Literature update week 44 (2019)

[1] *Gu J, Yin ZF, Pan JA et al.* **Author's Reply**. Anatol J Cardiol 2019; 22:278.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31674941
ABSTRACT

[2] *Sookaromdee P, Wiwanitkit V*. **Visit-to-visit variability in low-density lipoprotein cholesterol**. Anatol J Cardiol 2019; 22:278.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31674927
ABSTRACT

[3] *Tuncez A, Altunkeser BB, Ozturk B et al.* **Comparative effects of atorvastatin 80 mg and rosuvastatin 40 mg on the levels of serum endocan, chemerin, and galectin-3 in patients with acute myocardial infarction**. Anatol J Cardiol 2019; 22:240-249.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31674929
ABSTRACT
OBJECTIVE: Endocan, chemerin, and galectin-3 are discrete biomarkers associated with cardiovascular diseases and acting through different pathophysiological pathways. The aim of this study is to investigate and compare the effects of high doses of atorvastatin and rosuvastatin on serum endocan, chemerin, and galectin-3 levels in patients with acute myocardial infarction (AMI). METHODS: Sixty-three patients with AMI were randomized to receive atorvastatin (80 mg/day) or rosuvastatin (40 mg/day) after percutaneous revascularization. Serum levels of endocan, chemerin, and galectin-3 were evaluated at baseline and after 4-week therapy. RESULTS: Endocan levels were not decreased statistically significantly with atorvastatin 80 mg, but rosuvastatin 40 mg markedly decreased the levels of endocan according to baseline [from 110.27 (86.03-143.69) pg/mL to 99.22 (78.30-122.87) pg/mL with atorvastatin 80 mg and from 110.73 (77.28-165.22) pg/mL to 93.40 (70.48-115.13) pg/mL with rosuvastatin 40 mg, p=0.242 for atorvastatin 80 mg and p=0.014 for rosuvastatin 40 mg]. Chemerin levels significantly decreased in both groups according to baseline [from 264.90 (196.00-525.95) ng/mL to 135.00 (105.95-225.65) ng/mL with atorvastatin 80 mg and from 309.95 (168.87-701.27) ng/mL to 121.25 (86.60-212.65) ng/mL with rosuvastatin 40 mg, p<0.001, respectively, for both groups]. Galectin-3 levels did not change markedly with atorvastatin 80 mg, but they decreased with rosuvastatin 40 mg [from 17.00 (13.10-22.25) ng/mL to 19.30 (15.25-23.45) ng/mL with atorvastatin 80 mg, p=0.721, and from 18.25 (12.82-23.82) ng/mL to 16.60 (10.60-20.15) ng/mL with rosuvastatin 40 mg, p=0.074]. There were no significant between-group differences in terms of absolute and percentage changes of endocan, chemerin, and galectin-3 at 4 weeks. CONCLUSION: We reported that both statins similarly decreased the endocan levels, whereas rosuvastatin seems to have more prominent effects on the reduction of the chemerin and galectin-3 levels in patients with AMI.

[4] *Zaveri S, Price LZ, Tupper H, Tadros RO*. **Atheroembolism to the Breast**. Annals of vascular surgery 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31669478
ABSTRACT
We report the case of a woman presenting with livedo reticularis of the breast who was found to have atheroembolism to the breast following upper extremity percutaneous access.

Atheroembolism is the embolization of cholesterol crystals off an atherosclerotic plaque that can occur spontaneously or as a result of vascular intervention. This is a unique presentation of an otherwise well-described complication of vascular catheterization, and we propose that livedo reticularis of the breast can be interpreted as a sign of atheroembolism in the appropriate clinical context.

[5] *Khorolskaya VG, Gureev AP, Shaforostova EA et al.* **[The fenofibrate effect on genotoxicity in brain and liver and on the expression of genes regulating fatty acids metabolism of mice]**. Biomeditsinskaia khimiia 2019; 65:388-397.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31666411
ABSTRACT
Fibrates are well-known agonists of the PPAR family (peroxisome proliferator-activated receptors). This class of drugs is used for the treatment of dyslipidemia and atherosclerosis. Fenofibrate is one of the members of this class of synthetic PPARalpha receptor ligands. The oral administration of 0.3% fenofibrate caused a decrease in strength due to loss of body weight in laboratory animals when improving behavioural features. Analysis of the mitochondrial DNA of liver cells showed a genotoxic effect of fenofibrate, due to accumulation of reactive oxygen species, which could be attributed to activation of peroxisomal beta-oxidation processes, as well as to the lack of increase in the expression of genes encoding antioxidant defense proteins. Treatment with fenofibrate did not cause brain mtDNA damage. It has been shown that fenofibrate induced mitochondrial beta-oxidation in the brain, as indicated by the increased expression of the Acadm and Cpt1a and Ppargc1a and Ppara. The study found no effect of fenofibrate on the increase of mitochondrial biogenesis in brain and liver cells. Thus, we can conclude that fenofibrate significantly affects lipid metabolism in the liver and brain, but in the liver it is associated with an increase of oxidative stress, resulting in mtDNA oxidative damage. However, fenofibrate-induced increase in the expression of Ppargc1a is not associated with an increase of mitochondrial biogenesis. This is consistent with the recent suggestion that PGC-1alpha might not be a master regulator of mitochondrial biogenesis.

[6] *Schmidt AF, Holmes MV, Preiss D et al.* **Phenome-wide association analysis of LDL-cholesterol lowering genetic variants in PCSK9**. BMC cardiovascular disorders 2019; 19:240.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31664920
ABSTRACT
BACKGROUND: We characterised the phenotypic consequence of genetic variation at the PCSK9 locus and compared findings with recent trials of pharmacological inhibitors of PCSK9. METHODS: Published and individual participant level data (300,000+ participants) were combined to construct a weighted PCSK9 gene-centric score (GS). Seventeen randomized placebo controlled PCSK9 inhibitor trials were included, providing data on 79,578 participants. Results were scaled to a one mmol/L lower LDL-C concentration. RESULTS: The PCSK9 GS (comprising 4 SNPs) associations with plasma lipid and apolipoprotein levels were consistent in direction with treatment effects. The GS odds ratio (OR) for myocardial infarction (MI) was 0.53 (95% CI 0.42; 0.68), compared to a PCSK9 inhibitor effect of 0.90 (95% CI 0.86; 0.93). For ischemic stroke ORs were 0.84 (95% CI 0.57; 1.22) for the GS, compared to 0.85 (95% CI 0.78; 0.93) in the drug trials. ORs with type 2 diabetes mellitus (T2DM) were 1.29 (95% CI 1.11; 1.50)

for the GS, as compared to 1.00 (95% CI 0.96; 1.04) for incident T2DM in PCSK9 inhibitor trials. No genetic associations were observed for cancer, heart failure, atrial fibrillation, chronic obstructive pulmonary disease, or Alzheimer's disease - outcomes for which large-scale trial data were unavailable. CONCLUSIONS: Genetic variation at the PCSK9 locus recapitulates the effects of therapeutic inhibition of PCSK9 on major blood lipid fractions and MI. While indicating an increased risk of T2DM, no other possible safety concerns were shown; although precision was moderate.

