Literature update week 49 (2019)

[1] *De Ferrari GM, Stevens SR, Ambrosio G et al.* **Low-density lipoprotein cholesterol treatment and outcomes in patients with type 2 diabetes and established cardiovascular disease: Insights from TECOS**. American heart journal 2019; 220:82-88.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31790905
ABSTRACT
BACKGROUND: Type 2 diabetes (T2D) patients are at increased risk for cardiovascular (CV) events. Most guidelines recommend treating low-density lipoprotein cholesterol (LDL-C) levels to </=70 mg/dL (1.8 mM) for patients with T2D and established atherosclerotic CV disease, and some a more aggressive target of </=55 mg/dL (1.4 mM). Our objective was to assess the degree to which these LDL-C targets are achieved in routine practice. METHODS: Using data from TECOS, an international pragmatic CV outcomes trial of sitagliptin vs placebo, we assessed lipid-lowering treatment among patients with T2D and CV disease, baseline lipid values, and the association between baseline LDL-C and 5-year risk for major adverse cardiac events (MACE; ie, CV death, nonfatal myocardial infarction, or nonfatal stroke). RESULTS: Overall, 11,066 of 14,671 TECOS participants (75.4%) had LDL-C measured at baseline. Median age was 65 years, 72% were male, and median T2D duration was 10 years. Overall, 82.5% of patients were on statins; only 5.8% were on ezetimibe. At baseline, 14.3% had LDL-C </=55 mg/dL, 18.4% between 55.1 and 70 mg/dL, 35% between 70.1 and 100 mg/dL, and 32.3% >100 mg/dL. Each 10 mg/dL higher LDL-C value was associated with a higher risk of MACE (HR 1.05, 95% CI 1.03-1.07) or CV death (HR 1.06, 95% CI 1.04-1.09). CONCLUSIONS: Although most high-risk patients with T2D and CV disease were on lipid-lowering therapy, only 1:3 had LDL-C <70 mg/dL and 1:6 had LDL-C <55 mg/dL. Each 10 mg/dL higher LDL-C value was associated with a 5% and 6% higher 5-year incidence of MACE and CV death, respectively. (TECOS, NCT00790205).

[2] *Gupta RM, Libby P, Barton M*. **Linking regulation of nitric oxide to endothelin-1: The Yin and Yang of vascular tone in the atherosclerotic plaque**. Atherosclerosis 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31810569
ABSTRACT

[3] *Lamiquiz-Moneo I, Restrepo-Cordoba MA, Mateo-Gallego R et al.* **Predicted pathogenic mutations in STAP1 are not associated with clinically defined familial hypercholesterolemia**. Atherosclerosis 2019; 292:143-151.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31809983
ABSTRACT
BACKGROUND AND AIMS: Autosomal dominant familial hypercholesterolemia (FH) is caused by mutations in LDLR,APOB and PCSK9. Two new putative loci causing FH have been identified recently, the p.(Leu167del) mutation in APOE and new mutations in the signal transducing adaptor family member STAP1. We aimed at investigating the role of STAP1 mutations in the etiology of FH. METHODS: We sequenced LDLR, APOB, PCSK9, LDLRAP1, APOE, LIPA and STAP1 with the LipidInCode platform in 400 unrelated subjects from Spain with a clinical diagnosis of FH. All subjects carrying rare predicted pathogenic variants in STAP1 gene, described as pathogenic by at least three bioinformatic analysis and having an allelic frequency lower than 1% in general population, were selected for family study. Available relatives were recruited, including both hypercholesterolemic and non-hypercholesterolemic family members. RESULTS: Sequencing

analysis of STAP1 gene revealed seventeen rare variants, four of them being described as pathogenic by bioinformatic analysis. We studied the cosegregation with hypercholesterolemia of four rare predicted pathogenic variants, c.-60A > G, p.(Arg12His), p.(Glu97Asp), p.(Pro176Ser) in seven families. We did not observe any cosegregation between genotype and phenotype, even carriers of rare variants in STAP1 had lower LDL cholesterol levels than non-carriers. CONCLUSIONS: This study analyzes the family cosegregation of four rare predicted pathogenic variants of STAP1, p.(Arg12His), p.(Glu97Asp), p.(Pro176Ser) and c.-60A > G, in seven families, showing absence of cosegregation in all of them. These results would suggest that STAP1 gene is not involved in hypercholesterolemia of these families.

[4] *Ramaswami U, Futema M, Bogsrud MP et al.* **Comparison of the characteristics at diagnosis and treatment of children with heterozygous familial hypercholesterolaemia (FH) from eight European countries**. Atherosclerosis 2019; 292:178-187.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31809987
ABSTRACT
BACKGROUND AND AIMS: For children with heterozygous familial hypercholesterolaemia (HeFH), European guidelines recommend consideration of statin therapy by age 8-10 years for those with a low density lipoprotein cholesterol (LDL-C) >3.5 mmol/l, and dietary and lifestyle advice. Here we compare the characteristics and lipid levels in HeFH children from Norway, UK, Netherlands, Belgium, Czech Republic, Austria, Portugal and Greece. METHODS: Fully-anonymized data were analysed at the London centre. Differences in registration and on treatment characteristics were compared by standard statistical tests. RESULTS: Data was obtained from 3064 children. The median age at diagnosis differed significantly between countries (range 3-11 years) reflecting differences in diagnostic strategies. Mean (SD) LDL-C at diagnosis was 5.70 (+/-1.4) mmol/l, with 88% having LDL-C>4.0 mmol/l. The proportion of children older than 10 years at follow-up who were receiving statins varied significantly (99% in Greece, 56% in UK), as did the proportion taking Ezetimibe (0% in UK, 78% in Greece). Overall, treatment reduced LDL-C by between 28 and 57%, however, in those >10 years, 23% of on-treatment children still had LDL-C>3.5 mmol/l and 66% of those not on a statin had LDL-C>3.5 mmol/l. CONCLUSIONS: The age of HeFH diagnosis in children varies significantly across 8 countries, as does the proportion of those >10 years being treated with statin and/or ezetimibe. Approximately a quarter of the treated children and almost three quarters of the untreated children older than 10 years still have LDL-C concentrations over 3.5 mmol/l. These data suggest that many children with FH are not receiving the full potential benefit of early identification and appropriate lipid-lowering treatment according to recommendations.

[5] *Robert C, Couedelo L, Vaysse C, Michalski MC*. **Vegetable lecithins: A review of their compositional diversity, impact on lipid metabolism and potential in cardiometabolic disease prevention**. Biochimie 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31786232
ABSTRACT
Vegetable lecithins, widely used in the food industry as emulsifiers, are a mixture of naturally occurring lipids containing more than 50% of phospholipids (PL). PL exert numerous important physiological effects. Their amphiphilic nature notably enables them to stabilise endogenous lipid droplets, conferring them an important role in lipoprotein transport, functionality and metabolism.

In addition, beneficial effects of dietary lecithin on metabolic disorders have been reported since the 1990s. This review attempts to summarize the effects of various vegetable lecithins on lipid and lipoprotein metabolism, as well as their potential application in the treatment of dyslipidemia associated with metabolic disorders. Despite controversial data concerning the impact of vegetable lecithins on lipid digestion and intestinal absorption, the beneficial effect of lecithin supplementation on plasma and hepatic lipoprotein and cholesterol levels is unequivocal. This is especially true in hyperlipidemic patients. Furthermore, the immense compositional diversity of vegetable lecithins endows them with a vast range of biochemical and biological properties, which remain to be explored in detail. Data on the effects of vegetable lecithins alternative to soybean, both as supplements and as ingredients in different foods, is undoubtedly lacking. Given the exponential demand for vegetable products alternative to those of animal origin, it is of primordial importance that future research is undertaken in order to elucidate the mechanisms by which individual fatty acids and PL from various vegetable lecithins modulate lipid metabolism. The extent to which they may influence parameters associated with metabolic disorders, such as intestinal integrity, low-grade inflammation and gut microbiota must also be assessed.

