C) levels by statins, ezetimibe and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors has been shown to significantly reduce cardiovascular events risk. However, fasting and postprandial hypertriglyceridemia as well as reduced high-density lipoprotein cholesterol (HDL-C) remain as residual risk factors of atherosclerotic cardiovascular diseases (ASCVD). To treat patients with hypertriglyceridemia and/or low HDL-C, drugs such as fibrates, nicotinic acids, and n-3 polyunsaturated fatty acids have been used. However, fibrates were demonstrated to cause side effects such as liver dysfunction and increase in creatinine levels, and thus large-scale clinical trials of fibrates have shown negative results for prevention of ASCVD. The failure could be attributed to their low selectivity and potency for binding to peroxisome proliferator-activated receptor (PPAR) alpha. To resolve these issues, the concept of selective PPARalpha modulator (SPPARMalpha) with a superior balance of efficacy and safety has been proposed and pemafibrate (K-877) has been developed. RECENT FINDINGS: Pemafibrate, one of SPPARMsalpha, was synthesized by Kowa Company, Ltd. for better efficiency and safety. Clinical trials in Japan have established the superiority of pemafibrate on effects on serum triglycerides (TG) reduction and HDL-C elevation as well safety. Although available fibrates showed worsening of liver and kidney function test values, pemafibrate indicated improved liver function test values and was less likely to increase serum creatinine or decrease estimated glomerular filtration rate (eGFR). Very few drug-drug interactions were observed even when used concomitantly with statins. Furthermore, pemafibrate is metabolized in the liver and excreted into the bile, while many of available fibrates are mainly excreted from the kidney. Therefore, pemafibrate can be used safely even in patients with impaired renal function since there is no significant increase in its blood concentration. A large-scale trial of pemafibrate, PROMINENT, for dyslipidemic patients with type 2 diabetes is ongoing. Pemafibrate is one of novel SPPARMsalpha and has superior benefit-risk balance compared to conventional fibrates and can be applicable for patients for whom the usage of existing fibrates is difficult such as those who are taking statins or patients with renal dysfunction. In the current review, all the recent data on pemafibrate will be summarized.

[18] *Thapa K, Grewal AS, Kanojia N et al.* **Alcoholic and Non-Alcoholic Liver Diseases: Promising Molecular Drug Targets and their Clinical Development**. Curr Drug Discov Technol 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31965945
ABSTRACT
Alcoholic and non-alcoholic fatty liver diseases have become a serious concern whole over the world. Both these liver diseases have an identical pathology, starting from simple steatosis to cirrhosis and ultimately to hepatocellular carcinoma. Treatment options for alcoholic liver disease (ALD) are still same as it was 50 years ago which includes corticosteroids, pentoxifylline, antioxidants, nutritional support and abstinence; and for non-alcoholic fatty liver disease (NAFLD) weight loss, insulin sensitizers, lipid lowering agents and anti-oxidants are the only treatment options. Despite of broad research in understanding the disease pathophysiology, limited treatments are available for clinical use. Some therapeutic strategies based on targeting a specific molecule have been developed to lessen

the consequences of disease and are under clinical investigation. Therefore, focus on multiple molecular targets will help to develop an efficient therapeutic strategy. This review comprises of brief overview of pathogenesis of ALD and NAFLD; recent molecular drug targets explored for ALD and NAFLD that may prove to be effective for multiple therapeutic regimens and also clinical status of these promising drug targets for liver diseases.

[19] *Morieri ML, Shah HS, Sjaarda J et al.* **A PPARA Polymorphism Influences the Cardiovascular Benefit of Fenofibrate in Type 2 Diabetes: Findings From ACCORD Lipid**. Diabetes 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31974142
ABSTRACT
The cardiovascular benefits of fibrates have been shown to be heterogeneous and to depend on the presence of atherogenic dyslipidemia. We investigated whether genetic variability in the PPARA gene, coding for the pharmacological target of fibrates (PPAR-alpha), could be used to improve the selection of patients with type 2 diabetes who may derive cardiovascular benefit from addition of this treatment to statins. We identified a common variant at the PPARA locus (rs6008845, C/T) displaying a study-wide-significant influence on the effect of fenofibrate on major cardiovascular events (MACE) among 3,065 self-reported White subjects treated with simvastatin and randomized to fenofibrate or placebo in the Action-to-Control-Cardiovascular-Risk-in-Diabetes (ACCORD) Lipid Trial. T/T homozygotes (36% of participants) experienced a 51% MACE reduction in response to fenofibrate (HR=0.49; 95%C.I. 0.34-0.72) whereas no benefit was observed for other genotypes (p for interaction=3.7x10(-4)). The "rs6008845-by-fenofibrate" interaction on MACE was replicated in African-Americans from ACCORD (N=585, p=0.02) and in external cohorts (ACCORD-Blood-Pressure, ORIGIN, and TRIUMPH, total N=3059, p=0.005). Remarkably, rs6008845 T/T homozygotes experienced a cardiovascular benefit from fibrate even in the absence of atherogenic dyslipidemia. Among these individuals, but not among carriers of other genotypes, fenofibrate treatment was associated with lower circulating levels of CCL11 - a pro-inflammatory and atherogenic chemokine also known as eotaxin (p for rs6008845-by-fenofibrate interaction=0.003). The Genotype-Tissue Expression (GTEx) dataset revealed regulatory functions of rs6008845 on PPARA expression in many tissues. In summary, we have found a common PPARA regulatory variant that influences the cardiovascular effects of fenofibrate and that could be used to identify T2D patients who would derive benefit from fenofibrate treatment, in addition to those with atherogenic dyslipidemia.

[20] *Liu A, Li K, Xu L et al.* **Metformin Delays the Development of Atherosclerosis in Type 1 Diabetes Mellitus via the Methylglyoxal Pathway**. Diabetes Ther 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31955370
ABSTRACT
INTRODUCTION: The aim of our study was to determine the effect of metformin administration on juvenile type 1 diabetes mellitus and atherosclerosis in apolipoprotein E null (ApoE(-/-)) mice and to explore the mechanism involved. METHODS: Eighteen male ApoE(-/-) mice were injected with streptozotocin to induce diabetes (diabetic group) and 18 mice who received no streptozotocin injection were assigned to the control (non-diabetic) group. Six mice in each group were then orally administered metformin, simvastatin, or vehicle, respectively, following which the mice were euthanized and tissue samples collected. RESULTS: Fasting plasma glucose, low-density lipoprotein-cholesterol, and triglyceride concentrations were significantly higher in the three diabetic groups than

in the three non-diabetic groups. Plasma N(in)-(carboxymethyl)lysine and N(in)-(carboxyethyl)lysine concentrations were higher in the diabetic mice than in the non-diabetic mice, but metformin treatment reduced these concentrations more effectively than simvastatin. All three diabetic groups demonstrated obvious arterial plaques, but these were largest in the vehicle-treated diabetic group. The expression of extracellular nitric oxide synthase was highest in the simvastatin-treated non-diabetic group, and in diabetic mice it was higher in the simvastatin-treated group than in the other two groups. No significant expression of AMP-activated protein kinase (AMPK) was measured in the three diabetic groups, but a low level of AMPK expression was detected in the non-diabetic groups. CONCLUSIONS: Metformin can limit the development of atherosclerosis secondary to diabetes in young diabetic mice. A possible mechanism is the removal of methylglyoxal, thereby reducing the formation of advanced glycation endproducts, rather than by lowering the blood glucose level. FUNDING: This work was supported by the National Natural Science Foundation of China (81901106) and Jinan clinical medical science and technology innovation plan (201907002).