[7] *Jukema RA, Ahmed TAN, Tardif JC*. **Does low-density lipoprotein cholesterol induce inflammation? If so, does it matter? Current insights and future perspectives for novel therapies**. BMC medicine 2019; 17:197.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31672136
ABSTRACT
BACKGROUND: Dyslipidemia and inflammation are closely interrelated contributors in the pathogenesis of atherosclerosis. Disorders of lipid metabolism initiate an inflammatory and immune-mediated response in atherosclerosis, while low-density lipoprotein cholesterol (LDL-C) lowering has possible pleiotropic anti-inflammatory effects that extend beyond lipid lowering. MAIN TEXT: Activation of the immune system/inflammasome destabilizes the plaque, which makes it vulnerable to rupture, resulting in major adverse cardiac events (MACE). The activated immune system potentially accelerates atherosclerosis, and atherosclerosis activates the immune system, creating a vicious circle. LDL-C enhances inflammation, which can be measured through multiple parameters like high-sensitivity C-reactive protein (hsCRP). However, multiple studies have shown that CRP is a marker of residual risk and not, itself, a causal factor. Recently, anti-inflammatory therapy has been shown to decelerate atherosclerosis, resulting in fewer MACE. Nevertheless, an important side effect of anti-inflammatory therapy is the potential for increased infection risk, stressing the importance of only targeting patients with high residual inflammatory risk. Multiple (auto-)inflammatory diseases are potentially related to/influenced by LDL-C through inflammasome activation. CONCLUSIONS: Research suggests that LDL-C induces inflammation; inflammation is of proven importance in atherosclerotic disease progression; anti-inflammatory therapies yield promise in lowering (cardiovascular) disease risk, especially in selected patients with high (remaining) inflammatory risk; and intriguing new anti-inflammatory developments, for example, in nucleotide-binding leucine-rich repeat-containing pyrine receptor inflammasome targeting, are currently underway, including novel pathway interventions such as immune cell targeting and epigenetic interference. Long-term safety should be carefully monitored for these new strategies and cost-effectiveness carefully evaluated.

[8] *Zhu Y, Hu H, Yang J et al.* **The efficacy and safety of statin in combination with ezetimibe compared with double-dose statin in patients with high cardiovascular risk: A meta-analysis**. Bosnian journal of basic medical sciences / Udruzenje basicnih mediciniskih znanosti = Association of Basic Medical Sciences 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31668143
ABSTRACT

Currently, statins are the first-line therapies for dyslipidemia and atherosclerotic cardiovascular disease, however, their hypolipidemic effects have not been satisfactory. We performed a meta-analysis to compare lipid-lowering efficacy and safety of ezetimibe and statin combination therapy with double-dose statin monotherapy in patients with high cardiovascular risk. Fourteen studies involving 3,105 participants were included in the final analysis; 1,558 (50.18%) participants received ezetimibe and statin combination therapy and 1,547 (49.82%) received double-dose statin monotherapy. Eight studies reported the percentages of changes in several lipid parameters from baseline to endpoint in both groups. Lipid parameters changed more significantly in patients co-administered with ezetimibe and statin (low-density lipoprotein cholesterol [LDL-C]: MD = -9.39, 95% CI -13.36 to -5.42; non-high-density lipoprotein cholesterol [non-HDL-C]: MD = -10.36, 95% CI -14.23 to -6.50; total cholesterol [TC]: MD = -8.11, 95% CI -10.95 to -5.26; and triglyceride [TG]: MD = -5.96, 95% CI -9.12 to -2.80), with moderate to high heterogeneity among the studies. Two out of fourteen studies investigated several different statins. Our subgroup analysis showed that, compared with double-dose atorvastatin monotherapy, ezetimibe and atorvastatin combination therapy significantly decreased LDL-C, non-HDL-C, TC, and TG levels by 14.16%, 14.01%, 11.06%, and 5.96%, respectively ($p < 0.001$). No significant difference was found in the incidence of laboratory-related adverse events (AEs) between statin combination therapy and monotherapy. Overall, ezetimibe and statin combination therapy significantly decreased LDL-C, non-HDL-C, and TC levels in patients with high cardiovascular risk, among which ezetimibe combined with atorvastatin had the best therapeutic effect. Compared with ezetimibe and statin combination therapy, double-dose statin monotherapy did not increase the risk of AEs.

[9] *Turner RM, Fontana V, FitzGerald R et al.* **Investigating the clinical factors and co-medications associated with circulating levels of atorvastatin and its major metabolites in secondary prevention**. British journal of clinical pharmacology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31656041

ABSTRACT

AIMS: The lipid-lowering drug, atorvastatin (ATV), is one of the most commonly prescribed medications worldwide. The aim of this study was to comprehensively investigate and characterise the clinical factors and co-medications associated with circulating levels of ATV and its metabolites in secondary prevention clinical practice. METHODS: The plasma concentrations of ATV, 2-hydroxy (2-OH) ATV, ATV lactone (ATV L) and 2-OH ATV L were determined in patients one month after hospitalisation for a non-ST elevation acute coronary syndrome. Factors were identified using all subsets multivariable regression and model averaging with the Bayesian information criterion. Exploratory genotype-stratified analyses were conducted using ABCG2 rs2231142 (Q141K) and CYP2C19 metaboliser status to further investigate novel associations. RESULTS: A total of 571 patients were included; 534 and 37 were taking ATV 80mg and 40mg daily, respectively. Clinical factors associated with ATV and/or its metabolite levels included age, sex, body mass index, and CYP3A inhibiting co-medications. Smoking was newly associated with increased ATV lactonization and reduced hydroxylation. Proton pump inhibitors (PPIs) and loop diuretics were newly associated with modestly increased levels of ATV (14% and 38%, respectively) and its metabolites. An interaction between PPIs and CYP2C19 metaboliser status on exposure to specific ATV analytes (e.g. interaction p=0.0071 for 2-OH ATV L) was observed.

Overall model R(2) values were 0.14-0.24. CONCLUSIONS: Multiple factors were associated with circulating ATV and metabolite levels, including novel associations with smoking and drug-drug(-gene) interactions involving PPIs and loop diuretics. Further investigations are needed to identify additional factors that influence ATV exposure.