[6] *Spence JD*. **The need for clinical judgement in the application of evidence-based medicine**. BMJ evidence-based medicine 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31806620
ABSTRACT
BACKGROUND: Evidence-based medicine (EBM) has no doubt resulted in great improvements in the practice of medicine. However, there are problems with overly zealous application of EBM, that for some amounts to religious practice. When good evidence exists, it should guide therapeutic and diagnostic choices. However, when evidence is lacking for a given patient, medicine is best practised by extrapolation from available evidence, interpreted in the light of the pathophysiology of the condition under consideration, and effects of various therapies in relation to that pathophysiology. OBJECTIVE: To assess ways in which the unthinking application of EBM can go wrong; these include withholding therapy in patients whose subgroup was excluded from clinical trials, blind acceptance of the numbers, reliance on studies with crucial design flaws and reliance on intention-to-treat analysis when it is not appropriate. STUDY SELECTION: Examples assessed included withholding cholesterol-lowering therapy in the elderly, not using B-vitamin therapy for stroke prevention, not using revascularisation for true renovascular hypertension and avoiding statin therapy for fear of intracerebral haemorrhage. FINDINGS: Zealous application of EBM is often inappropriate. CONCLUSIONS: In some instances, when there is a lack of evidence, or faulty interpretation of the evidence, clinical judgement should inform the application of EBM.

[7] *Masson W, Lobo M, Molinero G, Rossi E*. **Should all patients with psoriasis receive statins? Analysis according to different strategies**. Anais brasileiros de dermatologia 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31789271
ABSTRACT
BACKGROUND: Different strategies have been proposed for the cardiovascular risk management of patients with psoriasis. OBJECTIVE: To estimate the cardiovascular risk and evaluate two cardiovascular prevention strategies in patients with psoriasis, analyzing which proportion of patients would be candidates to receive statin therapy. METHODS: A retrospective cohort was

selected from a secondary database. All patients >18 years with psoriasis without cardiovascular disease or lipid-lowering treatment were included. The atherosclerotic cardiovascular disease calculator (2018 American College of Cardiology/American Heart Association guidelines) and the Systematic Coronary Risk Evaluation risk calculator (2016 European Society of Cardiology/European Society of Atherosclerosis guidelines) were calculated. The SCORE risk value was adjusted by a multiplication factor of 1.5. The recommendations for the indication of statins suggested by both guidelines were analyzed. RESULTS: A total of 892 patients (mean age 59.9+/-16.5 years, 54.5% women) were included. The median atherosclerotic cardiovascular disease calculator and Systematic Coronary Risk Evaluation values were 13.4% (IQR 6.1-27.0%) and 1.9% (IQR 0.4-5.2), respectively. According to the atherosclerotic cardiovascular disease calculator, 20.1%, 11.0%, 32.9%, and 36.4% of the population was classified at low, borderline, moderate, or high risk. Applying the Systematic Coronary Risk Evaluation, 26.5%, 42.9%, 20.8%, and 9.8% of patients were stratified as having low, moderate, high, or very high risk, respectively. The proportion of subjects with statin indication was similar using both strategies: 60.1% and 60.9% for the 2018 American College of Cardiology/American Heart Association and 2016 European Society of Cardiology/European Society of Atherosclerosis guidelines, respectively. STUDY LIMITATIONS: This was a secondary database study. Data on the severity of psoriasis and pharmacological treatments were not included in the analysis. CONCLUSION: This population with psoriasis was mostly classified at moderate-high risk and the statin therapy indication was similar when applying the two strategies evaluated.

[8] *Piccinni C, Antonazzo IC, Maggioni AP et al.* **PCSK9 Inhibitors' New Users: Analysis of Prescription Patterns and Patients' Characteristics from an Italian Real-world Study**. Clinical drug investigation 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31797311
ABSTRACT
BACKGROUND AND OBJECTIVE: Cardiovascular (CV) diseases represent a major cause of death and severe medical condition worldwide. Different therapeutic options are available to control low-density lipoprotein cholesterol (LDL-C) level in order to prevent CV events. In recent years, two new drugs were approved for patients who are unable to reduce circulating LDL-C with the current therapies: evolocumab and alirocumab (proprotein convertase subtilisin/kexin type nine [PCSK9] inhibitors). This study was aimed to characterise patients who started treatment with PCSK9 inhibitors in the Tuscany region of Italy during the first year of public healthcare service reimbursement and to describe the pattern of PCSK9 inhibitor use in the first 6 months of treatment. METHODS: Patients on PCSK9 inhibitor treatment in Tuscany (3.7 million inhabitants) from 07/2017 to 06/2018 were selected from regional healthcare administrative databases. Concomitant use of lipid-lowering therapies (LLTs), adherence and persistence during the 6 months preceding the first PCSK9 inhibitor dispensing, as well as comorbidities since 1996, were described. In the first 6 months of PCSK9 inhibitor treatment, adherence, persistence and concomitant LLTs were assessed. RESULTS: There were 269 (176 evolocumab, 93 alirocumab) new users of PCSK9 inhibitors. Patients (mean age of 59.1 years) were mainly male (71.0%) in secondary prevention (70.2%) and affected by familial hypercholesterolaemia (53.5%). Sixty-six patients (24.5%) had diabetes mellitus and 12 (4.5%) chronic renal failure. In the 6 months prior to the first PCSK9 inhibitor administration, 61.3% of patients received at least one prescription of ezetimibe or high-

intensity statins and 45.7% were persistent to these drugs. During follow-up, 79.9% of patients were adherent to PCSK9 inhibitor and 73.3% were persistent. CONCLUSIONS: During the first year of availability, the rate of prescription of PCSK9 inhibitors appears below expectations. Patients were mainly in secondary prevention and had been slightly persistent to previous LLTs. During follow-up, the PCSK9 inhibitor monotherapy showed high levels of adherence and persistence. This real-world study sets the stage for future longer-term investigations useful to improve our knowledge on the appropriateness, drug access and public healthcare sustainability of PCSK9 inhibitors.

[9] *Blasco M, Ascaso JF*. **Control of the overall lipid profile**. Clinica e investigacion en arteriosclerosis : publicacion oficial de la Sociedad Espanola de Arteriosclerosis 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31785850
ABSTRACT
The importance of overall lipid control in cardiovascular prevention is reviewed. Several studies and meta-analyses show that the control of LDL cholesterol (LDL-C) still maintains a high cardiovascular risk, which is related to the presence of triglyceride-rich lipoproteins, and therefore with an increase in plasma triglycerides and the values of apolipoprotein B (apoB) containing these lipoproteins. The importance of this relationship is due to the change in the lipid profile of our population in recent years. This is related to the increase in obesity and insulin resistance, and is called atherogenic dyslipidaemia. Thus, hypertriglyceridaemia should be considered a cardiovascular risk factor, especially when the desirable objectives of LDL-C have been achieved. The indications for treatment with fibrates in primary and secondary prevention, using the medical evidence-based recommendations, are described, along with its importance in the reduction of cardiovascular risk. Finally, the established indications of the combined statin-fibrate treatment are presented, always after changes in lifestyle.

[10] *Brea A, Hernandez-Mijares A, Millan J et al.* **Non-HDL cholesterol as a therapeutic goal**. Clinica e investigacion en arteriosclerosis : publicacion oficial de la Sociedad Espanola de Arteriosclerosis 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31806265
ABSTRACT
Although cholesterol linked to low-density lipoproteins (c-LDL) is well established as a risk factor for cardiovascular disease, there is often a more complex dyslipidaemia pattern that contributes to the formation of atherosclerotic plaque. Non-HDL cholesterol (c-NO-HDL) is used to estimate the total amount of atherogenic lipoproteins in plasma, some of which are not usually determined in daily clinical practice. c-NO-HDL is easily calculated from the subtraction of total plasma cholesterol from the cholesterol content carried by high density lipoproteins. The c-NO-HDL has a predictive value superior to that of C-LDL to estimate the risk of major cardiovascular events in epidemiological studies. Genetic studies by analysis of the complete genome, together with those based on Mendelian randomisation, point to the aetiological character of c-NO-HDL on ischaemic heart disease (IHD). Intervention studies, and the meta-analyses derived from them, close the causal circle between c-NO-HDL and IHD, by demonstrating that any intervention that decreases the concentrations of the former reduces the incidence of arteriosclerotic heart disease. The European ESC/EAS 2016 guide for the management of dyslipidaemia considers c-NO-HDL as a therapeutic

target with a Class IIa recommendation (should be performed) Level B (data from a single randomised clinical trial [RCT]) or from several non-RCTs), and sets its target at less than 100 or 130mg/dL for those patients with very high risk or high risk, respectively. These achievable c-NO-HDL values are easily calculated by adding 30mg/dL to the c-LDL targets.