[21] *Wada H, Ogita M, Suwa S et al.* **Guideline adherence and long-term clinical outcomes in patients with acute myocardial infarction: a Japanese Registry of Acute Myocardial Infarction Diagnosed by Universal Definition (J-MINUET) substudy**. European heart journal. Acute cardiovascular care 2020:2048872620902024.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31976749
ABSTRACT
BACKGROUND: The association between guideline adherence and long-term outcomes in patients with acute myocardial infarction in real-world clinical practice remains unclear. METHODS: We investigated 3283 consecutive patients with acute myocardial infarction who were selected from a prospective, nation-wide, multicentre registry (J-MINUET) database covering 28 institutions in Japan between July 2012 and March 2014. Among the 2757 eligible patients, we evaluated the use of seven guideline-recommended therapies, including urgent revascularisation, door-to-balloon time of 90 minutes or less, and five discharge medications (P2Y12 inhibitors on aspirin, beta-blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, statins, lipid-lowering drugs). The primary endpoint was a composite of all-cause death, non-fatal myocardial infarction, non-fatal stroke, cardiac failure and urgent revascularisation for unstable angina up to 3 years. RESULTS: The overall median composite guideline adherence was 85.7%. Patients were divided into the following three groups: complete (100%) adherence group (n=862); moderate adherence (75% to <100%) group (n=911); and low adherence (0-75%) group (n=984). The rate of adverse cardiovascular events was significantly lower in the complete adherence group than in the low and moderate adherence groups (log rank P<0.0001). Multivariate Cox regression analysis showed complete guideline adherence was also significantly associated with lower adverse cardiovascular events compared with low guideline adherence (hazard ratio 0.66; 95% confidence interval 0.52-0.85; P=0.001). CONCLUSION: The use of guideline-based therapies for patients with acute myocardial infarction in contemporary clinical practice was associated with significant decreases in adverse long-term clinical outcomes. TRIAL REGISTRATION: UMIN Unique trial Number: UMIN000010037.

[22] *Rerup SA, Rorth R, Bang LE et al.* **Room for improvement: Initiation of lipid lowering treatment and achievement of lipid target levels - a Danish registry-based study**. European heart journal. Quality of care & clinical outcomes 2020.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31958115

ABSTRACT

AIMS: Prevention of adverse outcomes in individuals with high cholesterol levels may be improved by intensified lipid lowering treatment (LLT). We studied whether treatment goals of low density lipoprotein cholesterol (LDL-C) were reached within one year from baseline (defined as first LDL-C measurement) in a Danish population. METHODS AND RESULTS: Danish registries were used to identify all persons in the Northern Region of Denmark who had LDL-C measured between 1997-2012 and who were naive to LLT. Patients were categorized in LDL-C <5 or >/= 5 mmol/L and further subdivided into low, high, and very high predicted cardiovascular (CV)-risk as suggested by European guidelines for risk stratification. Initiation of LLT and lipid target levels were assessed after one year (3.0, 2.5 and 1.8 mmol/L, respectively).In this study we examined the intensity of LLT and whether treatment goals were reached. More patients with LDL-C >/=5 mmol/L, regardless of the CV-risk, initiated LLT compared with patients who had a very high CV-risk and LDL-C <5 mmol/l. In total 37.7% (n = 32,581) of all patients with a follow-up LDL-C, and 25.1% (n = 3,229) of patients with LDL-C >/=5 mmol/l, had achieved their target levels after one year. Only 45.2% (n = 4,545) of the LDL-C >/=5 mmol/l high risk patients with a follow up LDL-C had started LLT 12 months after baseline. CONCLUSION: Less than half of patients presenting with an LDL-C >/=5 mmol/l start LLT within one year, representing a missed opportunity for both primary and secondary prevention of cardiovascular disease.

[23] *Mujaj B, Bos D, Kavousi M et al.* **Serum insulin levels are associated with vulnerable plaque components in the carotid artery: the Rotterdam Study**. European journal of endocrinology / European Federation of Endocrine Societies 2020.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31958313

ABSTRACT

To investigate the association between fasting serum insulin and glucose levels with atherosclerotic plaque composition in the carotid artery. Impaired insulin and glucose levels are implicated in the etiology of cardiovascular disease, however, their influence on the formation and composition of atherosclerotic plaque remains unclear. Methods In 1740 participants (mean age 72.9 years, 46% women, 14.4 % diabetes mellitus) from the population-based Rotterdam Study, we performed carotid MRI to evaluate the presence of calcification, lipid core, and intraplaque hemorrhage in carotid atherosclerosis. All participants also underwent blood sampling to obtain information on serum insulin and glucose levels. Using logistic regression models, we assessed the association of serum insulin and glucose levels (per standard deviation (SD) and in tertiles) with the different plaque components, while adjusting for sex, age, intima-media thickness, and cardiovascular risk factors. Results Serum insulin levels were associated with the presence of intraplaque hemorrhage [adjusted odds ratio (OR): 1.42 (95% confidence interval (CI) 1.12-1.7)]. We found no association with the presence of calcification or lipid core. Sensitivity analyses restricted to individuals without diabetes mellitus yielded similar results. No associations were found between serum glucose levels and any of the plaque components. Conclusions Serum insulin levels are associated with the presence of vulnerable components of carotid plaque, specifically with intraplaque hemorrhage. These findings suggest a complex role for serum insulin in the pathophysiology of carotid atherosclerosis and in plaque vulnerability. Key Words: carotid artery, insulin, glucose, intraplaque hemorrhage, lipid core, calcification, MRI, atherosclerosis, epidemiology.

[24] *Danese MD, Pemberton-Ross P, Catterick D, Villa G*. **Estimation of the increased risk associated with recurrent events or polyvascular atherosclerotic cardiovascular disease in the United Kingdom**. European journal of preventive cardiology 2020:2047487319899212.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31964187
ABSTRACT
AIMS: The aims of this study were to re-estimate the international REduction of Atherothrombosis for Continued Health (REACH) risk equation using United Kingdom data and to distinguish different relative hazards for specific atherosclerotic cardiovascular disease event histories. METHODS AND RESULTS: Patients in the UK Clinical Research Practice Datalink (CPRD) were included as of 1 January 2005 if they were 40 years or older, had 2 or more years of prior data, received one or more moderate or high-intensity statin in the previous year, and had a history of myocardial infarction, ischemic stroke, or other atherosclerotic cardiovascular disease. Patients were followed until a composite endpoint of myocardial infarction, ischemic stroke or cardiovascular death, loss to follow-up, or end of observation. We re-estimated the REACH risk equation hazard ratios (HRs) using CPRD data (re-estimated REACH model). Our event history model replaced the REACH vascular bed variables with more specific event histories. There were 60,838 patients with 5.25 years of mean follow-up. In the validation model, HRs were in the same direction, and generally greater than REACH. In the event history model, HRs compared to other atherosclerotic cardiovascular disease alone included: recurrent myocardial infarction (HR 1.19, 95% confidence interval (CI) 1.05-1.34), recurrent ischemic stroke (HR 1.36, 95% CI 1.03-1.80), myocardial infarction and other atherosclerotic cardiovascular disease (HR 1.31, 95% CI 1.23-1.38), ischemic stroke and other atherosclerotic cardiovascular disease (HR 1.40, 95% CI 1.23-1.60), myocardial infarction and ischemic stroke (HR 1.94, 95% CI 1.23-3.04), and myocardial infarction, ischemic stroke and other atherosclerotic cardiovascular disease (HR 1.93, 95% CI 1.47-2.54). CONCLUSION: A detailed cardiovascular event history may be useful for estimating the relative risk of future cardiovascular events.