[10] *Sukkar L, Talbot B, Jun M et al.* **Protocol for the Study of Heart and Renal Protection-Extended Review: Additional 5-Year Follow-up of the Australian, New Zealand, and Malaysian SHARP Cohort**. Canadian journal of kidney health and disease 2019; 6:2054358119879896.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31662874

ABSTRACT

Background: There are limited studies on the effects of statins on outcomes in the moderate chronic kidney disease (CKD) population and their trajectory to end-stage kidney disease. Objective: To examine the long-term effects of lipid-lowering therapy on all-cause mortality, cardiovascular morbidity, CKD progression, and socioeconomic well-being in Australian, New Zealand, and Malaysian SHARP (Study of Heart and Renal Protection) trial participants-a randomized controlled trial of a combination of simvastatin and ezetimibe, compared with placebo, for the reduction of cardiovascular events in moderate to severe CKD. Design: Protocol for an extended prospective observational follow-up. Setting: Australian, New Zealand, and Malaysian participating centers in patients with advanced CKD. Patients: All SHARP trial participants alive at the final study visit. Measurements: Primary outcomes were measured by participant self-report and verified by hospital administrative data. In addition, secondary outcomes were measured using a validated study questionnaire of health-related quality of life, a 56-item economic survey. Methods: Participants were followed up with alternating face-to-face visits and telephone calls on a 6-monthly basis until 5 years following their final SHARP Study visit. In addition, there were 6-monthly follow-up telephone calls in between these visits. Data linkage to health registries in Australia, New Zealand, and Malaysia was also performed. Results: The SHARP-Extended Review (SHARP-ER) cohort comprised 1136 SHARP participants with a median of 4.6 years of follow-up. Compared with all SHARP participants who originally participated in the Australian, New Zealand, and Malaysian regions, the SHARP-ER participants were younger (57.2 [48.3-66.4] vs 60.5 [50.3-70.7] years) with a lower proportion of men (61.5% vs 62.8%). There were a lower proportion of participants with hypertension (83.7% vs 85.0%) and diabetes (20.0% vs 23.5%). Limitations: As a long-term follow-up study, the surviving cohort of SHARP-ER is a selected group of the original study participants, which may limit the generalizability of the findings. Conclusion: The SHARP-ER study will contribute important evidence on the long-term outcomes of cholesterol-lowering therapy in patients with advanced CKD with a total of 10 years of follow-up. Novel analyses of the socioeconomic impact of CKD over time will guide resource allocation. Trial Registration: The SHARP trial was registered at ClinicalTrials.gov NCT00125593 and ISRCTN 54137607.

[11] *Caselli C, Del Turco S, Ragusa R et al.* **Association of PCSK9 plasma levels with metabolic patterns and coronary atherosclerosis in patients with stable angina**. Cardiovascular diabetology 2019; 18:144.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31672148

ABSTRACT

OBJECTIVE: Aim of this study was to evaluate the relationship of plasma PCSK9 with metabolic and inflammatory profile and coronary atherosclerotic burden in patients with suspected CAD enrolled in the EVINCI study. METHODS: PCSK9 was measured in 539 patients (60.3 +/- 8.6 years, 256 males) with symptoms of CAD characterized by risk factors, bio-humoral profiles, and treatment. N = 412 patients underwent coronary computed tomography angiography (CTA) to assess the presence and characteristics of coronary atherosclerosis. A CTA score, combining extent, severity, composition, and location of plaques was computed. RESULTS: Patients were divided according to PCSK9 quartiles: I (< 136 ng/mL), II-III (136-266 ng/mL), and IV quartile (> 266 ng/mL). Compared with patients in quartile IV, patients in quartile I had a higher prevalence of the metabolic syndrome and higher values of body mass index. LDL- and HDL-cholesterol were significantly lower in patients in the quartile I than in those in quartile IV. Coronary CTA documented normal vessels in 30% and obstructive CAD in 35% of cases without differences among PCSK9 quartiles. Compared with patients with the highest levels, patients with the lowest PCSK9 levels had a higher CTA score mainly due to higher number of mixed non-obstructive coronary plaques. At multivariable analysis including clinical, medications, and lipid variables, PCSK9 was an independent predictor of the CTA score (coefficient - 0.129, SE 0.03, P < 0.0001), together with age, male gender, statins, interleukin-6, and leptin. CONCLUSION: In patients with stable CAD, low PCSK9 plasma levels are associated with a particular metabolic phenotype (low HDL cholesterol, the metabolic syndrome, obesity, insulin resistance and diabetes) and diffuse non-obstructive coronary atherosclerosis. Trial registration ClinicalTrials.gov NCT00979199. Registered September 17, 2009.

[12] *Wu MF, Xu KZ, Guo YG et al.* **Lipoprotein(a) and Atherosclerotic Cardiovascular Disease: Current Understanding and Future Perspectives**. Cardiovascular drugs and therapy / sponsored by the International Society of Cardiovascular Pharmacotherapy 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31655942

ABSTRACT

PURPOSE: To review current knowledge of elevated lipoprotein(a) [Lp(a)] levels in relation to atherosclerotic cardiovascular disease (ASCVD) and discuss their potential use as biomarkers and therapeutic approaches in clinical practice. METHODS: We summarized the current understanding and recent advances in the structure, metabolism, atherogenic mechanisms, standardized laboratory measurement, recommended screening populations, and prognostic value of Lp(a), with a special focus on the current potential treatment approaches for hyperlipoprotein(a)emia in patients with ASCVD. RESULTS: Lp(a) is composed of LDL-like particle and characteristic apolipoprotein(a) [apo(a)] connected by a disulfide bond. Substantial evidence shows that elevated plasma Lp(a) level is a heritable, independent, and possibly causal risk factor for ASCVD through its proatherogenic, proinflammatory, and potentially prothrombotic properties. Current guidelines recommend Lp(a) measurement for patients with an intermediate-high risk of ASCVD, familial hypercholesterolemia, a family history of early ASCVD or elevated Lp(a), and progressive ASCVD despite receiving optimal therapy. Traditional Lp(a)-lowering approaches such as niacin, PCSK9 inhibitors, mipomersen, lomitapide, and lipoprotein apheresis were associated with a non-specific and limited reduction of Lp(a), intolerable side effects, invasive procedure, and high expense. The phase 2 randomized controlled trial of antisense oligonucleotide against the apo(a) encoding gene LPA mRNA

showed that IONIS-APO(a)-LRX could specifically reduce the level of Lp(a) by 90% with good tolerance, which may become a promising candidate for the prevention and treatment of ASCVD in the future. CONCLUSIONS: It is reasonable to measure Lp(a) levels to reclassify ASCVD risk and manage individuals with elevated Lp(a) to further reduce the residual risk of ASCVD, especially with IONIS-APO(a)-LRX.

[13] *Wagmann L, Hemmer S, Caspar AT, Meyer MR*. **Method development for quantitative determination of seven statins including four active metabolites by means of high-resolution tandem mass spectrometry applicable for adherence testing and therapeutic drug monitoring**. Clin Chem Lab Med 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31665111
ABSTRACT
Background Statins are used to treat and prevent cardiovascular diseases (CVDs) by reducing the total serum cholesterol concentration. Unfortunately, dose-related side effects and sub-optimal response, attributed to non-adherence amongst others, were described. Therefore, a fast and sensitive liquid chromatography-high-resolution tandem mass spectrometry (LC-HRMS/MS) method for adherence testing and therapeutic drug monitoring of all currently marketed statins and their active metabolites in human blood plasma should be developed, validated and tested for applicability. Methods Atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin, as well as ortho- and para-hydroxy-atorvastatin, lovastatin hydroxy acid and simvastatin hydroxy acid were included and several internal standards (IS) tested. Validation was performed according to the guideline of the European Medicines Agency including selectivity, carry-over, accuracy, precision, matrix effects, dilution integrity and analyte stability. Finally, applicability was tested using 14 patient samples submitted for regular toxicological analysis. Results Due to an analytical interference of atorvastatin-d5, diazepam-d5 and pentobarbital-d5 were chosen as IS for positive and negative ionization mode, respectively. All statins and metabolites fulfilled the validation acceptance criteria except for fluvastatin, which could not be quantified reliably and reproducibly, most probably due to instability. Analyses of human plasma samples revealed concentrations of statins and metabolites below the reference plasma concentrations in the case of eight patients. However, nothing was known concerning patients' adherence and time between intake and sampling. Conclusions An LC-HRMS/MS method for identification and quantification of atorvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin and four active metabolites was successfully developed and applicability demonstrated.