[11] *Hieronimus B, Stanhope KL*. **Dietary fructose and dyslipidemia: new mechanisms involving apolipoprotein CIII**. Current opinion in lipidology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31789670
ABSTRACT
PURPOSE OF REVIEW: Chronic consumption of fructose and fructose-containing sugars leads to dyslipidemia. Apolipoprotein (apo) CIII is strongly associated with elevated levels of triglycerides and cardiovascular disease risk. We reviewed the effects of fructose consumption on apoCIII levels and the role of apoCIII in fructose-induced dyslipidemia. RECENT FINDINGS: Consumption of fructose increases circulating apoCIII levels compared with glucose. The more marked effects of fructose compared with glucose on apoCIII concentrations may involve the failure of fructose consumption to stimulate insulin secretion. The increase in apoCIII levels after fructose consumption correlates with increased postprandial serum triglyceride. Further, RNA interference of apoCIII prevents fructose-induced dyslipidemia in nonhuman primates. Increases in postprandial apoCIII after fructose, but not glucose consumption, are positively associated with elevated triglycerides in large triglyceride-rich lipoproteins and increased small dense LDL levels. SUMMARY: ApoCIII might be causal in the lipid dysregulation observed after consumption of fructose and fructose-containing sugars. Decreased consumption of fructose and fructose-containing sugars could be an effective strategy for reducing circulating apoCIII and subsequently lowering triglyceride levels.

[12] *Ulven SM, Holven KB*. **Metabolomic and gene expression analysis to study the effects of dietary saturated and polyunsaturated fats**. Current opinion in lipidology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31789669
ABSTRACT
PURPOSE OF REVIEW: Give an update on recent dietary intervention studies that have used peripheral blood mononuclear cell gene expression analysis and/or metabolic profiling to understand how intake of polyunsaturated and saturated fat affects and biological pathways linked to cardiovascular disease. RECENT FINDINGS: Several studies showed that intake of fish oil and vegetable oil, high in omega-3 fatty acids, reduced expression level of genes involved in inflammation. One intervention study showed that gene transcripts encoding genes involved inflammation and lipid metabolism increased after intake of polyunsaturated fat (mainly omega-6 fatty acids) compared to saturated fat. Additionally, using targeted metabolomics, the concentrations of atherogenic lipoprotein particles and several metabolites including palmitoylcarnitine, myristoylcarnitine, and kynurenine were reduced after intake of polyunsaturated fat compared to saturated fat, whereas acetate and acetoacetate were increased. The use of targeted metabolomics showed that overfeeding with polyunsaturated fat reduced the serum concentration of ceramides, dihydroceramides, glucosylceramides, and lactosylceramides, whereas overfeeding with saturated fat increased serum concentration of these metabolites.

SUMMARY: The use of gene expression profiling and metabolomics are promising tools to identify possible new biomarkers linking fat quality to cardiovascular disease risk.

[13] *Okosun IS, Okosun B, Lyn R, Airhihenbuwa C*. **Surrogate indexes of insulin resistance and risk of metabolic syndrome in non-Hispanic White, non-Hispanic Black and Mexican American**. Diabetes & metabolic syndrome 2019; 14:3-9.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31805471
ABSTRACT
AIM: To compare the strength of associations between surrogate indexes of insulin resistance (sIR) and risk of metabolic syndrome (MetS) in non-Hispanic White (NHW), non-Hispanic Black (NHB) and Mexican American (MA) adults. METHODS: The 2013-2016 US National Health and Nutrition Examination Survey data (n = 3435) were used for this study. The associations between sIR that includes Triglyceride/HDL cholesterol ratio (TG/HDL-C), triglyceride glucose (TG) index, visceral adiposity index (VAI), lipid accumulation product (LAP), TG-body mass index (TG-BMI), and TG-waist circumference (TG-WC) and risk for MetS were determined using the prevalence odds ratio (OR) from the logistic regression analyses. Pseudo-R-squared tests were used to estimate the proportion of variance in MetS accounted for by each sIR. Akaike Information Criterion and Bayesian Information Criterion from the multinomial logistic regression analysis were used to compare models that included each sIR and its components separately as predictors of MetS. Areas under curves (AUC) from the receiver-operating characteristic (ROC) were used to detect their diagnostic capabilities. RESULTS: Compared with other sIR, TG-WC (AUC = 0.899; 95% CI: 0.884-0.913 in NHW) and (AUC = 0.893; 95% CI:0.871-0.915 in NHB), and LAP (AUC = 877; 95% CI: 0.861-0.894 in MA) exhibited the highest diagnostic and predictive accuracy for MetS. Compared with other sIR, TG-WC (OR = 22.8; 95% CI:16.6-31.0 in NHW) and (OR = 22.7; 95% CI:13.1-39.3 in NHB), and LAP (OR = 10.6; 95%:6.6-17.0 in MA) were most significantly associated with increased odds of MetS, adjusting for eGFR, age, marital status, CHD, CHF, income, education, physical activity, alcohol use, smoking and use of cholesterol-lowering medication. CONCLUSIONS: TG-WC in NHW and NHB, and LAP in MA are more powerful than other proxies of IR in predicting MetS. TG-WC and LAP can serve as adjunctive tools for screening for MetS in NHW, NHB, and MA.

[14] *Harari F, Barregard L, Ostling G et al.* **Blood Lead Levels and Risk of Atherosclerosis in the Carotid Artery: Results from a Swedish Cohort**. Environmental health perspectives 2019; 127:127002.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31808705
ABSTRACT
BACKGROUND: Lead exposure has been associated with increased incidence of adverse clinical cardiovascular outcomes. Atherosclerosis has been suggested as one of the underlying mechanisms, and findings from experimental studies support this, but human data are scarce. OBJECTIVES: Our objective was to determine the association between environmental lead exposure based on blood lead (B-Pb) concentrations and the prevalence of atherosclerotic plaque in the carotid artery. METHODS: We used cross-sectional data from the Malmo Diet and Cancer Study cardiovascular cohort (MDCS-CC; recruitment in 1991-1994) covering 4,172 middle-aged men and women. B-Pb at baseline, measured by inductively coupled plasma mass spectrometry, was used as the exposure biomarker. The presence of atherosclerotic plaque in the carotid artery was

determined by B-mode ultrasonography. We used logistic regression to estimate odds ratios (ORs) for prevalence of plaque in the carotid artery according to B-Pb quartiles. RESULTS: The median B-Pb was 25mug/L (range: 1.5-258), and 36% of the cohort had any atherosclerotic plaque. After controlling for confounders and known cardiovascular risk factors, the OR for prevalence of plaque in the highest quartile (Q4) of B-Pb compared with the lowest quartile (Q1) was 1.35 (95% CI: 1.09, 1.66) in the total group, 1.58 (95% CI: 1.20, 2.08) among women, and 1.18 (95% CI: 0.83, 1.69) among men. Among women, associations were limited to those who were postmenopausal [OR for Q4 vs. Q1=1.72 (95% CI: 1.26, 2.34) vs. OR=0.96 (95% CI: 0.49, 1.89 in premenopausal women)]. Associations were weak and nonsignificant in never-smokers [OR for Q4 vs. Q1=1.14 (95% CI: 0.81, 1.61)]. DISCUSSION: Our study shows an association between B-Pb concentrations and occurrence of atherosclerotic plaque in the carotid artery, adding evidence for an underlying pro-atherogenic role of lead in cardiovascular disease. Associations appeared to be limited to postmenopausal (vs. premenopausal) women. https://doi.org/10.1289/EHP5057.