[25] *Feng C, Xiao L, Yu JC et al.* **Simvastatin promotes osteogenic differentiation of mesenchymal stem cells in rat model of osteoporosis through BMP-2/Smads signaling pathway**. European review for medical and pharmacological sciences 2020; 24:434-443.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31957858
ABSTRACT
OBJECTIVE: By establishing osteoporosis (OP) model in rats, the specific regulatory effect of simvastatin on promoting the differentiation of mesenchymal stem cells (MSCs) into osteoblasts through the bone morphogenetic protein 2 (BMP-2)/Smads signaling pathway was investigated. MATERIALS AND METHODS: A total of 45 Sprague-Dawley rats were selected to establish the OP model by performing ovariectomy. The rats were divided into OP model group (OP group, n=15), 10-7 mmol/L simvastatin treatment group (SIM group, n=15), and normal control group (Control group, n=15). After the experimental period, the enzyme-linked immunosorbent assay (ELISA) was applied to observe the serum levels of tumor necrosis factor-alpha (TNF-alpha), interleukin-6 (IL-6), and IL-1. Reverse Transcription-Polymerase Chain Reaction (RT-PCR) was adopted to detect the contents of the differentiation-associated genes [runt-related transcription factor 2 (RUNX2) and Osterix (Osx)]. Later, the bone marrow MSCs (BMSCs) were selected and divided into Control group, 10-7 mol/L simvastatin group (SIM group), and osteoinduction medium group (OM group). Cell morphology in each group was observed. The Cell Counting Kit-8 (CCK-8) was performed to determine the proliferation activity of

BMSCs. ELISA was performed to measure the level of alkaline phosphatase (ALP). RT-PCR was conducted to examine the levels of key differentiation-associated gene RUNX2 and those in BMP-2/Smads pathway. Moreover, the Western blotting was adopted to analyze the expressions of RUNX2 and genes in BMP-2/Smads pathway. RESULTS: The serum levels of TNF-alpha, IL-6, and IL-1 in OP group were remarkably higher than those in the Control group, and their levels in the SIM group were close to those in the Control group. The elevated messenger ribonucleic acid (mRNA) levels of the key differentiation-associated factors RUNX2, osteoprotegerin (OPG), osteopontin (OPN), and Osx were observed in the SIM group. In vitro cell culture revealed that the cells were in a favorable growth status in the SIM group and OM group, mostly manifesting in fusiform or spindle shape, and proliferated rapidly. In addition, the ALP level notably increased in the two groups compared with that in the Control group ($p<0.05$). Both SIM group and OM group had evidently higher mRNA expression levels of RUNX2, OPG, OPN, and Osx than those in the Control group ($p<0.05$), consistent with the expression trends of the genes in BMP-2/Smads pathway. The Western blotting indicated that the expression levels of RUNX2 and genes in BMP-2/Smads pathway in the SIM group were significantly higher than those in the Control group. CONCLUSIONS: Simvastatin can promote the differentiation of MSCs into osteoblasts in the OP rat model through the BMP-2/Smads signaling pathway.

[26] *Licito A, Marotta G, Battaglia M et al.* **Assessment of pharmacogenomic SLCO1B1 assay for prediction of neuromuscular pain in type 2 diabetes mellitus and cardiovascular patients: preliminary results**. European review for medical and pharmacological sciences 2020; 24:469-477.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31957862

ABSTRACT

OBJECTIVE: At present, several strategies for preventing neuromuscular pain in Type 2 Diabetes Mellitus (T2DM) have been investigated. Recently, findings on genetic variants associated with adverse events to statin-based therapy have been reported. The study aimed at measuring whether Pharmacogenomics (PGx) profile can affect neuromuscular pain in patients carrying T2DM and cardiovascular diseases. An extensive panel of 5 polymorphisms on 4 candidate genes, previously validated as significant markers related to Sulphonylureas and Glitinides (SU-G) plus Simvastatin neuromuscular toxicity, is herein analyzed and discussed. PATIENTS AND METHODS: We genotyped 76 T2DM patients carrying cardiovascular dyscrasia undergone anti-diabetic and anti-cholesterolemic polypharmacy. 35 subjects out of the total received concurrent SU-G and Statin-based therapy. Candidate variants consisted of drug transporters, such as Solute Carrier Organic 1B1 (SLCO1B1) Val174Ala ATP-binding cassette subfamily B member (ABCB1), subfamily C member 8 (ABCC8), and drug biotransformers of Cytochrome P450 Family (CYP) including CYP2C9*2 CYP2C9*3 CYP2C8*3, and CYP3A4*22. Moreover, we also focused on an early outline evaluation of the genotyping costs and benefits. RESULTS: 6 out of 35 patients treated with SU-G plus statins (17.1% experienced adverse neuropathy events). Pharmacogenomics analysis showed a lack of any correlation between candidate gene polymorphisms and toxicity, except for the SLCO1B1 T521C allele; 14.3% of patients had a high risk for grade >2 neuromuscular pain (Odds Ratio [OR] 2.61.95% CI 0.90-7.61, p=0.03). CONCLUSIONS: The clinical polymorphism effectiveness outlined therein will be assured by diagnostic improvements suitable for driving treatment decisions. In light of our experimental results and literature data, the analysis of the SLCO1B1 T521C variant will allow clinicians to take advantage from a better treatment planned for their patients in order to minimize neuromuscular pain and maximize benefits.

[27] *Khoury E, Brisson D, Gaudet D*. **Preclinical discovery and development of evolocumab for the treatment of hypercholesterolemia**. Expert opinion on drug discovery 2020:1-12.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31973581
ABSTRACT
Introduction: Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a serine protease that binds and promotes the lysosomal degradation of the low-density lipoprotein receptors (LDLR). Upon its discovery in 2002, PCSK9 inhibition has subsequently emerged as a novel target for lowering LDL-cholesterol (LDL-C) and reducing coronary heart disease. Evolocumab, a monoclonal antibody directed against human PCSK9, was approved in 2015 as an adjunct to lipid-lowering therapy for treating patients with familial hypercholesterolemia (FH) or patients with high cardiovascular risk, who are treated with maximally tolerated lipid-lowering agents and have not reached the recommended LDL-C levels.Areas covered: The authors illustrate the rapid pace of the drug development process that monoclonal antibodies, including evolocumab, have demonstrated during the last decade. In less than 15 years from its discovery, this lipid-lowering target has successfully progressed from bench-side to clinical practice and has been recently approved to reduce cardiovascular events in patients with established atherosclerotic cardiovascular disease (ASCVD).Expert opinion: Evolocumab has demonstrated a good safety profile and robust efficacy in terms of its lipid-lowering effect and ASCVD risk reduction, yet affordability, accessibility, and cost-effectiveness of PCSK9 monoclonal antibodies remain a hurdle in the 'real-world' setting. These challenges facing the upcoming generation of precision medicine therapies must be addressed upfront.

[28] *Pang J, Sullivan DR, Brett T et al.* **Familial Hypercholesterolaemia in 2020: A Leading Tier 1 Genomic Application**. Heart, lung & circulation 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31974028
ABSTRACT
Familial hypercholesterolaemia (FH) is caused by a major genetic defect in the low-density lipoprotein (LDL) clearance pathway. Characterised by LDL-cholesterol elevation from birth, FH confers a significant risk for premature coronary artery disease (CAD) if overlooked and untreated. With risk exposure beginning at birth, early detection and intervention is crucial for the prevention of CAD. Lowering LDL-cholesterol with lifestyle and statin therapy can reduce the risk of CAD. However, most individuals with FH will not reach guideline recommended LDL-cholesterol targets. FH has an estimated prevalence of approximately 1:250 in the community. Multiple strategies are required for screening, diagnosing and treating FH. Recent publications on FH provide new data for developing models of care, including new therapies. This review provides an overview of FH and outlines some recent advances in the care of FH for the prevention of CAD in affected families. The future care of FH in Australia should be developed within the context of the National Health Genomics Policy Framework.