[14] *Peters KM, Borradaile NM*. **Microarray data and pathway analyses for human microvascular endothelial cells supplemented with low dose vitamin D or niacin during lipotoxicity**. Data in brief 2019; 26:104490.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31667254
ABSTRACT
Low dose niacin and vitamin D can directly improve human microvascular endothelial cell angiogenic function under lipotoxic conditions Peters et al.,2019. Despite exerting similar benefits on in vitro angiogenic function, these vitamins are known to signal through independent receptors, raising the possibility that differential changes in gene expression may

underlie these effects. Here we provide data collected using Affymetrix GeneChip microarrays to compare gene expression in human microvascular endothelial cells treated for 16 h with growth medium containing BSA alone, or BSA complexed with the saturated fatty acid palmitate, and supplemented with 10 muM niacin or 10 nM vitamin D (1,25-dihydroxyvitamin D3). Data sets of differential gene expression included many genes involved in cellular stress responses. Pathway analyses of genes specific to vitamin D treatment identified a robust overrepresentation of pathways related to the cell cycle and DNA replication and repair.

[15] *Son C, Kasahara M, Tanaka T et al.* **Rationale, Design, and Methods of the Study of Comparison of Canagliflozin vs. Teneligliptin Against Basic Metabolic Risks in Patients with Type 2 Diabetes Mellitus (CANTABILE study): Protocol for a Randomized, Parallel-Group Comparison Trial**. Diabetes Ther 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31677134
ABSTRACT
BACKGROUND: Dipeptidyl peptidase-4 (DPP-4) inhibitors and sodium-glucose co-transporter 2 (SGLT2) inhibitors are widely used antidiabetic drugs. However, to date, no studies have directly compared the effects of these two drugs on the components of the metabolic syndrome in patients with type 2 diabetes mellitus (T2DM). OBJECTIVES: The Comparison of Canagliflozin vs. Teneligliptin against Basic Metabolic Risks in Patients with T2DM (CANTABILE) study aims to examine whether the DPP-4 inhibitor (teneligliptin) or the SGLT2 inhibitor (canagliflozin) is the more effective drug for reducing metabolic risk factors as a composite in Japanese patients with T2DM. METHODS: The CANTABILE study is a prospective, multicenter, open-label, randomized, parallel-group comparison study. A total of 200 patients with T2DM treated with metformin alone or without glucose-lowering agents will be enrolled if they have one or more of the metabolic risk factors, such as obesity, borderline high blood pressure, and dyslipidemia. They will then will be randomized into the Teneligliptin group or the Canagliflozin group and treated for 24 weeks. The primary endpoint is the composite ratio of subjects with one or more improved metabolic risk factors. The secondary endpoints are the changes in each component of the primary endpoint. PLANNED OUTCOMES: The CANTABILE study provides valuable evidence to indicate the suitability of SGLT2 inhibitors or DPP-4 inhibitors for Japanese patients with T2DM and metabolic risks. TRIAL REGISTRATION NUMBER: University Hospital Medical Information Network Clinical Trial Registry number: UMIN000030343. FUNDING: Mitsubishi Tanabe Pharma Corporation.

[16] *Sugane H, Kataoka Y, Otsuka F, Yasuda S.* **Cholesterol-crystalized coronary atheroma as a potential precursor lesion causing acute coronary syndrome: a case report**. European heart journal. Case reports 2019; 3:ytz128.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31660499
ABSTRACT
Background: Histopathological studies have reported the presence of cholesterol crystals in the culprit lesion in patients with sudden cardiac death. Given that cholesterol crystals themselves promote pro-inflammatory cascades, they may destabilize atherosclerotic plaques, leading to the occurrence of acute coronary events. Case summary: A 60-year-old man presented with ST-segment elevation myocardial infarction. Emergent coronary angiography revealed a severely

stenotic lesion (=culprit lesion) and another non-obstructive lesion in the proximal and middle segments of the left anterior descending artery (LAD), respectively. Optical coherence tomography (OCT) imaging showed that both lesions exhibited lipid-rich plaque with cholesterol crystals, and the non-obstructive lesion in the mid-LAD did not have a thin fibrous cap (its thickness = 230 mum). A drug-eluting stent was successfully implanted at the culprit lesion in the proximal LAD. On non-contrast T1-weighted magnetic resonance imaging performed 10 days after percutaneous coronary intervention (PCI), a high-intensity signal was identified at the non-obstructive mid-LAD lesion. This lesion was medically managed with aspirin, clopidogrel, and rosuvastatin due to the absence of myocardial ischaemia. However, 12 months after PCI, the patient was hospitalized again due to unstable angina pectoris. Coronary angiography revealed substantial progression of the mid-LAD lesion. Optical coherence tomography imaging prior to the second PCI showed a severely narrowed lesion containing cholesterol crystals and covered by organized thrombus. This lesion harbored an extensive amount of lipidic materials on near-infrared spectroscopy (maximum 4-mm lipid core burden index = 809). Discussion: In our case, atherosclerotic plaques containing cholesterol crystals was associated with the occurrence of acute coronary syndrome. Our findings suggest that plaque with cholesterol crystals is a potential precursor to future acute coronary events.

[17] *Kloer HU, Belardinelli R, Ruchong O, Rosenfeldt F*. **Combining Ubiquinol With a Statin May Benefit Hypercholesterolaemic Patients With Chronic Heart Failure**. Heart, lung & circulation 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31668616
ABSTRACT
Heart failure (HF) is one of the most common causes of death in Western society. Recent results underscore the utility of coenzyme Q10 (CoQ10) addition to standard medications in order to reduce mortality and to improve quality of life and functional capacity in chronic heart failure (CHF). The rationale for CoQ10 supplementation in CHF is two-fold. One is the well-known role of CoQ10 in myocardial bioenergetics, and the second is its antioxidant property. Redox balance is also improved by oral supplementation of CoQ10, and this effect contributes to enhanced endothelium-dependent relaxation. Previous reports have shown that CoQ10 concentration is decreased in myocardial tissue in CHF and by statin therapy, and the greater the CoQ10 deficiency the more severe is the cardiocirculatory impairment. In patients with CHF and hypercholesterolaemia being treated with statins, the combination of CoQ10 with a statin may be useful for two reasons: decreasing skeletal muscle injury and improving myocardial function. Ubiquinol, the active reduced form of CoQ10, presents higher bioavailability than the oxidised form ubiquinone, and should be the preferred form to be added to a statin. The combination ezetimibe/simvastatin may have advantages over single statins. Since ezetimibe reduces absorption of cholesterol and does not affect CoQ10 synthesis in the liver, the impact of this combination on CoQ10 tissue levels will be much less than that of high dose statin monotherapy at any target low density lipoprotein-cholesterol (LDL-C) level to be reached. This consideration makes the ezetimibe/statin combination the ideal LDL-lowering agent to be combined with ubiquinol in CHF patients. However, particular caution is advisable with the use of strategies of extreme lowering of cholesterol that may negatively impact on myocardial

function. All in all there is a strong case for considering co-administration of ubiquinol with statin therapy in patients with depressed or borderline myocardial function.