[15] *Shimizu Y, Kawashiri SY, Kiyoura K et al.* **Gamma-glutamyl transpeptidase (gamma-GTP) has an ambivalent association with hypertension and atherosclerosis among elderly Japanese men: a cross-sectional study**. Environmental health and preventive medicine 2019; 24:69.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31785607
ABSTRACT
BACKGROUND: Even though there is bidirectional association between hypertension and atherosclerosis, atherosclerosis itself is involved in the process of endothelial repair. To clarify the association of endothelial repair with hypertension, a cross-sectional study was conducted. METHODS: We conducted a cross-sectional study of 562 elderly Japanese men aged 60-69. As gamma-glutamyl transpeptidase (gamma-GTP) could act as a marker of oxidative stress that injures endothelial cell and higher levels of CD34-positive cell indicate a higher activity of endothelial repair, we therefore performed a CD34-positive level specific analysis of gamma-GTP on atherosclerosis and hypertension. RESULTS: In the present study population, hypertension was independently and positively associated with atherosclerosis (multivariable odds ratio (OR) = 2.09 (1.30, 3.35)). Among participants with high CD34-positive cells, gamma-GTP showed significant and positive association with atherosclerosis (OR of the log-transformed value of gamma-GTP (OR) = 2.26 (1.32, 3.86)) but not with hypertension (OR = 0.77 (0.51, 1.17)). Among participants with low CD34-positive cells, even gamma-GTP showed no significant association with atherosclerosis (OR = 0.92 (0.51, 1.68)), but was significantly and positively associated with hypertension (OR = 1.99 (1.27, 3.12)). CONCLUSIONS: gamma-GTP revealed to have ambivalent association with hypertension and atherosclerosis. Active endothelial repair that is associated with atherosclerosis might have beneficial association with hypertension.

[16] *Wang BX, Li KP, Yu T, Feng HY*. **Rosuvastatin promotes osteogenic differentiation of mesenchymal stem cells in the rat model of osteoporosis by the Wnt/beta-catenin signal**. European review for medical and pharmacological sciences 2019; 23:10161-10168.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31799688
ABSTRACT
OBJECTIVE: The aim of this study was to explore the promoting effect of rosuvastatin on the osteogenic differentiation of mesenchymal stem cells in the rat model of osteoporosis through the

Wnt/beta-catenin signal. MATERIALS AND METHODS: A total of 30 rats were purchased from the Animal Research Center of Shanxi Medical University. All rats were randomly allocated into three groups, including: group A (control group, n=10), group B (ovariectomized group, n=10), and group C (rosuvastatin gavage group, n=10). The bone metabolism indexes, bone mineral density (BMD) and the Wnt/beta-catenin signaling pathway-related proteins in blood samples of rats in each group were measured, respectively. Furthermore, the bone marrow mesenchymal stem cells of rats were used for alkaline phosphatase (ALP) staining. All data were analyzed using the Statistical Product and Service Solutions (SPSS) 22.0 software (IBM Corp., Armonk, NY, USA). RESULTS: The rats firstly received 9 consecutive weeks of feeding with drug intervention. The imaging results revealed that trabecular thickness in group A was significantly higher than that of group B and group C, showing statistically significant differences ($p<0.05$). After 9 consecutive weeks of feeding with drug intervention, BMD of the femurs of rats in group A and group C was significantly higher than that of group B, showing statistically significant differences ($p<0.05$). However, there was no significant difference in BMD between group A and group C ($p>0.05$). The level of calcium representing bone absorption level in serum of rats in group B was remarkably higher than that of group A, and the difference was statistically significant ($p<0.05$). However, the level of ALP representing bone absorption level in the serum of rats in group B was significantly lower than that of group A ($p<0.05$). No significant differences were found in the levels of calcium and ALP that represented bone absorption level between group C and group A ($p>0.05$). Meanwhile. the levels of phosphorus in the three groups were similar, showing no statistically significant difference ($p>0.05$). Moreover, the expression of ALP-positive cells in the rats of group A and group C was markedly higher than that of group B ($p<0.05$). After drug intervention through feeding for 9 consecutive weeks, no evident difference was found in the relative expression of Wnt/beta-catenin signaling pathway-related protein glycogen synthase kinase-3beta (GSK-3beta) among the three groups. The relative expression of the protein phosphorylated GSK-3beta (p-GSK-3beta) in group C was significantly lower than that of group B ($p<0.05$). Furthermore, the relative protein expressions of beta-catenin and cyclin D1 in group C were significantly higher than those in group B ($p<0.05$). CONCLUSIONS: Rosuvastatin can improve bone metabolism in osteoporosis rats and increasing BMD of bone tissues in rats with osteoporosis. Besides, the Wnt/beta-catenin signaling pathway plays a crucial role in the regulation of the stem cell self-renewal and bone genesis.

[17] *Kraker K, O'Driscoll JM, Schutte T et al.* **Statins Reverse Postpartum Cardiovascular Dysfunction in a Rat Model of Preeclampsia**. Hypertension 2020; 75:202-210.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31786987

ABSTRACT

Preeclampsia is associated with increased cardiovascular long-term risk; however, the underlying functional and structural mechanisms are unknown. We investigated maternal cardiac alterations after preeclampsia. Female rats harboring the human angiotensinogen gene [TGR(hAogen)L1623] develop a preeclamptic phenotype with hypertension and albuminuria during pregnancy when mated with male rats bearing the human renin gene [TGR(hRen)L10J] but behave physiologically normal before and after pregnancy. Furthermore, rats were treated with pravastatin. We tested the hypothesis that statins are a potential therapeutic intervention to reduce cardiovascular alterations due to simulated preeclamptic pregnancy. Although hypertension persists for only 8 days in pregnancy, former preeclampsia rats exhibit significant cardiac hypertrophy 28 days after

pregnancy observed in both speckle tracking echocardiography and histological staining. In addition, fibrosis and capillary rarefaction was evident. Pravastatin treatment ameliorated the remodeling and improved cardiac output postpartum. Preeclamptic pregnancy induces irreversible structural changes of cardiac hypertrophy and fibrosis, which can be moderated by pravastatin treatment. This pathological cardiac remodeling might be involved in increased cardiovascular risk in later life.

[18] *Mahdi A, Kovamees O, Pernow J*. **Improvement in endothelial function in cardiovascular disease - Is arginase the target?** International journal of cardiology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31785959
ABSTRACT
Endothelial dysfunction represents an early change in the vascular wall in areas prone to atherosclerotic plaque formation and is present in association with several risk factors for cardiovascular disease. The underlying mechanisms behind endothelial dysfunction are multifactorial and complex. Arginase has emerged as a key player in the regulation of endothelial integrity by the ability of reciprocally inhibits nitric oxide formation and promoting oxidative stress. A chain of evidence suggest that arginase is implicated in the pathogenesis underlying endothelial dysfunction induced by several cardiovascular risk factors and established cardiovascular disease including diabetes, hypercholesteremia, ischemia/reperfusion, atherosclerosis, obesity, ageing and hypertension. Recent data has unveiled a key role of arginase as one of the key mechanisms underlying endothelial dysfunction in diabetes and may serve as a potential therapeutic target in previously overlooked compartments including red blood cells. The current review is devoted to discuss arginase as a key mediator in endothelial dysfunction and the potential for therapeutic possibilities to target this enzyme in various diseases, especially type 2 diabetes, atherosclerosis and ischemia/reperfusion with focus on translational and clinical aspects. Moreover, approaches of how and in which patient group(s) arginase may be targeted in future clinical trials are discussed.