[29] *Jiao L, Zhuang Y, Jiang M et al.* **Angiopoietin-like 2 has auxo-action in atherosclerosis by promoting atherosclerotic calcification**. International journal of clinical and experimental pathology 2017; 10:9084-9091.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31966781
ABSTRACT
OBJECTIVE: To study the effects of angiopoietin-like 2 (Angptl2) on atherosclerotic calcification in aortic artery of ApoE(-/-) mice. METHODS: Twelve 6-week-old male mice were randomly divided into control

group (n=6) and interventional group (n=6), the control group were fed with high fat diet and the interventional group were fed with high fat diet and at the eighth week interventional group mice were infused (intravenously) with purified recombinant Angptl-2 once a week for one month. All mice were sacrificed when the mice were 16 weeks old, blood was collected and plasma triglyceride (TG), total cholesterol (TC), low density lipoprotein cholesterol (LDLC) were measured, aortic sections were stained with hematoxylin and eosin (HE) or Von Kossa and were observed under microscope. Calcium content and alkaline phosphatase activity of aorta were measured to measure the degree of vascular calcification. The expressions of Runx2 protein and mRNA levels in aortic sections of mice were detected by immunohistochemistry, Western Blot and qRT-PCR respectively. RESULTS: The plasma TG, TC and LDLC level in interventional group was significantly higher than that in control group and the expression of Runx2 in aortic had the similar results. HE staining demonstrated significant thickening of the intima, with typical atherosclerotic plaque formation in interventional group mice, and Von Kossa staining showed spotty black clumps of aortic calcification under the fibrous cap plaque, while control group had atherosclerotic plaques without significant calcium deposits formation; The quantitative analysis showed that aortic vascular wall calcium and alkaline phosphatase activity were significantly higher in the intervention group than that of the control group (P<0.01). CONCLUSIONS: Angptl-2 could increase ApoE(-/-) mice plasma lipid level, it also facilitate the expression of Runx2, calcium content and ALP activity in aortic and then accelerate atherosclerotic calcification. Our experiments demonstrated that Angptl2 could accelerate atherosclerotic calcification. It reminded us that by controlling or decreasing the Anglt-2 level in plasma could help inhibit atherosclerotic calcification and then provides a new target to prevent coronary heart disease.

[30] *Zhu L, Ji X, Jiang L et al.* **Utility of genetic variants to predict prognosis in coronary artery disease patients receiving statin treatment**. International journal of clinical and experimental pathology 2017; 10:8795-8803.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31966745
ABSTRACT
Statins are widely used drugs for lowering low-density lipoprotein cholesterol (LDL-C) and can prevent cardiovascular events. This study aimed to evaluate the influence of single nucleotide polymorphisms (SNPs) and their cumulative effects on the prognosis of coronary artery disease (CAD) patients treated with statins. Sixteen SNPs were genotyped in 785 CAD patients receiving statin therapy, and their associations with clinical features and prognosis of patients were investigated. Four SNPs (rs2296651, rs11206510, rs8192870, and rs1801133) were significantly associated with complications of CAD (P<0.05). Four SNPs (rs8192870, rs4149056, rs12916, and rs2231142) affected blood lipid levels (P<0.05). Furthermore, rs1801133 showed a weak but significant association with fasting plasma glucose (P = 0.033). Survival analyses showed that rs11206510 (adjusted HR = 1.891, 95% CI: 1.188-3.010, P = 0.007) and rs1801133 (adjusted HR = 1.499, 95% CI: 1.141-1.971, P = 0.004) were independently associated with an increased risk of major cardiovascular events, and exhibited cumulative effect on even-free survival (adjusted HR = 1.810, 95% CI: 1.179-2.802, P = 0.007). In conclusion, rs11206510 and rs1801133 were independent risk factors for clinical outcome in CAD patients treated with statins.

[31] *Huang J, Wang D, Huang LH, Huang H*. **Roles of Reconstituted High-Density Lipoprotein Nanoparticles in Cardiovascular Disease: A New Paradigm for Drug Discovery**. International journal of molecular sciences 2020; 21.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31979310
ABSTRACT
Epidemiological results revealed that there is an inverse correlation between high-density lipoprotein (HDL) cholesterol levels and risks of atherosclerotic cardiovascular disease (ASCVD). Mounting evidence supports that HDLs are atheroprotective, therefore, many therapeutic approaches have been developed to increase HDL cholesterol (HDL-C) levels. Nevertheless, HDL-raising therapies, such as cholesteryl ester transfer protein (CETP) inhibitors, failed to ameliorate cardiovascular outcomes in clinical trials, thereby casting doubt on the treatment of cardiovascular disease (CVD) by increasing HDL-C levels. Therefore, HDL-targeted interventional studies were shifted to increasing the number of HDL particles capable of promoting ATP-binding cassette transporter A1 (ABCA1)-mediated cholesterol efflux. One such approach was the development of reconstituted HDL (rHDL) particles that promote ABCA1-mediated cholesterol efflux from lipid-enriched macrophages. Here, we explore the manipulation of rHDL nanoparticles as a strategy for the treatment of CVD. In addition, we discuss technological capabilities and the challenge of relating preclinical in vivo mice research to clinical studies. Finally, by drawing lessons from developing rHDL nanoparticles, we also incorporate the viabilities and advantages of the development of a molecular imaging probe with HDL nanoparticles when applied to ASCVD, as well as gaps in technology and knowledge required for putting the HDL-targeted therapeutics into full gear.

[32] *O'Neill D, Stone NJ, Forman DE*. **Primary Prevention Statins in Older Adults: Personalized Care for a Heterogeneous Population**. J Am Geriatr Soc 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31967323
ABSTRACT
The 2018 American College of Cardiology/American Heart Association guidelines on the management of cholesterol acknowledge a lack of robust randomized clinical trial data to support routine use of statin therapy for primary prevention in adults older than 75 years. Shared decision making is emphasized because potential recommendations should reflect limitations of the current data, as well as heterogeneity of the older adult population, spanning the robust to the most frail. Although the National Institute on Aging recently funded PRagmatic EValuation of EvENTs And Benefits of Lipid-Lowering in OldEr Adults (PREVENTABLE), a trial to study benefits of statins in very old adults, data are not anticipated for 5 years. Thus interim guidance is essential. Furthermore, even when PREVENTABLE is completed, individual idiosyncrasies among older adults suggest that decisions for each patient will still need to be personalized, relative to their unique clinical situation. In this article, we present three case studies to highlight dynamics that commonly impact choices regarding statins in older adults. Details underlying shared decision making are also described including the evolving application of coronary artery calcium to inform this practice.