[18] *Sieg SF, Bazdar DA, Zidar D et al.* **Highly oxidized low density lipoprotein mediates activation of monocytes but does not confer IL-1beta secretion nor IL-15 transpresentation function**. Immunology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31663113
ABSTRACT
Oxidized LDL contributes to cardiovascular disease in part by mediating activation and maturation of monocytes and macrophages. Furthermore, co-localization studies using histochemical approaches have implicated a potential role for oxidized LDL as a mediator of IL-15 expression in myeloid cells of atherosclerotic plaque. The latter activity could be an important pro-inflammatory mechanism that mediates myeloid cell/T cell crosstalk. Here, we examined responses of primary human monocytes to highly oxidized LDL molecules. Oxidized LDL readily induced secretion of chemokines MCP-1 (CCL2) and GRO-alpha (CXCL1) but unlike LPS, has limited capacity to induce a variety of other cytokines including TNF- alpha, IL-6, IL-1beta and IP-10 and also displayed a poor capacity to induce p-Akt or P-S6 signaling. Failure of oxidized LDL to induce IL-1beta secretion was associated with limited induction of caspase-1 activation. Furthermore, despite finding evidence that oxidized LDL could enhance the expression of IL-15 and IL-15R expression in monocytes, we found no evidence that it could confer IL-15 transpresentation capability to these cells. This observation contrasted with induction of IL-15 transpresentation in LPS stimulated monocytes. Overall, our data suggest that highly oxidized LDL is a selective inducer of monocyte activation. Sterile inflammatory mediators, particularly those implicated in TLR4 signaling, may play a role in vascular pathology but the activities of these agents are not uniform.

[19] *Dharmarajan TS, Choi H, Hossain N et al.* **Deprescribing as a Clinical Improvement Focus**. Journal of the American Medical Directors Association 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31672564
ABSTRACT
OBJECTIVES: Polypharmacy is a concern in the practice of geriatrics because of consequences such as adverse drug events and poorer quality of life. Deprescribing, a response to polypharmacy, refers to the systematic, programmed, and appropriate reduction in drug number and dose. Although now broadly recognized, challenges exist in practice for effective implementation. This study was conducted to determine the deprescribing success rate and relate it to drug classes and clinical settings, and to identify factors that influence the deprescribing process. DESIGN: As a performance improvement (PI) project, fellows in geriatric medicine, under supervision of faculty geriatricians, attempted deprescribing during at least 1 encounter daily at 2 long-term care (LTC) facilities and an outpatient geriatrics clinic (C) in Bronx, New York, from August 2018 to January 2019. Deprescribing was initiated following discussion and consent from patient or caregiver. Following the data collection, involved fellows and faculty physicians participated in a survey to identify factors that influenced the process. RESULTS: Out of 449 encounters, 383 encounters were included for analysis. Average patient age was 78.2 years (LTC: 77.9, C: 79.1). Average patient comorbidities was 6.5 (LTC: 6.7,

C: 5.8). Deprescribing was successful in 90.1% of encounters (LTC: 96.9%, C: 67.4%). On average, 1.3 medications were deprescribed per encounter (LTC: 1.4, C: 1.0). Analgesics (32.2%), multivitamin-minerals supplements (29.7%), lipid-lowering agents (22.9%), antihistamines (46.7%), and acid blockers (26.2%) had highest success. CONCLUSIONS AND IMPLICATIONS: Deprescribing is possible in practice in both LTC and community settings at each encounter, until it is no longer applicable. Factors that contribute to successful deprescribing primarily include meaningful and earnest provider effort, ideally in collaboration with interdisciplinary team members (nurses, pharmacists, social worker, and others), besides interactions with consultants for the patient. Certain medication classes such as vitamins, minerals, analgesics, and proton pump inhibitors can be deprescribed with high success, as noted in our study, whereas antipsychotic agents, antidepressants, and ophthalmic preparations, prescribed by specialists, proved harder to deprescribe. An understanding of barriers to deprescribing (outlined in the article) and addressing them are crucial in enabling success. The study demonstrates that as a performance improvement project in collaborative effort with multiple disciplines, deprescribing is possible in health care. Factors promoting success and barriers to deprescribing are detailed. Appropriate deprescribing has the potential to help lower adverse drug events, costs of care, and possibly improve quality of life.

[20] *Qi Y, Liu J, Wang W et al.* **High sdLDL Cholesterol can be Used to Reclassify Individuals with Low Cardiovascular Risk for Early Intervention: Findings from the Chinese Multi-Provincial Cohort Study**. Journal of atherosclerosis and thrombosis 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31666437
ABSTRACT
AIM: A high-risk strategy has been implemented for lipid-lowering therapy in the primary prevention of cardiovascular disease. However, atherosclerosis and cardiovascular events are common among individuals with low cardiovascular risk. This study aimed to determine whether the small dense low-density lipoprotein cholesterol (sdLDLC) level can predict carotid atherosclerosis progression and identify high-risk individuals. METHODS: Baseline sdLDLC and low-density lipoprotein cholesterol (LDLC) were measured in 808 participants from the Chinese Multi-provincial Cohort Study, aged 45-74 years. Adjusted relative risk was calculated using a modified Poisson regression model to assess the relationship between sdLDLC and 5-year atherosclerosis progression, as indicated by the progression, incidence, and multi-territorial extent of carotid plaque. RESULTS: The 5-year atherosclerosis progression increased significantly with increased sdLDLC. Baseline sdLDLC was significantly associated with the short-term risk of plaque progression after multivariable adjustment, even in participants with low LDLC or a 10-year estimated cardiovascular risk. sdLDLC predicted plaque progression (relative risk 2.05; 95% confidence interval 1.43-2.93) in participants with LDLC 130 mg/dL. Furthermore, participants with the highest sdLDLC but intermediate or low cardiovascular risk (accounting for 16% of the cohort) had double the risk of plaque progression, which was comparable to those with the same sdLDLC and high cardiovascular risk, relative to those with the lowest sdLDLC levels and low cardiovascular risk. CONCLUSIONS: sdLDLC is independently associated with the progression of carotid atherosclerosis, which may provide a basis for clinicians to reclassify individuals believed to be at low cardiovascular risk into the high-risk category, and those with high sdLDLC may benefit from more aggressive cholesterol-lowering treatment.