[19] *Orringer CE, Jacobson TA, Maki KC*. **National Lipid Association Scientific Statement on the use of icosapent ethyl in statin-treated patients with elevated triglycerides and high or very-high ASCVD risk**. Journal of clinical lipidology 2019; 13:860-872.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31787586
ABSTRACT
Representatives from the National Lipid Association (NLA) participated in the development of the 2018 American Heart Association/American College of Cardiology/Multisociety Guideline on the Management of Blood Cholesterol, which reaffirmed that lifestyle changes and statin treatment are therapeutic cornerstones for atherosclerotic cardiovascular disease (ASCVD) risk reduction. It also updated prior recommendations to incorporate newer data demonstrating ASCVD risk reduction with ezetimibe and proprotein convertase subtilisin kexin type 9 inhibitors as adjuncts to statin therapy for patients at high and very-high ASCVD risk. The 2018 Guideline was finalized shortly before full results were available from a randomized, placebo-controlled cardiovascular outcomes trial [Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial (REDUCE-IT)] that examined the effects of icosapent ethyl (IPE) 4 g/d on major adverse cardiovascular events in selected high- or very high-risk, statin-treated patients with elevated triglycerides. The primary outcome variable of first major adverse cardiovascular event (cardiovascular death, myocardial

infarction, stroke, coronary revascularization and hospitalization for unstable angina) was reduced by 25% (95% confidence interval 17%-32%, P < .001). REDUCE-IT served as the primary basis for the NLA's review of evidence for the use of IPE for ASCVD risk reduction. Based on this review, the NLA position is that for patients aged >/=45 years with clinical ASCVD, or aged >/=50 years with diabetes mellitus requiring medication plus >/=1 additional risk factor, with fasting triglycerides 135 to 499 mg/dL on high-intensity or maximally tolerated statin therapy (+/-ezetimibe), treatment with IPE is recommended for ASCVD risk reduction (evidence rating: class I; evidence level: B-R).

[20] *Saraswathi V, Heineman R, Alnouti Y et al.* **A combination of Omega-3 PUFAs and COX inhibitors: A novel strategy to manage obesity-linked dyslipidemia and adipose tissue inflammation**. Journal of diabetes and its complications 2019:107494.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31787562
ABSTRACT
We previously reported that fish oil in combination with cyclooxygenase (COX) inhibitors exerts enhanced hypolipidemic and anti-inflammatory effects in mice. Here, we sought to determine the effects of omega-3 polyunsaturated fatty acids (omega-3 PUFAs) in combination with naproxen (NX), a COX inhibitor, on dyslipidemia and gene expression in adipose tissue (AT) in humans. Obese dyslipidemic patients were randomly assigned to one of these interventions for 12 wk: 1) Standard nutrition counseling (control), 2) omega-3 PUFAs (2g twice daily), 3) NX (220mg twice daily), and 4) omega-3 PUFAs (2g twice daily)+NX (220mg twice daily). The serum triglycerides showed a trend towards a reduction and a significant reduction (P<0.05) in omega-3 and omega3+NX-treated subjects, respectively, compared to control. The mRNA expression of vascular cell adhesion molecule-1 (Vcam1), an inflammatory marker, increased significantly in AT of omega-3 PUFA-treated subjects but not in omega-3 PUFAs+NX-treated group. The plasma level of glycine-conjugated hyodeoxycholic acid, a secondary bile acid with hypolipidemic property, increased significantly in omega-3 PUFAs + NX-treated group. Our data suggest that combining NX with omega-3 PUFAs increases their effectiveness in reducing serum TG and favorably altering AT gene expression and plasma bile acid profile.

[21] *Brunner FJ, Waldeyer C, Ojeda F et al.* **Application of non-HDL cholesterol for population-based cardiovascular risk stratification: results from the Multinational Cardiovascular Risk Consortium**. Lancet 2019; 394:2173-2183.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31810609
ABSTRACT
BACKGROUND: The relevance of blood lipid concentrations to long-term incidence of cardiovascular disease and the relevance of lipid-lowering therapy for cardiovascular disease outcomes is unclear. We investigated the cardiovascular disease risk associated with the full spectrum of bloodstream non-HDL cholesterol concentrations. We also created an easy-to-use tool to estimate the long-term probabilities for a cardiovascular disease event associated with non-HDL cholesterol and modelled its risk reduction by lipid-lowering treatment. METHODS: In this risk-evaluation and risk-modelling study, we used Multinational Cardiovascular Risk Consortium data from 19 countries across Europe, Australia, and North America. Individuals without prevalent cardiovascular disease at baseline and with robust available data on cardiovascular disease outcomes were included. The primary composite endpoint of atherosclerotic cardiovascular

disease was defined as the occurrence of the coronary heart disease event or ischaemic stroke. Sex-specific multivariable analyses were computed using non-HDL cholesterol categories according to the European guideline thresholds, adjusted for age, sex, cohort, and classical modifiable cardiovascular risk factors. In a derivation and validation design, we created a tool to estimate the probabilities of a cardiovascular disease event by the age of 75 years, dependent on age, sex, and risk factors, and the associated modelled risk reduction, assuming a 50% reduction of non-HDL cholesterol. FINDINGS: Of the 524 444 individuals in the 44 cohorts in the Consortium database, we identified 398 846 individuals belonging to 38 cohorts (184 055 [48.7%] women; median age 51.0 years [IQR 40.7-59.7]). 199 415 individuals were included in the derivation cohort (91 786 [48.4%] women) and 199 431 (92 269 [49.1%] women) in the validation cohort. During a maximum follow-up of 43.6 years (median 13.5 years, IQR 7.0-20.1), 54 542 cardiovascular endpoints occurred. Incidence curve analyses showed progressively higher 30-year cardiovascular disease event-rates for increasing non-HDL cholesterol categories (from 7.7% for non-HDL cholesterol <2.6 mmol/L to 33.7% for >/=5.7 mmol/L in women and from 12.8% to 43.6% in men; p<0.0001). Multivariable adjusted Cox models with non-HDL cholesterol lower than 2.6 mmol/L as reference showed an increase in the association between non-HDL cholesterol concentration and cardiovascular disease for both sexes (from hazard ratio 1.1, 95% CI 1.0-1.3 for non-HDL cholesterol 2.6 to <3.7 mmol/L to 1.9, 1.6-2.2 for >/=5.7 mmol/L in women and from 1.1, 1.0-1.3 to 2.3, 2.0-2.5 in men). The derived tool allowed the estimation of cardiovascular disease event probabilities specific for non-HDL cholesterol with high comparability between the derivation and validation cohorts as reflected by smooth calibration curves analyses and a root mean square error lower than 1% for the estimated probabilities of cardiovascular disease. A 50% reduction of non-HDL cholesterol concentrations was associated with reduced risk of a cardiovascular disease event by the age of 75 years, and this risk reduction was greater the earlier cholesterol concentrations were reduced. INTERPRETATION: Non-HDL cholesterol concentrations in blood are strongly associated with long-term risk of atherosclerotic cardiovascular disease. We provide a simple tool for individual long-term risk assessment and the potential benefit of early lipid-lowering intervention. These data could be useful for physician-patient communication about primary prevention strategies. FUNDING: EU Framework Programme, UK Medical Research Council, and German Centre for Cardiovascular Research.

[22] *Shah RA, Kowdley KV*. **Current and potential treatments for primary biliary cholangitis**. The lancet. Gastroenterology & hepatology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31806572
ABSTRACT
Up to 40% of patients with primary biliary cholangitis have an incomplete response to first-line treatment with ursodeoxycholic acid. Obeticholic acid was approved by the US Food and Drug Administration in 2016 as a second-line treatment for patients with primary biliary cholangitis who are unresponsive to ursodeoxycholic acid; however, approximately 50% of patients might need additional treatments to reach therapeutic goals. A considerable need exists for effective treatment options to prevent progression to liver transplantation or death in these patients. Drugs that might modulate immunological abnormalities in primary biliary cholangitis have been studied but their effectiveness varies. Budesonide, ciclosporin, and rituximab have shown potential in modifying the disease process. Bezafibrate, a pan-peroxisome proliferator-activated receptor

agonist, has been shown to ameliorate deranged bile acid homoeostasis and attenuate raised concentrations of liver enzymes associated with primary biliary cholangitis. As the mechanisms underlying the pathogenesis and progression of primary biliary cholangitis are further clarified, specific targeted therapies are under development with promising early results. Various therapeutic target bile acid homeostasis, immune dysfunction, and fibrogenetic pathways are being studied. A better understanding of the biochemical and clinical effects of the therapies in development bear discussion, both to guide the discovery of new therapies and to inform clinicians so that rational treatment regimens can be tailored to patients once they become available.