[33] *Hwang HS, Kim JS, Kim YG et al.* **Circulating PCSK9 Level and Risk of Cardiovascular Events and Death in Hemodialysis Patients**. Journal of clinical medicine 2020; 9.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31963408
ABSTRACT

Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a promising new target for the prevention of cardiovascular (CV) events. However, the clinical significance of circulating PCSK9 is unclear in hemodialysis (HD) patients. A total of 353 HD patients were prospectively enrolled from June 2016 to August 2019 in a K-cohort. Plasma PCSK9 level was measured at the time of study enrollment. The primary endpoint was defined as a composite of CV event and death. Plasma PCSK9 level was positively correlated with total cholesterol level in patients with statin treatment. Multivariate linear regression analysis revealed that baseline serum glucose, albumin, total cholesterol, and statin treatment were independent determinants of circulating PCSK9 levels. Cumulative rates of composite and CV events were significantly higher in patients with tertile 3 PCSK9 ($p = 0.017$ and $p = 0.010$, respectively). In multivariate Cox-regression analysis, PCSK9 tertile 3 was associated with a 1.97-fold risk of composite events (95% CI, 1.13-3.45), and it was associated with a 2.31-fold risk of CV events (95% CI, 1.17-4.59). In conclusion, a higher circulating PCSK9 level was independently associated with incident CV events and death in HD patients. These results suggest the importance of future studies regarding the effect of PCSK9 inhibition.

[34] *Juraschek SP, Simpson LM, Davis BR et al.* **The effects of antihypertensive class on gout in older adults: secondary analysis of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial**. Journal of hypertension 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31977576
ABSTRACT
OBJECTIVES: Gout is a common complication of blood pressure management and a frequently cited cause of medication nonadherence. Little trial evidence exists to inform antihypertensive selection with regard to gout risk. METHODS: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) was a randomized clinical trial on the effects of first-step hypertension therapy with amlodipine, chlorthalidone, or lisinopril on fatal coronary heart disease or nonfatal myocardial infarction (1994-2002). Trial participants were linked to CMS and VA gout claims (ICD9 274.XX). We determined the effect of drug assignment on gout with Cox regression models. We also determined the adjusted association of self-reported atenolol use (ascertained at the 1-month visit for indications other than hypertension) with gout. RESULTS: Claims were linked to 23 964 participants (mean age 69.8 +/- 6.8 years, 45% women, 31% black). Atenolol use was reported by 928 participants at the 1-month visit. Over a mean follow-up of 4.9 years, we documented 597 gout claims. Amlodipine reduced the risk of gout by 37% (hazard ratio 0.63; 95% CI 0.51--0.78) compared with chlorthalidone and by 26% (hazard ratio 0.74; 95% CI 0.58--0.94) compared with lisinopril. Lisinopril nonsignificantly lowered gout risk compared with chlorthalidone (hazard ratio 0.85; 95% CI 0.70--1.03). Atenolol use was not associated with gout risk (adjusted hazard ratio 1.18; 95% CI 0.78--1.80). Gout risk reduction was primarily observed after 1 year of follow-up. CONCLUSION: Amlodipine lowered long-term gout risk compared with lisinopril or chlorthalidone. This finding may be useful in cases where gout risk is a principal concern among patients being treated for hypertension.This trial is registered at clinicaltrials.gov, number: NCT00000542.

[35] *Heward E, Lau AS*. **Epistaxis and atorvastatin: is there an association and are clinicians aware? A retrospective audit of 100 patients**. The Journal of laryngology and otology 2020:1-3.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31964433
ABSTRACT

OBJECTIVE: Epistaxis is a common ENT presentation. The British National Formulary lists epistaxis as a common side effect of atorvastatin. This study aimed to better understand the relationship between epistaxis and atorvastatin use, and determine whether ENT doctors are aware of its side effect profile. METHODS: A retrospective analysis over 10 months identified 100 individuals who presented to hospital with epistaxis. A questionnaire of 24 ENT registrars was undertaken. RESULTS: Of the 100 patients admitted with epistaxis, 27 were receiving atorvastatin and 21 simvastatin. None of the 24 ENT registrars were aware that epistaxis was a listed common side effect of atorvastatin. CONCLUSION: There was no apparent difference in the proportion of patients admitted with epistaxis taking atorvastatin versus simvastatin. Epistaxis is an unknown side effect of atorvastatin; doctors have an obligation to be aware of the pharmaceutical literature and to consider alternatives, particularly in re-admissions cases.

[36] *Hurt-Camejo E*. **Combination ANGPTL3, PCSK9 and statin therapy drives remarkable reductions in hyperlipidemia and atherosclerosis in a mouse model**. Journal of lipid research 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31980481
ABSTRACT

[37] *Safakheil M, Safakheil H*. **The Effect of Exosomes Derived from Bone Marrow Stem Cells in Combination with Rosuvastatin on Functional Recovery and Neuroprotection in Rats After Ischemic Stroke**. Journal of molecular neuroscience : MN 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31974756
ABSTRACT
Rosuvastatin, known as a cholesterol-lowering agent, has been used as an alternative therapy after the onset of stroke. In this study, neuroprotection and functional recovery of exosomes in combination with rosuvastatin have been investigated. Sixty adult male Wistar rats were subjected to middle cerebral artery occlusion (MCAO). Exosome at the dose of 100 mug and/or rosuvastatin at the dose of 20 mg/kg/day for 7 days were administered to rats as a therapeutic strategy. The elevated body swing test (EBST) and Garcia score were conducted as behavioral tests for the measurement of functional recovery. The histopathological and immunohistochemical analyses were also performed for the assessment of infarcted volume and neuroprotection in the brain of rats. The real-time PCR method was carried out to determine the relative expressions of the NLRP-3 and NLRP1 genes. After 7 days of treatment with exosome and rosuvastatin in rats which underwent MCAO, the decrease in infarct volume of the animals treated with exosome was more pronounced compared with those treated only with exosome. The combination therapy remarkably lowered the size of infarct volume. Our observation was confirmed by the downregulation of the NLRP1 and NLRP3 genes in response to combinatory treatment of rats induced by MCOA, denoting a lower rate of cell death. The number of GFAP-positive cells were reduced in the exosome-treated group compared with the MCAO group. The rate of lipid peroxidation was measured by malondialdehyde (MDA) levels which demonstrated a significant reduction of MDA in the exosome- and rotuvastatin-treated groups when compared with the MCAO group. However, the levels of the SOD enzyme did not significantly alter when the treatment groups were compared with the MCAO group. According to our findings, it seems that the use of exosomes and rosuvastatin, as a novel treatment regimen, might promote neurological recovery after the onset of stroke.

Literature update week 04 (2020)

[38] *Takeda H, Izumi Y, Tamura S et al.* **Lipid profiling of serum and lipoprotein fractions in response to pitavastatin using an animal model of familial hypercholesterolemia**. J Proteome Res 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31965805
ABSTRACT
Statins are widely used for the treatment of atherosclerotic cardiovascular diseases. They inhibit cholesterol biosynthesis in the liver and cause pleiotropic effects including anti-inflammatory and antioxidant effects. To develop novel therapeutic drugs, the effect of blood-borne lipid molecules on the pleiotropic effects of statins must be elucidated. Myocardial-infarction-prone Watanabe heritable hyperlipidemic (WHHLMI) rabbits, an animal model for hypercholesterolemia, are suitable for the determination of lipid molecules in blood in response to statins because their lipoprotein metabolism is similar to that of humans. Herein, lipid molecules were investigated by lipidome analysis in response to pitavastatin using WHHLMI rabbits. Various lipid molecules in the blood were measured using a supercritical fluid chromatography triple quadrupole mass spectrometry. Cholesterol and cholesterol ester blood levels decreased by reducing the secretion of very low density lipoproteins from the liver. Independent of the inhibition effects of cholesterol biosynthesis, the concentrations of some lipids with anti-inflammation and antioxidant effects (phospholipid molecules with n-6 fatty acid side chains, lysophosphatidylcholines, phosphatidylethanolamine plasmalogens, and ceramide molecules) were significantly altered. These findings may lead to further investigation of the mechanism of statin action.