[21] *Liu N, Yang G, Liu Y et al.* **The effect of Cytochrome P450 7A1(CYP7A1) polymorphism on lipid responses to simvastatin treatment**. Journal of cardiovascular pharmacology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31663874

ABSTRACT

BACKGROUND: Identifying patients with high-risk of low-response to statin therapy is important for optimization of lipid-lowering therapy. Cholesterol 7alpha-hydroxylase, a rate-limiting enzyme encoded by Cytochrome P450 7A1(CYP7A1)gene, is considered to be associated with statin efficacy. This study aimed to investigate the association between a novel CYP7A1 single-nucleotide polymorphism (SNP) rs3824260 and statin treatment response for hypercholesteremic patients in Chinese Han population. METHODS: A total of 336 subjects were prescribed with simvastatin for 12 weeks after enrollment. Plasma lipid parameters were measured at enrollment and after 12-weeks simvastatin treatment separately. Subjects were classified into high- and low-response groups depending on their TC, LDL-C and TG changes, and increase or reduction groups according to their HDL-C levels changing after simvastatin treatment. The CYP7A1 rs3824260 was genotyped from blood samples with a SNaPshot assay. RESULTS: At baseline, the LDL-C level and TG level were significantly higher in the AA genotype, while the HDL-C level was significantly higher in the GG genotype of CYP7A1 rs3824260. Patients carrying AA genotype are at an increased risk of low-response for LDL-C reduction (OR=2.295, 95% CI=1.164-4.524, p=0.016). Furthermore, the GG genotype of rs3824260 was significantly associated with a high risk of HDL-C reduction response after simvastatin therapy (OR=2.240, 95% CI=1.137-4.413, p=0.025). CONCLUSIONS: The CYP7A1 gene polymorphism rs3824260 is related to inappropriate response of simvastatin treatment for hypercholesterolemia patients in Chinese Han population.

[22] *Bronden A, Larsen EL, Karstoft K et al.* **Changes in oxidative nucleic acid modifications and inflammation following one-week treatment with the bile acid sequestrant sevelamer: Two randomised, placebo-controlled trials**. Journal of diabetes and its complications 2019:107446.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31672458

ABSTRACT

AIMS: Sevelamer has been reported to have anti-oxidative and anti-inflammatory effects as well as effects on glycaemic control and plasma lipids. The aim of this study was to determine the effects of one-week treatment with sevelamer on oxidative nucleic acid modifications and inflammation markers. METHODS: Two double-blinded studies including 30 patients with type 2 diabetes (T2D) and 20 healthy individuals were conducted. Participants were randomised to one week of treatment with sevelamer (1600mg three times daily) or placebo. RNA and DNA oxidation, measured by urinary excretion of 8-oxo-7,8-dihydroguanosine(8-oxoGuo) and (8-oxo-7,8-dihydro-2'-deoxyguanosine(8-oxodG), and markers of inflammation were determined before and after the intervention. RESULTS: In patients with T2D there was no significant placebo-corrected reduction in 8-oxoGuo or 8-oxodG. However, a reduction in 8-oxoGuo was observed within the group treated with sevelamer (8-oxoGuo/creatinine (median[IQR]): -0.04 [-0.24; 0.01] nmol/mmol, p=0.02). A sevelamer-mediated reduction in interleukin-2 (p=0.04) and a trend towards reduction in interleukin-6 (p=0.053) were found in patients with T2D. CONCLUSIONS: This study reveals a potential effect of sevelamer treatment on inflammation

and possible oxidative RNA modifications. The potential protective effects of sevelamer in terms of cardiovascular disease in patients with T2D need further investigation.

[23] *Takano K, Saeki C, Oikawa T et al.* **IgM response is a prognostic biomarker of primary biliary cholangitis treated with ursodeoxycholic acid and bezafibrate**. Journal of gastroenterology and hepatology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31677185
ABSTRACT
AIM: Primary biliary cholangitis (PBC) patients who are refractory to ursodeoxycholic acid (UDCA) are at risk for progression to cirrhosis and liver failure. Bezafibrate could be an alternative second-line therapeutic option in these patients. This study aimed to evaluate the long-term outcome(s) of combined UDCA and bezafibrate therapy in UDCA-refractory PBC patients and identify prognostic factors. METHODS: Among 445 patients treated with UDCA, 150 patients inadequately responded to UDCA monotherapy and received long-term UDCA plus bezafibrate (median, 15 years). Data from these patients were used for this retrospective analysis. RESULTS: Combination therapy resulted in significant improvements in serum biochemistry and liver transplantation risk estimated using the UK-PBC-risk and the GLOBE scores. The cumulative normalization rates of alkaline phosphatase, gamma-glutamyltransferase, and immunoglobulin M (IgM) were significantly higher in patients without cirrhosis-related symptoms or liver-related events than in those with them. Overall, IgM constantly emerged as a significant factor associated with cirrhosis-related symptoms and liver-related events at all-time points. Cumulative survival rates were significantly lower in patients with IgM >/=240 mg/dL than in patients with IgM <240 mg/dL. Thus, normalization of IgM levels was a good surrogate predictor of long-term prognosis. None of the patients discontinued combination therapy due to any adverse events during the follow-up period. CONCLUSIONS: Our findings point to the beneficial effects of long-term UDCA plus bezafibrate combination therapy for UDCA-refractory PBC patients, and IgM response can be a useful predictive biomarker of long-term clinical outcomes.

[24] *Schoergenhofer C, Matzneller P, Muhlbacher J et al.* **PCSK9 decreases during Experimental Endotoxemia**. Journal of internal medicine 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31660669
ABSTRACT
We read Rannikko et al.'s article about proprotein convertase subtilisin/kexin type 9 (PCSK9) levels in patients with bacteremia [1] with great interest. In these patients PCSK9 levels were increased compared to healthy controls, which is in line with other published data and probably caused by the associated inflammatory response [2]. Interestingly, within the patient cohort, patients with lower PCSK9 levels were more likely to die at day 7, 28 and 90, which was surprising, because in contrast to this Boyd et al. reported that high PCSK9 levels were associated with organ failure in septic patients in the emergency department [2]. It is noteworthy that the genetic function of PCSK9 was not assessed in Rannikko et al.'s study.