[23] *Hayashi K, Nakazato Y, Morito N et al.* **Fluvastatin is effective against thymic carcinoma**. Life sciences 2019; 240:117110.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31786191
ABSTRACT
AIMS: Thymic carcinoma is a rare epithelial tumor, for which, optimal pharmacotherapeutic methods have not yet been established. To develop new drug treatments for thymic carcinoma, we investigated the effects of fluvastatin-mediated pharmacological inhibition of 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGCR) on thymic carcinoma. MAIN METHODS: Thymic carcinoma tissue was surgically excised and HMGCR expression was assessed by immunohistochemistry. Ty82 human thymic carcinoma cells were treated with fluvastatin (1-10 muM) and their growth was monitored. KEY FINDINGS: HMGCR was expressed on carcinoma cells but not on normal epithelial cells in thymic tissue. Inhibition of HMGCR by fluvastatin suppressed cell proliferation and induced the death of Ty-82 human thymic carcinoma cells. Fluvastatin mediated its antitumor effects by blocking the production of geranylgeranyl-pyrophosphate (GGPP), an isoprenoid that is produced from mevalonate and binds to small GTPases, which promotes cell proliferation. SIGNIFICANCE: Fluvastatin showed marked antitumor effects on thymic carcinoma. The results suggest that the statin has clinical benefits in thymic carcinoma management.

[24] *Zia S, Batool S, Shahid R*. **Could PCSK9 be a new therapeutic target of Eugenol? In vitro and in silico evaluation of hypothesis**. Medical hypotheses 2019; 136:109513.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31812013
ABSTRACT
PCSK9 (Proprotein convertase Subtilisin/Kexin Type 9), an important regulator of lipid metabolism, has been shown to play a role in hepatocellular carcinoma by promoting metastasis. PCSK9 interferes with LDL metabolism and causes dyslipidemias in hematological malignancies particularly acute lymphoblastic leukemia. Nutraceuticals like berberine, curcumin and polydatin have been found effective in modulating PCSK9 expression by lowering LDL levels. Eugenol, a nutraceutical has shown a promising role in cancer due to its antioxidant and antihypercholesterolemic effects. In the present study, PCSK9 expression was measured in acute lymphoblastic leukemia (ALL) patients and was found to be significantly induced. Based on the results of expression analysis, a plausible hypothesis was made. Eugenol being an antioxidant will prevent oxidation of LDL. In the absence of ox-LDL, LOX1 scavenger receptor, which regulates PCSK9 expression, will not be activated. As the circulating LDL is reduced, it will no longer be able to support leukemia cell growth. The hypothesis was validated by an in silico and in vitro study. Molecular docking revealed hydrophobic

interactions between ligand eugenol and macromolecules PCSK9 and LOX1. Expression of both PCSK9 and LOX1 were significantly reduced by eugenol in Jurkat cells. To conclude, PCSK9 could therapeutically be targeted by eugenol in leukemia cells.

[25] *Sheridan C*. **PCSK9-gene-silencing, cholesterol-lowering drug impresses**. Nature biotechnology 2019; 37:1385-1387.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31796927
ABSTRACT

[26] *Ruiz-Iruela C, Candas-Estebanez B, Pinto-Sala X et al.* **Genetic contribution to lipid target achievement with statin therapy: a prospective study**. The pharmacogenomics journal 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31806882
ABSTRACT
Statin therapy response is highly variable. Variants of lipid metabolism genes and statin pharmacokinetic modulators could play a role, however, the impact of most of these variants remains unconfirmed. A prospective and multicenter study included 252 patients was carried out in order to assess, according to achievement of LDL-C or non-HDL-C therapeutic targets and quantitative changes in lipid profiles, the impact of CETP, ABCA1, CYP2D6, and CYP2C9 gene candidate variants on the simvastatin, atorvastatin, and rosuvastatin response. Patients carrier ABCA1 rs2230806 and CYP2D6*3 variants are less likely to achieve therapeutic lipid targets (p = 0.020, OR = 0.59 [0.37, 0.93]; p = 0.040, OR = 0.23 [0.05, 0.93], respectively). Among CETP variants, rs708272 was linked to a 10.56% smaller reduction in LDL-C with rosuvastatin (95% CI = [1.27, 19.86] %; p = 0.028). In contrast, carriers of rs5882 had a 13.33% greater reduction in LDL-C (95% CI = [25.38, 1.28]; p = 0.032). If these findings are confirmed, ABCA1, CYP2D6, and CETP genotyping could be used to help predict which statin and dosage is appropriate in order to improve personalized medicine.

[27] *Li X, Li Y, Zhang T et al.* **Role of cardioprotective agents on chemotherapy-induced heart failure: A systematic review and network meta-analysis of randomized controlled trials**. Pharmacological research : the official journal of the Italian Pharmacological Society 2019; 151:104577.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31790821
ABSTRACT
BACKGROUND: Although previous clinical randomized controlled trials (RCTs) have tested the effect of a variety of cardioprotective agents on cancer therapy-induced cardiotoxicity, the number of included patients was limited, and the results remained controversial. In this study, we aimed to evaluate the preventive or therapeutic effects of cardioprotective agents on heart failure (HF) caused by cardiotoxicity induced by cancer therapy. METHODS: We included trials of the following cardioprotective drugs: Angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, beta-blockers, aldosterone antagonists and stains. We extracted the relevant information with predefined data extraction forms, and assessed the risk of bias in randomized controlled trials with the Cochrane risk of bias tool. The primary outcome was the left ventricular ejection fraction of patients after chemotherapy. We used the random-effects model to carry out pair-wise meta-analysis, and then carry out the random-effects network meta-analysis within the Bayesian

framework. RESULTS: Twenty-two relevant RCTs, including 1 916 patients (79.6 % women) with a mean age of 48.4 years, were included. Based on the evaluation of all drug species from 20 studies (26 comparisons), the analysis found that 4 therapies, aldosterone antagonists (MD, 12.78 [95 % CI, 2.87-22.69] and MD, 13.75 [95 % CI, 2.21-25.30]), ACEIs (MD, 6.79 [95 % CI, 2.11-11.48] and MD, 7.76 [95 % CI, 2.64-12.88]), statin (MD, 8.35 [95 % CI, 1.11-15.59]), and beta-blockers (MD, 4.00 [95 % CI, 0.87-7.14]), had a higher efficacy than placebo and/or control, suggesting an LVEF protective effect of cardioprotective therapy. In the analysis classified by single drug or drug combination, based on 22 studies (31 comparisons), spironolactone (MD, 12.77 [95 % CI, 1.76-23.79] and MD, 14.62 [95 % CI, 1.70-27.55]), a combination of candesartan and carvedilol (MD, 12.40 [95 % CI, 0.99-23.81]), enalapril (MD, 7.35 [95 % CI, 1.16-13.54] and MD, 9.20 [95 % CI, 2.61-15.79]), and statin (MD, 8.36 [95 % CI, 0.36-16.36]) showed significant benefits in protecting left ventricular (LV) systolic function compared with the placebo and/or control. CONCLUSION: When classified according to drug type, aldosterone antagonists, ACEIs, statins, and beta-blockers could substantially improve the LV systolic function. In the analysis classified by single drug or drug combination, spironolactone, enalapril, and statin have a significant cardioprotective effect. However, ARBs have no cardioprotective effect and fail to improve the LVEF.