[39] *Sallinen H, Pietila A, Salomaa V, Strbian D*. **Risk Factors of Intracerebral Hemorrhage: A Case-Control Study**. Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association 2020:104630.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31959502
ABSTRACT
BACKGROUND: Hypertension is a well-known risk factor for intracerebral hemorrhage (ICH). On many of the other potential risk factors, such as smoking, diabetes, and alcohol intake, results are conflicting. We assessed risk factors of ICH, taking also into account prior depression and fatigue. METHODS: This is a population-based case-control study of 250 primary ICH patients, conducted in Helsinki University Hospital, Finland. The controls (n=750) were participants of the FINRISK study, a large Finnish population survey on risk factors of chronic noncommunicable diseases, matched with cases by sex and age. Ages were matched in 5-year age bands. However, as the oldest FINRISK participants were 74-year-olds, controls for the age group 75-84 were selected from the age group of 70-74 years. Patients aged greater than or equal to 85 years were excluded. Patients and controls were compared in univariate analyses. The age categories less than 70, and greater than or equal to 70 years were also analyzed separately. Binary logistic regression analysis was performed for variables with P less than .1 in univariate analysis. RESULTS: Analyzing all cases and controls, the cases had more hypertension, history of heart attack, lipid-lowering medication, and reported more frequently fatigue prior to ICH. In persons aged less than 70 years, hypertension and fatigue were more common among cases. In persons aged greater than or equal to 70 years, factors associated with risk of ICH were fatigue prior to ICH, use of lipid-lowering medication, and overweight. CONCLUSIONS: Hypertension was associated with risk of ICH among all patients and in the group of patients under 70 years. Fatigue prior to ICH was more common among all ICH cases.

Literature update week 04 (2020)

[40] *van Rosendael AR, Narula J, Lin FY et al.* **Association of High-Density Calcified 1K Plaque With Risk of Acute Coronary Syndrome**. JAMA cardiology 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31968065
ABSTRACT
Importance: Plaque morphologic measures on coronary computed tomography angiography (CCTA) have been associated with future acute coronary syndrome (ACS). However, the evolution of calcified coronary plaques by noninvasive imaging is not known. Objective: To ascertain whether the increasing density in calcified coronary plaque is associated with risk for ACS. Design, Setting, and Participants: This multicenter case-control cohort study included individuals enrolled in ICONIC (Incident Coronary Syndromes Identified by Computed Tomography), a nested case-control study of patients drawn from the CONFIRM (Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter) registry, which included 13 study sites in 8 countries. Patients who experienced core laboratory-verified ACS after baseline CCTA (n = 189) and control individuals who did not experience ACS after baseline CCTA (n = 189) were included. Patients and controls were matched 1:1 by propensity scores for age; male sex; presence of hypertension, hyperlipidemia, and diabetes; family history of premature coronary artery disease (CAD); current smoking status; and CAD severity. Data were analyzed from November 2018 to March 2019. Exposures: Whole-heart atherosclerotic plaque volume was quantitated from all coronary vessels and their branches. For patients who underwent invasive angiography at the time of ACS, culprit lesions were coregistered to baseline CCTA lesions by a blinded independent reader. Low-density plaque was defined as having less than 130 Hounsfield units (HU); calcified plaque, as having more than 350 HU and subcategorized on a voxel-level basis into 3 strata: 351 to 700 HU, 701 to 1000 HU, and more than 1000 HU (termed 1K plaque). Main Outcomes and Measures: Association between calcium density and future ACS risk. Results: A total of 189 patients and 189 matched controls (mean [SD] age of 59.9 [9.8] years; 247 [65.3%] were male) were included in the analysis and were monitored during a mean (SD) follow-up period of 3.9 (2.5) years. The overall mean (SD) calcified plaque volume (>350 HU) was similar between patients and controls (76.4 [101.6] mm3 vs 99.0 [156.1] mm3; P = .32), but patients who experienced ACS exhibited less 1K plaque (>1000 HU) compared with controls (3.9 [8.3] mm3 vs 9.4 [23.2] mm3; P = .02). Individuals within the highest quartile of 1K plaque exhibited less low-density plaque, as a percentage of total plaque, when compared with patients within the lower 3 quartiles (12.6% [10.4%] vs 24.9% [20.6%]; P < .001). For 93 culprit precursor lesions detected by CCTA, the volume of 1K plaque was lower compared with the maximally stenotic lesion in controls (2.6 [7.2] mm3 vs 7.6 [20.3] mm3; P = .01). The per-patient and per-lesion results were similar between the 2 groups when restricted to myocardial infarction cases. Conclusions and Relevance: Results of this study suggest that, on a per-patient and per-lesion basis, 1K plaque was associated with a lower risk for future ACS and that measurement of 1K plaque may improve risk stratification beyond plaque burden.

[41] *Chen C, Song C, Zhang D et al.* **Effect of resveratrol combined with atorvastatin on re-endothelialization after drug-eluting stents implantation and the underlying mechanism**. Life sciences 2020:117349.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31981632
ABSTRACT
AIMS: To explore whether the combination of atorvastatins and resveratrol is superior to each individual drug alone regarding re-endothelialization after drug-eluting stents (DESs) implantation.

MATERIALS AND METHODS: Ninety-four rabbits were randomized into control, atorvastatin, resveratrol, and combined medication groups. Abdominal aorta injury was induced via ballooning, followed by DES implantation. Neointimal formation and re-endothelialization after stent implantation were assessed via optical coherence tomography and scanning electron microscopy. The effects of resveratrol and atorvastatin on bone marrow-derived mesenchymal derived stem cells (BMSCs) were assessed. KEY FINDINGS: Compared with the findings in the resveratrol and atorvastatin groups, the neointimal area and mean neointimal thickness were greater in the combined medication group, which also exhibited improved re-endothelialization. Compared with the effects of monotherapy, combined treatment further protected BMSCs against rapamycin-induced apoptosis and improved cell migration. Combined medication significantly upregulated Akt, p-Akt, eNOS, p-eNOS, and CXCR4 expression in BMSCs compared with the effects of monotherapy, and these effects were abolished by the phosphatidylinositol 3-kinase (PI3K) inhibitor LY294002. SIGNIFICANCE: The combination of atorvastatin and resveratrol has the potential of accelerating re-endothelialization after stent implantation, reducing the risk of thrombosis and improving the safety of DESs.

[42] *Li J, Yan M, Qin J et al.* **Severe peripheral arterial diseases in hemodialysis patient: A case report**. Medicine (Baltimore) 2020; 99:e18760.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31977867
ABSTRACT
RATIONALE: Peripheral arterial diseases (PADs) is defined as a systemic arterial disorders involving the lower extremity arteries, iliac, and carotid, which is developed more common in patients with chronic kidney disease (CKD) than individual with normal renal function. Concurrence of mesenteric artery disease and lower extremity artery disease (LEAD) is rare. The presence of PADs in patients receiving hemodialysis leads to a dramatic increase in risk of cardiovascular mortality. However, the early diagnosis of PADs in patient with CKD remains a challenge to nephrologists, which adds an adverse effect on prognosis. PATIENT CONCERNS: A 48-year-old man received regular hemodialysis due to end-stage renal failure caused by type 2 diabetes mellitus (T2DM) for 7 years, who was admitted into hospital for acute, severe rest pain of the right lower extremity at the first time. The computed tomography angiography showed severe, diffuse stenosis of the distal third of femoral artery. After discharged, he was readmitted into hospital for abdominal pain and the recurred right lower limb pain. A diagnostic angiography confirmed the initial occlusion of superior mesenteric artery, severe obstruction of the distal segment of femoral artery and diffuse, irregular stenosis of arteria peronea and arteria tibialis posterior. DIAGNOSIS: The patient was diagnosed as PADs including LEAD and mesenteric artery disease. INTERVENTIONS: The percutaneous transulminal angioplasty (PTA) combined with antiplatelet therapy and beraprost were performed. Moreover, the cinacalcet and lanthanum carbonate were prescribed to control calcium-phosphorus- parathyroid hormone metabolism. OUTCOMES: The patient was free of abdominal pain and partly relieved from the ache of lower limb after PTA. However, he finally succumbed to acute myocardial infarction. LESSONS: The incidence of PADs is higher in dialysis patients due to a unique set of biochemical and endocrine abnormalities. As there is a high uremic status and PADs burden in patients with hemodialysis, the short term risk of cardiovascular disesase mortality markedly increases. There is a need for nephrologists and cardiovascular physicians to identify these patients and then provide early and proper treatment.