[25] *Formisano E, Pasta A, Cremonini AL et al.* **Efficacy of Nutraceutical Combination of Monacolin K, Berberine, and Silymarin on Lipid Profile and PCSK9 Plasma Level in a Cohort of Hypercholesterolemic Patients**. Journal of medicinal food 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31663806
ABSTRACT
The guidelines for the treatment of dyslipidemias include the use of nutraceuticals (NUTs) in association with lifestyle modifications to achieve therapeutic goals. In NUT pill, different substances may be associated; in this study we investigated a combined NUT containing monacolin K (MonK)+KA (1:1), berberine (BBR), and silymarin. The aim of the study was to evaluate low-density lipoprotein cholesterol (LDL-C) reduction in 53 patients suffering from polygenic hypercholesterolemia, characterized by a low/intermediate cardiovascular risk calculated with SCORE algorithm. The effects on lipid profile of 2-month treatment with NUT containing MonK+KA (1:1), BBR, and sylimarin, were compared with Atorvastatin (ATO) 10 mg administrated in a matched control group. Serum proprotein convertase subtilisin/kexin type 9 (PCSK9) levels and the cholesterol loading capacity (CLC) were determined at baseline and at the end of the study in NUT-treated group; variations were assessed. NUT was effective as lipid-lowering agent with a wide interindividual response variability (mean LDL-C from 170.8 +/- 19.9 to 123.8 +/- 20.0 with a change of -47.0 +/- 21.5 mg/dL; $P < .001$) and the effect was similar to that induced by ATO. The use of NUT significantly modified PCSK9 levels ($P < .01$) and CLC ($P < .001$), ultimately suppressing the serum-mediated foam cell generation directly measured on human macrophages. NUT reduces LDL-C levels with an effect similar to what is induced by 10 mg of ATO and ex vivo improves the functional profile of lipoproteins with antiatherogenic action.

[26] *Garcia-Jaramillo M, Lytle KA, Spooner MH, Jump DB*. **A Lipidomic Analysis of Docosahexaenoic Acid (22:6, omega3) Mediated Attenuation of Western Diet Induced Nonalcoholic Steatohepatitis in Male Ldlr (-/-) Mice**. Metabolites 2019; 9.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31661783
ABSTRACT
Nonalcoholic fatty liver disease (NAFLD) is a major public health problem worldwide. NAFLD ranges in severity from benign steatosis to nonalcoholic steatohepatitis (NASH), cirrhosis, and primary hepatocellular cancer (HCC). Obesity and type 2 diabetes mellitus (T2DM) are strongly associated with NAFLD, and the western diet (WD) is a major contributor to the onset and progression of these chronic diseases. Our aim was to use a lipidomic approach to identify potential lipid mediators of diet-induced NASH. We previously used a preclinical mouse (low density lipoprotein receptor null mouse, Ldlr (-/-)) model to assess transcriptomic mechanisms linked to WD-induced NASH and docosahexaenoic acid (DHA, 22:6, omega3)-mediated remission of NASH. This report used livers from the previous study to carry out ultra-high-performance liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) and high-performance liquid chromatography coupled with dynamic multi-reaction monitoring (HPLC-dMRM) to assess the impact of the WD and DHA on hepatic membrane lipid and oxylipin composition, respectively. Feeding mice the WD increased hepatic saturated and monounsaturated fatty acids and arachidonic acid (ARA, 20:4, omega6) in membrane lipids and suppressed omega3 polyunsaturated fatty acids (PUFA) in membrane lipids and omega3 PUFA-

derived anti-inflammatory oxylipins. Supplementing the WD with DHA lowered hepatic ARA in membrane lipids and ARA-derived oxylipins and significantly increased hepatic DHA and its metabolites in membrane lipids, as well as C20-22 omega3 PUFA-derived oxylipins. NASH markers of inflammation and fibrosis were inversely associated with hepatic C20-22 omega3 PUFA-derived Cyp2C- and Cyp2J-generated anti-inflammatory oxylipins (false discovery rate adjusted p-value; q </= 0.026). Our findings suggest that dietary DHA promoted partial remission of WD-induced NASH, at least in part, by lowering hepatic pro-inflammatory oxylipins derived from ARA and increasing hepatic anti-inflammatory oxylipins derived from C20-22 omega3 PUFA.

[27] *Dolatshahi M, Davoudi S, Paridar Y et al.* **Pharmacological evidence for the involvement of the opioid system in the antidepressant-like effect of simvastatin in mice: Without tolerance and withdrawal syndrome**. Neurosci Lett 2019:134578.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31669314
ABSTRACT
Statins, 3-hydroxy-3-methylglutaryl co-enzyme A (HMG-CoA) reductase inhibitors, have been shown to be effective in reducing depression in animal models. The present study aimed to investigate the potential antidepressant-like activity of simvastatin and the possible involvement of opioid systems in the mouse forced swimming test (FST). After assessment of locomotor behavior in the open-field test (OFT), FST was applied for evaluation of depressive behavior in mice. Simvastatin (20, 30, and 40 mg/kg, i.p.) or morphine (0.01, 0.1, 1 and 10 mg/kg, i.p.) were administrated 30 min before the OFT or FST. Results showed that simvastatin produced antidepressant effect in a dose-dependent manner. The effect of simvastatin (30 mg/kg) was prevented by the pre-treatment of mice with naloxone (1 mg/kg, i.p., a nonselective opioid receptor antagonist). In addition, a sub-effective dose of simvastatin (20 mg/kg) produced a synergistic antidepressant-like effect in the FST with a sub-effective dose of morphine (0.1 mg/kg) that it was reversed by naloxone. Moreover, in contrast to morphine, treatment with simvastatin for six days induced neither tolerance to the antidepressant-like effect nor withdrawal signs. In conclusion, these findings demonstrated that simvastatin elicited antidepressant-like action possibly through the stimulation of opioidergic pathways, without inducing tolerance and withdrawal signs.

[28] *Van den Hof M, Klein Haneveld MJ, Blokhuis C et al.* **Elevated Lipoprotein(a) in Perinatally HIV-Infected Children Compared With Healthy Ethnicity-Matched Controls**. Open Forum Infect Dis 2019; 6:ofz301.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31660394
ABSTRACT
Background: HIV-associated cardiovascular disease (CVD) risk in combination antiretroviral therapy (cART)-treated perinatally HIV-infected patients (PHIV+) remains unknown due to the young age of this population. Lipoprotein(a) (Lp(a)) has been established as an independent causal risk factor for CVD in the general population but has not been well established in the population of PHIV+. Methods: We cross-sectionally compared lipid profiles, including nonfasting Lp(a), together with total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglycerides between 35 cART-treated PHIV+ children aged

8-18 years and 37 controls who were matched for age, sex, ethnicity, and socioeconomic status. We explored associations between Lp(a) and disease- and treatment-related factors (inflammation, monocyte activation, and vascular), biomarkers, and neuroimaging outcomes using linear regression models. Results: PHIV+ children had significantly higher levels of Lp(a) compared with controls (median, 43.6 [21.6-82.4] vs 21.8 [16.8-46.6] mg/dL; P = .033). Other lipid levels were comparable between groups. Additional assessment of apolipoprotein B, apolipoprotein CIII, apolipoprotein E, and APOE genotype revealed no significant differences. Higher Lp(a) levels were associated with higher plasma apoB levels and with lower monocyte chemoattractant protein-1 and TG levels in PHIV+ children. Lp(a) was not associated with HIV- or cART-related variables or with neuroimaging outcomes. Conclusions: cART-treated PHIV+ children appear to have higher levels of Lp(a) compared with ethnicity-matched controls, which may implicate higher CVD risk in this population. Future research should focus on the association between Lp(a) and (sub)clinical CVD measurements in cART-treated PHIV+ patients. Dutch Trial Register number: NRT4074.