[28] *Sureda A, Daglia M, Arguelles Castilla S et al.* **Oral microbiota and Alzheimer's disease: Do all roads lead to Rome?** Pharmacological research : the official journal of the Italian Pharmacological Society 2019; 151:104582.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31794871
ABSTRACT
Alzheimer's disease (AD) is a progressive neurodegenerative pathology affecting milions of people worldwide associated with deposition of senile plaques. While the genetic and environmental risk factors associated with the onset and consolidation of late onset AD are heterogeneous and sporadic, growing evidence also suggests a potential link between some infectious diseases caused by oral microbiota and AD. Oral microbiota dysbiosis is purported to contribute either directly to amyloid protein production, or indirectly to neuroinflammation, occurring as a consequence of bacterial invasion. Over the last decade, the development of Human Oral Microbiome database (HOMD) has deepened our understanding of oral microbes and their different roles during the human lifetime. Oral pathogens mostly cause caries, periodontal disease, and edentulism in aged population, and, in particular, alterations of the oral microbiota causing chronic periodontal disease have been associated with the risk of AD. Here we describe how different alterations of the oral microbiota may be linked to AD, highlighting the importance of a good oral hygiene for the prevention of oral microbiota dysbiosis.

[29] *Gagnon ME, Sirois C, Simard M, Plante C*. **Polypharmacy and Pharmacological Treatment of Diabetes in Older Individuals: A Population-Based Study in Quebec, Canada**. Pharmacy (Basel, Switzerland) 2019; 7.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31805662
ABSTRACT
Our objectives were to describe the use of pharmacological treatments in older adults with diabetes and to identify the factors associated with the use of a combination of hypoglycemic, antihypertensive and lipid-lowering agents. Using the Quebec Integrated Chronic Disease

Surveillance System, we conducted a population-based cohort study among individuals aged 66-75 years with diabetes in 2014-2015. We described the number of medications and the classes of medications used and calculated the proportion of individuals using at least one medication from each of these classes: hypoglycemics, antihypertensives and lipid-lowering agents. We identified the factors associated with the use of this combination of treatments by performing robust Poisson regressions. The 146,710 individuals used an average of 12 (SD 7) different medications, mostly cardiovascular (91.3% of users), hormones, including hypoglycemic agents (84.5%), and central nervous system medications (79.8%). The majority of individuals (59%) were exposed to the combination of treatments and the factor most strongly associated was the presence of cardiovascular comorbidities (RR: 1.29; 99% CI: 1.28-1.31). Older individuals with diabetes are exposed to a large number of medications. While the use of the combination of treatments is significant and could translate into cardiovascular benefits at the population level, the potential risk associated with polypharmacy needs to be documented.

[30] *Guarnieri F, Kulp JL, Jr., Kulp JL, 3rd, Cloudsdale IS*. **Fragment-based design of small molecule PCSK9 inhibitors using simulated annealing of chemical potential simulations**. PloS one 2019; 14:e0225780.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31805108
ABSTRACT
PCSK9 is a protein secreted by the liver that binds to the low-density lipoprotein receptor (LDLR), causing LDLR internalization, decreasing the clearance of circulating LDL particles. Mutations in PCSK9 that strengthen its interactions with LDLR result in familial hypercholesterolemia (FH) and early onset atherosclerosis, while nonsense mutations of PCSK9 result in cardio-protective hypocholesterolemia. These observations led to PCSK9 inhibition for cholesterol lowering becoming a high-interest therapeutic target, with antibody drugs reaching the market. An orally-available small molecule drug is highly desirable, but inhibiting the PCSK9/LDLR protein-protein interaction (PPI) has proven challenging. Alternate approaches to finding good lead candidates are needed. Motivated by the FH mutation data on PCSK9, we found that modeling the PCSK9/LDLR interface revealed extensive electron delocalization between and within the protein partners. Based on this, we hypothesized that compounds assembled from chemical fragments could achieve the affinity required to inhibit the PCSK9/LDLR PPI if they were selected to interact with PCSK9 in a way that, like LDLR, also involves significant fractional charge transfer to form partially covalent bonds. To identify such fragments, Simulated Annealing of Chemical Potential (SACP) fragment simulations were run on multiple PCSK9 structures, using optimized partial charges for the protein. We designed a small molecule, composed of several fragments, predicted to interact at two sites on the PCSK9. This compound inhibits the PPI with 1 muM affinity. Further, we designed two similar small molecules where one allows charge delocalization though a linker and the other doesn't. The first inhibitor with charge delocalization enhances LDLR surface expression by 60% at 10 nM, two orders of magnitude more potent than the EGF domain of LDLR. The other enhances LDLR expression by only 50% at 1 muM. This supports our conjecture that fragments can have surprisingly outsized efficacy in breaking PPI's by achieving fractional charge transfer leading to partially covalent bonding.

[31] *Man REK, Gan AHW, Fenwick EK et al.* **Prevalence, determinants and association of unawareness of diabetes, hypertension and hypercholesterolemia with poor disease control in a multi-ethnic Asian population without cardiovascular disease**. Population health metrics 2019; 17:17.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31806040

ABSTRACT
BACKGROUND: To explore the prevalence and determinants of unawareness of diabetes, hypertension and hypercholesterolemia and its association with poor disease control in a multi-ethnic Asian population without cardiovascular disease (CVD). METHODS: We included 6904 Chinese, Malay and Indian individuals (mean age [SD] 58.2 [10.2] years; 52.6% female) with diabetes, hypertension and/or hypercholesterolemia from the cross-sectional population-based Singapore Epidemiology of Eye Diseases study (2004-2011). Diabetes was defined as random blood glucose >/= 11.1 mmol/L or HbA1c > 6.5% or self-reported use of diabetes medication; hypertension as systolic blood pressure >/= 140 mmHg or diastolic blood pressure >/= 90 mmHg or self-reported use of anti-hypertensive treatment; and hypercholesterolemia as total cholesterol >/= 6.2 mmol/L or self-reported use of lipid-lowering medications. Unawareness was based on participants' answers to the questions: "Did your medical practitioner ever tell you that you have diabetes/hypertension/high cholesterol?" The determinants of unawareness, and its association with poor disease control, were assessed using multivariable binary logistic regression models adjusted for known potential confounders. RESULTS: Of the 2380 (34.5%), 5386 (78.0%) and 3607 (52.2%) with diabetes, hypertension and hypercholesterolemia, respectively, unawareness rates were 30.7%, 43.1% and 40.9%, respectively. Having a higher BMI, particularly if obese, and Malay ethnicity were associated with greater unawareness of diabetes; Malay and Indian ethnicities and current smoking with greater unawareness of hypertension; and education </=6 years, current smoking, and blue collar jobs or unemployment with greater unawareness of hypercholesterolemia (all P < 0.05). Lack of awareness of each condition was independently associated with poorer disease control in the case of hypertension and hypercholesterolemia, while the converse was true for diabetes (all P < 0.05). CONCLUSIONS: Unawareness of diabetes, hypertension, or hypercholesterolemia is high in Singapore, with risk factors varying across all three diseases, although Malay ethnicity is a consistent one. Unawareness was also associated with poor management for hypertension and hypercholesterolemia. Public health education and screening programs should target at-risk individuals, especially Malays, to reduce the likelihood of incident CVD.

[32] *Hai-Na Z, Xu-Ben Y, Cong-Rong T et al.* **Atorvastatin ameliorates depressive behaviors and neuroinflammatory in streptozotocin-induced diabetic mice**. Psychopharmacology (Berl) 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31786648

ABSTRACT
Depression is a chronic and progressive syndrome and commonly associated with several neuropsychiatric comorbidities, of which depression is the most studied. It has been demonstrated that statins also have anti-inflammatory and immunomodulatory properties, which being explored for potential benefits in depression. However, the role of statins in the treatment of diabetes-related depression has not been well examined. Herein, we investigated the effects of atorvastatin on depressive behaviors and neuroinflammation in streptozotocin-induced diabetic mice. Our data

indicated that oral administration of atorvastatin at 10 or 20 mg/kg for 3 weeks markedly ameliorated diabetes-associated depressive behaviors reflected by better performance in sucrose preference test (SPT), tail suspension test (TST), and novelty-suppressed feeding test (NSFT). The study further showed that atrovastatin decreased the expression of nucleus NF-kappaB p65 expression and ameliorated neuroinflammatory responses in prefrontal cortex as evidenced by less Iba-1-positive cells and lower inflammatory mediators including IL-1beta and TNF-alpha. As expected, atorvastatin-treated diabetic mice exhibited significant improvement of hyperlipidemia rather than hyperglycemia. These results suggest that atorvastatin has the potential to be employed as a therapy for diabetes-related depression.