Literature update week 04 (2020)

[43] *Watts GF, Gidding SS, Mata P et al.* **Familial hypercholesterolaemia: evolving knowledge for designing adaptive models of care**. Nature reviews. Cardiology 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31974482
ABSTRACT
Optimal care for familial hypercholesterolaemia (FH) requires patient-centred management, multidisciplinary teamwork, involvement of primary care practitioners, patient networks, support groups and high-quality clinical registries, implemented through models of care adapted to FH. Models of care - evidence-based and context-specific frameworks that aim to deliver the highest quality of care for patients and their families - allow the application of precision and multidisciplinary medicine to FH care and can serve as paradigms for the prevention of premature atherosclerotic cardiovascular disease in all at-risk patients and families worldwide. The exponential growth in the number of publications on diverse aspects of FH has provided new knowledge for developing essential elements of existing models of care. These elements include clinical diagnostic criteria and genetic testing; risk restratification strategies; LDL-cholesterol treatment targets; management protocols for children; care of women in pregnancy; use of pharmacotherapies, including ezetimibe and PCSK9 inhibitors; use of lipoprotein apheresis for severe FH; and addressing barriers to care. However, substantial gaps remain that need to be addressed by a broad research agenda, implementation strategies and global collaboration and advocacy, aimed at improving the uptake, cost-effectiveness and routine implementation of evidence-based standards. In this Review, we summarize the dramatic increase in knowledge that informs adaptive models of care, with an emphasis on articles published since 2014.

[44] *Lutski M, Weinstein G, Ben-Zvi S et al.* **Adherence to Mediterranean diet and subsequent cognitive decline in men with cardiovascular disease**. Nutritional neuroscience 2020:1-9.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31965911
ABSTRACT
Backgrounds and aims: Evidence from recent years highlighted the importance of the Mediterranean diet for brain health. We investigated the association between adherence to Mediterranean diet and change in cognitive functions two decades later in patients with cardiovascular disease (CVD).Methods: Participants were men with a history of CVD, who previously participated in the Bezafibrate Infarction Prevention (BIP) trial between 1990 and 1997, had a food diary record, and underwent cognitive evaluations 14.6 +/- 1.9 years (T1) and 19.9 +/- 1.0 years after baseline (T2) as part of the BIP Neurocognitive study (n = 200, mean age at 57.3 +/- 6.3 years). Adherence to the Mediterranean diet was determined from the self-administered 4-day food diary record, with patients categorized into high, middle and poor levels of adherence if they received >5, 4-5 and <4 points, respectively. Cognitive function was assessed using the NeuroTrax computerized battery. Linear mixed models were applied.Results: Among the 200 patients, 52 (26%) had poor adherence, 98 (49%) had middle adherence and 50 (25%) had high levels of adherence to the Mediterranean diet. Those categorized to the poor adherence level had poorer cognitive function at T1 compared to the other groups. Additionally, poor vs. high level of adherence was associated with a greater decline in overall cognitive performance [z-score = -0.23 and 95% confidence interval (CI), -0.43;-0.04; p = 0.021] and in visual spatial functions (-0.46 95% CI, -0.86;-0.06; p = 0.023).Conclusion: This study stresses the possible role of the Mediterranean diet in men with a high vascular burden and may set the ground for future intervention to reduce their risk for cognitive decline.

Literature update week 04 (2020)

[45] *McAllister MJ, Pigg BL, Renteria LI, Waldman HS*. **Time-restricted feeding improves markers of cardiometabolic health in physically active college-age men: a 4-week randomized pre-post pilot study**. Nutrition research (New York, N.Y.) 2019; 75:32-43.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31955013
ABSTRACT
Time-restricted feeding (TRF) has been shown to improve body composition, blood lipids, and reduce markers of inflammation and oxidative stress. However, most of these studies come from rodent models and small human samples, and it is not clear if the benefits are dependent upon a caloric deficit, or the time restriction nature of TRF. Based off of previous research, we hypothesized that humans following an ad libitum TRF protocol would reduce caloric intake and this caloric deficit would be associated with greater improvements in cardiometabolic health including blood pressure, body composition, blood lipids, and markers of inflammation and antioxidant status compared to an isocaloric TRF protocol. The purpose of this study was to: (1) examine the impact of TRF on markers of cardio-metabolic health and antioxidant status and (2) determine if the adaptations from TRF would differ under ad libitum compared to isocaloric conditions. Twenty-three healthy men were randomized to either an ad libitum or isocaloric 16:8 (fasting: feeding) TRF protocol. A total of 22 men completed the 28-day TRF protocol (mean+/-SD; age: 22+/-2.5 yrs.; height: 178.4+/-6.9 cm; weight: 90.3+/-24 kg; BMI: 28.5+/-8.3 kg/m(2)). Fasting blood samples were analyzed for glucose, lipids, as well as adiponectin, human growth hormone, insulin, cortisol, C-reactive protein, superoxide dismutase, total nitrate/nitrite, and glutathione. Time-restricted feeding in both groups was associated with significant (P<.05) reductions in body fat, blood pressure, and significant increases in adiponectin and HDL-c. No changes in caloric intake were detected. In summary, the results from this pilot study in metabolically healthy, active young men, suggest that TRF can improve markers of cardiometabolic health.

[46] *Shah Y, Iqbal Z, Ahmad L et al.* **Rosuvastatin pharmacokinetics in Pakistani healthy volunteers in comparison with other population**. Pak J Pharm Sci 2019; 32:2725-2732.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31969307
ABSTRACT
In current study, the pharmacokinetics (PK) of rosuvastatin were evaluated in Pakistani healthy volunteers and compared with those reported in other population. This was a randomized and open labeled clinical trial in which a single oral dose of 40 mg rosuvastatin was administered to the overnight fasted healthy volunteers. Plasma concentrations of rosuvastatin were quantified by a validated liquid chromatography-tandem mass spectrometry method. The PK parameters of rosuvastatin and its metabolite N-desmethyl-rosuvastatin were determined by PK specific software i.e., PK-Summit(R) (PK-Solutions). A total of 20 healthy volunteers having BMI in the normal ranges were included in this study. All PK parameters were represented as mean +/- SD and 95% confidence intervals of the means have been calculated. The Cmax (29.07 +/- 6.88 ng/mL), [AUC](x)o (206.65 +/- 55.27 ng/hr/mL) and CL/F (3275.26 +/- 1072.87 mL/hr) were slightly higher in our study, whereas the values of Vd (19377.23 +/- 9114.29 mL) and tmax (3.0 +/- 0.46 hr) were comparatively smaller. Overall, the PK parameters of rosuvastatin determined in our study were in compliance with other reported. Therefore, no adjustments in the dosing schedule or dose are warranted.