[33] *Calanca L, Alatri A, Lanzi S et al.* **[Lower extremity peripheral artery disease : local and systemic complications]**. Revue medicale suisse 2019; 15:2247-2250.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31804037
ABSTRACT
Lower extremity peripheral artery disease can lead to local complications but also to complications in other vascular areas, stressing the systemic impact of the atheromatous disease. The current concepts of MALE (Major Adverse Limb Events) and MACE (Major Adverse Cardiac Events) encompass these risks. The systemic vascular complications, as well as the ones at lower extremities, are associated with significant morbidity and mortality. An optimal therapeutic management and healthy lifestyle, such as regular exercise, are crucial to limit the risk of unfavorable progression of the arterial disease. A close collaboration between the general practitioner and the angiologist is a key to adequate initial management and follow-up of the patients.

[34] *Lanzi S, Ney B, Deslarzes-Dubuis C et al.* **[Exercise training therapy in patients with lower extremity peripheral artery disease]**. Revue medicale suisse 2019; 15:2252-2255.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31804038
ABSTRACT
Patients with lower extremity peripheral artery disease (PAD) have decreased functional capacities leading to decreased quality of life and increased cardiovascular morbidity and mortality. Exercise therapy is recommended among first-choice therapeutic options and improves overall physical function and quality of life in symptomatic patients with PAD. Exercise therapy is also effective in patients with PAD following revascularization. Other than walking, different training modalities are safe, feasible and effective to induce clinical benefits for these patients. We present here the role of exercise therapy and its specificities in the management of PAD.

[35] *Christophe B, Karatela M, Sanchez J et al.* **Statin Therapy in Ischemic Stroke Models: A Meta-Analysis**. Translational stroke research 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31788761
ABSTRACT
Statins, drugs known for lipid lowering capabilities and reduction of cardiovascular disease, have demonstrated neuroprotective effects following ischemic stroke in retrospective clinical and animal studies. However, dosing (methods, time, type of statin, and quantity) varies across studies, limiting the clinical applicability of these findings. Furthermore, a comprehensive review of statins

in edema and blood-brain barrier (BBB) breakdown is needed to provide insight on diverse, less explored neuroprotective effects. In the present study, we conduct a meta-analysis of publications evaluating statin administration in animal models of ischemic stroke. We review statins' most effective dosing regimen in four outcomes-infarct, edema, BBB breakdown, and functional outcome-to characterize several parameters of benefit associated with statin administration. A search term was constructed to identify experimental murine studies exploring statin use after transient middle cerebral artery occlusion (tMCAO) in PubMed, Web of Science, and Embase. Extracted data included statin type, dose, time and method of administration, and the four predetermined outcomes (functional outcome, edema, BBB breakdown, and infarction). A meta-analysis and stratified meta-regression were conducted using the standardized mean difference (SMD) method for continuous measurements. Included publications were assessed for bias using SYRCLE's RoB tool for animal studies. A total of 24 studies were included. Statin administration significantly reduced infarct volume ($p < 0.0001$), edema volume ($p < 0.002$), and neurological deficit ($p < 0.0001$). Simvastatin and pravastatin were most effective in reducing infarct volume when compared with atorvastatin ($p = 0.0475$, $p = 0.0004$) and rosuvastatin ($p = 0.0036$, $p < 0.0001$). Pravastatin outperformed all others in functional outcome. Subcutaneous (SC) injection was most effective in all outcomes. Statin therapy reduced BBB breakdown according to our systematic review. Mean study quality was 4.6/10. While statin therapy evidently improves neurological outcome following ischemic stroke, this analysis adds to our understanding of dosing and statins' effects on edema and BBB breakdown. These findings will aid the design of future studies investigating statin use and have larger implications for the clinical care of ischemic stroke patients.

[36] *Wassmuth S, Rohe K, Noack F et al.* **Adherence To Lipid-Lowering Therapy In Patients With Coronary Heart Disease From The State Of Saxony-Anhalt, Germany**. Vascular health and risk management 2019; 15:477-483.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31802881

ABSTRACT

Objectives: Treatment with lipid-lowering therapy (LLT) such as statins, cholesterol absorption inhibitors, or PCSK9 inhibitors is of major importance for the survival of patients with atherosclerotic diseases, and adherence to LLT is essential for treatment success. The intention of this study was to investigate adherence to LLT in patients with coronary heart disease (CHD) in a 12-month follow-up period in Saxony-Anhalt, the state with the highest incidence and mortality for CHD in Germany. Patients and methods: Data were taken from 542 hospitalized patients with angiographically documented CHD who were prospectively included in this study conducted in the Department of Medicine III of the University Clinics (Halle). We collected data concerning medication at discharge and after 3 and 12 months. Results: A total of 542 patients were included in this study. Mean age was 69.2 +/- 11.8 years. In all, 68.8% were males, 165 (30.4%) were smokers, 39.7% suffered from diabetes, and 86.9% had arterial hypertension. The follow-up time of this study was 12 months. At discharge, 463 patients (85.4%) were being treated with a statin. After 3 months 409 (75.5%) and after 12 months, 395 patients (72.9%) were still on statin therapy, respectively. In total treatment, adherence for the statin medication decreased by 15.7% in 12 months. Kaplan-Meier analyses showed that survival, taken as freedom of death from any cause, decreased significantly if statin treatment was stopped (p=0.001). This was confirmed by

multivariate Cox regression (HR 1.78, p=0.012). Ezetemibe was prescribed for 56 patients at discharge (10.3%). After 3 months, 40 patients (7.4%) were still taking ezetemibe. After 12 months, adherence to ezetemibe treatment decreased to 4.1% (22 patients). Conclusion: During follow-up for 3 and 12 months, adherence for statin therapy decreased by 15.7% and for ezetemibe by 46.6%. Here, low adherence to statin therapy was associated with fatal outcome.

[37] *Nandal S, Narayan O, Barlis P, Ponnuthurai FA*. **Management of atherosclerotic plaque in left internal mammary artery graft five years after angiographic patency: A case report**. World journal of cardiology 2019; 11:277-281.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31798794

ABSTRACT
BACKGROUND: The left internal mammary artery (LIMA) has demonstrated excellent long-term patency rates when used as a bypass conduit with complications usually occurring in the early postoperative period. The rapid development of de-novo atherosclerosis in a previously non-diseased LIMA, subsequently leading to an acute coronary syndrome (ACS) is rarely encountered. CASE SUMMARY: A 67-year-old man with history of triple coronary artery bypass graft (8 years ago) presented to our hospital with an ACS. He had undergone angiography 5 years ago to investigate episodic chest pain and imaging of the LIMA at the time did not demonstrate the atherosclerotic process. Emergent angiography demonstrated a severe diffuse stenosis in the proximal to mid segment of the LIMA, with embolization of a moderate sized thrombus to the distal skip segment. The LIMA stenosis was characterised by overlying haziness, consistent with acute plaque rupture, associated with residual luminal thrombus. The patient was managed with antithrombotic therapy to reduce the thrombus burden until repeat angiography after 72 h. At repeat angiography, the thrombus burden was substantially reduced at the distal skip segment as well as at the proximal to mid LIMA with the demonstration of multiple plaque cavities. This lesion was predilated and a 2.75 mm x 33 mm everolimus-eluting stent was implanted to a final diameter of 3.0 mm. The patient made a good clinical recovery and was discharged after 6 d. CONCLUSION: This case highlights the rapid and late development of atherosclerosis in a graft 5 years after documented patency and the importance for consideration of expectant thrombus management.