[47] *Karel M, Hechler B, Kuijpers M, Cosemans J*. **Atherosclerotic plaque injury-mediated murine thrombosis models: advantages and limitations**. Platelets 2020:1-8.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31957516

ABSTRACT

In spite of current treatment strategies, myocardial infarction and stroke are still major causes of death worldwide. These events are triggered by damage of an atherosclerotic plaque, resulting in occlusive thrombus formation. Mouse studies have significantly contributed to our understanding of the mechanisms of atherogenesis and of thrombosis following plaque injury, but the extent to which the mouse serves as an accurate model of human disease is open to discussion. In this review, we provide a detailed overview and comparison of the described mouse models for atherothrombosis including their (dis)advantages. Herein guidance is provided on how to select a suitable atherothrombosis model for research questions primarily relevant to the field of thrombosis.

[48] *Stol DM, Badenbroek IF, Hollander M et al.* **Effectiveness of a stepwise cardiometabolic disease prevention program: Results of a randomized controlled trial in primary care**. Prev Med 2020; 132:105984.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31954837

ABSTRACT

Effective preventive strategies for cardiometabolic disease (CMD) are needed. We aim to establish the effectiveness of a stepwise CMD risk assessment followed by individualized treatment if indicated compared to care as usual. We conducted a RCT between 2014 and 2017. Individuals (45-70 years) without CMD or CMD risk factors were invited for stepwise CMD risk assessment through a risk score (step1), additional risk assessment at the practice in case of high-risk (step2) and individualized follow-up treatment if indicated (step3). We compared newly detected CMD and newly prescribed drugs during one-year follow-up, and change in CMD risk profile between baseline and one-year follow-up among participants who completed step2 to matched controls. A CMD was diagnosed almost three times more often (OR 2.90, 95% CI 2.25: 3.72) in the intervention compared to the control group, in parallel with newly prescribed antihypertensive and lipid lowering drugs (OR 2.85, 95% CI 1.96: 4.15 and 3.23, 95% CI 2.03: 5.14 respectively). Waist circumference significantly decreased between the intervention compared to the control group (mean -3.08 cm, 95% CI -3.73: -2.43). No differences were observed for changes in BMI and smoking. Systolic blood pressure (mean -2.26 mmHg, 95% CI -4.01: -0.51) and cholesterol ratio (mean -0.11, 95% CI -0.19: -0.02) significantly decreased within intervention participants between baseline and one-year follow-up. In conclusion, implementation of the CMD prevention program resulted in the detection of two- to threefold more patients with CMD. A significant drop in systolic blood pressure and cholesterol levels was found after one year of treatment. Modelling of these results should confirm the effect on long term endpoints. Trial registration: Dutch trial Register number NTR4277.

[49] *Bernardini F, Gostoli S, Marchetti G et al.* **A survey on lifestyle and awareness of the use of statins in a sample of cardiopathic patients**. Psychology, health & medicine 2020:1-9.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31958983

ABSTRACT

Current guidelines highlight the importance of lifestyle modification in the treatment of hypercholesterolemia, in addition to lipid-lowering drugs. However, patients taking statins do not always follow the physician's prescriptions on lifestyle change.. The present research aims to understand the psychological characteristics associated with unhealthy lifestyle change/maintenance

among cardiopathic patients treated with statins.58 patients were enrolled and evaluated by both observer- (clinical distress, psychosomatic syndromes) and self-rated (lifestyle, subclinical distress, well-being) measures. Ad-hoc items were included to evaluate self-perceived lifestyle changes and awareness about cholesterol-lowering effects of statins.55.4% of the patients had not changed their lifestyle since taking statins and felt less contented ($p < 0.05$); 10.7% were unaware of the cholesterol-lowering effects of these drugs. Minor depression was the most frequent diagnosis(8.9%). It was significantly associated with the absence of lifestyle modification($p < 0.05$), even though all minor depressed patients were aware of the effects of statins. On the contrary, those who were unaware showed significantly lower well-being (positive relations [$p <0.05$]; purpose in life [$p<0.001$]). Minor depression and psychological well-being impairments should thus be assessed in patients taking statins in order to recognize potential psychological risk factors associated with maintenance of unhealthy behaviors. .

[50] *Roy P, Ali AJ, Kobiyama K et al.* **Opportunities for an atherosclerosis vaccine: From mice to humans**. Vaccine 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31964554
ABSTRACT
Atherosclerosis, the major underlying cause of cardiovascular diseases (CVD), is the number one killer globally. The disease pathogenesis involves a complex interplay between metabolic and immune components. Although lipid-lowering drugs such as statins curb the risks associated with CVD, significant residual inflammatory risk remains. Substantial evidence from experimental models and clinical studies has established the role of inflammation and immune effector mechanisms in the pathogenesis of atherosclerosis. Several stages of the disease are affected by host-mediated antigen-specific adaptive immune responses that play either protective or proatherogenic roles. Therefore, strategies to boost an anti-atherogenic humoral and T regulatory cell response are emerging as preventative or therapeutic strategies to lowering inflammatory residual risks. Vaccination holds promise as an efficient, durable and relatively inexpensive approach to induce protective adaptive immunity in atherosclerotic patients. In this review, we discuss the status and opportunities for a human atherosclerosis vaccine. We describe (1) some of the immunomodulatory therapeutic interventions tested in atherosclerosis (2) the immune targets identified in pre-clinical and clinical investigations (3) immunization strategies evaluated in animal models (4) past and ongoing clinical trials to examine the safety and efficacy of human atherosclerosis vaccines and (5) strategies to improve and optimize vaccination in humans (antigen selection, formulation, dose and delivery).

[51] *Kokkinidis DG, Arfaras-Melainis A, Giannopoulos S et al.* **Statin therapy for reduction of cardiovascular and limb-related events in critical limb ischemia: A systematic review and meta-analysis**. Vascular medicine (London, England) 2020:1358863x19894055.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31964311
ABSTRACT
High-intensity statins are recommended for patients with peripheral artery disease (PAD). Critical limb ischemia (CLI) is the most advanced presentation of PAD. The benefit of statins in the CLI population is unclear based on the existent studies. Our objective was to perform a systematic review and meta-analysis regarding the efficacy of statin therapy in patients with CLI. PRISMA guidelines were followed. PubMed, EMBASE, and Cochrane CENTRAL databases were reviewed up to April 30, 2019. The primary

outcomes included amputation rates and all-cause mortality. Secondary outcomes included primary patency rates, amputation-free survival and major adverse cardiac or cerebrovascular events (MACCE). Risk of bias was assessed with the Robins-I tool for observational studies. A random-effects model meta-analysis was performed. Heterogeneity was assessed with I(2). Funnel plots and Egger's test were used to assess publication bias. Nineteen studies including 26,985 patients with CLI were included in this systematic review. Among patients with known data on statin status, 12,292 (49.6%) were on statins versus 12,513 (50.4%) not on statins. Patients treated with statins were 25% less likely to undergo amputation (HR 0.75; 95% CI: 0.59-0.95; I(2) = 79%) and 38% less likely to have a fatal event (HR 0.62; 95% CI: 0.52-0.75; I(2) = 41.2%). Statin therapy was also associated with increased overall patency rates and lower incidence of MACCE. There was substantial heterogeneity in the analysis for amputation and amputation-free survival (I(2) > 70%). In conclusion, statins are associated with decreased risk for amputation, mortality, and MACCE, as well as increased overall patency rates among patients with CLI. Future studies should assess whether other lipid-lowering medications in addition to high-intensity statins can further improve outcomes among patients with CLI. (PROSPERO registration number: CRD42019134160).