[29] *He P, Smith A, Gelissen IC, Ammit AJ*. **The effect of statins and the synthetic LXR agonist T0901317 on expression of ABCA1 transporter protein in human lung epithelial cell lines in vitro**. Pharmacological reports : PR 2019; 71:1219-1226.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31669886
ABSTRACT
BACKGROUND: The pathogenesis of chronic obstructive pulmonary disease (COPD) is associated with dyslipidemia, an established co-morbidity. Statins treat hypercholesterolemia, but more recently have been trailed in the setting of COPD for their potential anti-inflammatory benefits. The outcomes of prospective trials however have been inconsistent. Thus, we hypothesize that the variation in results may have been due to statin-induced downregulation of ATP-binding cassette transporter A1 (ABCA1), thereby reducing cholesterol export. This study aims to elucidate whether statin treatment in a cellular model of COPD leads to a decrease in ABCA1 protein expression. METHODS: To mimic the inflammatory environment of COPD, two commonly used lung epithelial cell lines (BEAS-2B and A549) were treated with tumor necrosis factor (TNF), and co-treated with cholesterol/25-hydroxycholesterol (25-OH) to mimic dyslipidemia. ABCA1 protein was detected by Western Blotting. RESULTS: We unexpectedly showed that statins did not affect ABCA1 expression. However, the LXR agonist T0901317 significantly increased ABCA1 expression in both cell lines, while TNF, cholesterol or 25-OH induced ABCA1 protein upregulation in BEAS-2B cells, indicating cell line differences in response. There was also evidence of synergistic impacts of combined treatments on ABCA1 upregulation in BEAS-2B cells. CONCLUSION: Statins did not have an impact on ABCA1 expression in lung epithelial cell lines, disproving our original hypothesis. However, we showed for the first time, the effect of the inflammatory cytokine TNF, cholesterol/25-OH, statins and the LXR agonist T0901317 on expression of ABCA1 transporter protein in human lung epithelial cell lines in vitro. We hope that these in vitro studies may prove beneficial for addressing dyslipidemia in COPD in the future.

[30] *Kazi DS, Virani SS*. **Implications of cost-effectiveness analyses of lipid-lowering therapies: From the policy-maker's desk to the patient's bedside**. Prog Cardiovasc Dis 2019.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31672610

ABSTRACT

In our increasingly cost-conscious health system, patients, clinicians, hospitals, and payers all agree about the urgent need to rein in runaway healthcare costs. High pharmaceutical costs make drugs unaffordable to many patients who may benefit from them, including some insured patients who face prohibitive out-of-pocket costs. Health systems and payers can use the systematic framework of cost-effectiveness analysis and estimated budgetary impact to prioritize the adoption of new therapies and technologies. In this review article, we discuss basic principles of cost-effectiveness research for practicing clinicians, the concept of cost-effectiveness versus affordability, other considerations relevant to resource allocation, and limitations of cost-effectiveness research. We use the example of lipid lowering therapies to discuss application of cost-effectiveness research in informing health care policy, its use for health care systems and in the development of clinical practice guidelines, and its implications for clinicians and patients. As clinicians and patients become more cognizant of the cost-implications of new therapies, professional societies can help improve the quality of decision-making by incorporating unbiased value statements into their expert guidelines.

[31] *Miname MH, Santos RD*. **Reducing cardiovascular risk in patients with familial hypercholesterolemia: Risk prediction and lipid management**. Prog Cardiovasc Dis 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31669498

ABSTRACT

Familial hypercholesterolemia (FH) is a frequent genetic disorder characterized by elevated low-density lipoprotein (LDL)-cholesterol (LDL-C) levels and early onset of atherosclerotic cardiovascular disease. FH is caused by mutations in genes that regulate LDL catabolism, mainly the LDL receptor (LDLR), apolipoprotein B (APOB) and gain of function of proprotein convertase subtilisin kexin type 9 (PCSK9). However, the phenotype may be encountered in individuals not carrying the latter monogenic defects, in approximately 20% of these effects of polygenes predominate, and in many individuals no molecular defects are encountered at all. These so-called FH phenocopy individuals have an elevated atherosclerotic cardiovascular disease risk in comparison with normolipidemic individuals but this risk is lower than in those with monogenic disease. Individuals with FH are exposed to elevated LDL-C levels since birth and this explains the high cardiovascular, mainly coronary heart disease, burden of these subjects. However, recent studies show that this risk is heterogenous and depends not only on high LDL-C levels but also on presence of previous cardiovascular disease, a monogenic cause, male sex, smoking, hypertension, diabetes, low HDL-cholesterol, obesity and elevated lipoprotein(a). This heterogeneity in risk can be captured by risk equations like one from the SAFEHEART cohort and by detection of subclinical coronary atherosclerosis. High dose high potency statins are the main stain for LDL-C lowering in FH, however, in most situations these medications are not powered enough to reduce cholesterol to adequate levels. Ezetimibe and PCSK9 inhibitors should also be used in order to better treat LDL-C in FH patients.

[32] *Robinson JG*. **Lipid management beyond the guidelines**. Prog Cardiovasc Dis 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31669499

ABSTRACT

The 2018 AHA/ACC cholesterol guideline builds on the 2013 ACC/AHA cholesterol guideline statin recommendations to provide more detailed recommendations for the use of nonstatin therapy risk stratification for primary prevention statin use. New information has become available after the development of the 2018 AHA/ACC cholesterol guideline that can further inform clinical practice. Proprotein convertase subtilisin kexin type-9 (PCSK9) monoclonal antibodies are now a reasonable or even good value following over 60% reductions in their acquisition price, and the identification of high risk patient groups most likely to benefit from further low-density lipoprotein cholesterol (LDL-C) lowering. Meta-analyses and clinical trial data now show that patients with LDL-C>/=100mg/dl are more likely to experience progressively greater reductions in the risk of cardiovascular and total mortality and coronary heart disease events for progressively higher LDL-C levels. Icosapent ethyl, a highly concentrated form of modified EPA has been shown to reduce cardiovascular events in high risk patients with moderate hypertriglyceridemia on statin therapy. Comparisons with other statin guidelines revealed that statin initiation for those with >/=7.5% 10-year atherosclerotic cardiovascular disease (ASCVD) risk is the most effective strategy for reducing the most ASCVD events for the proportion of the population treated. Data from younger populations finally became available for coronary artery calcium (CAC) scoring (mean age of 51years) which confirmed the value of CAC>0 for identifying individuals at increased ASCVD risk most likely to benefit from statin initiation. This analysis also found that statins could keep CAC=0 in those with risk factors. Epidemiologic pooling studies now clearly show that LDL-C and non-high-density lipoprotein cholesterol levels in young adulthood confer excess risk for ASCVD later in life. Accumulating data support earlier risk factor intervention trials as the next research priority.

[33] *Macias Saint-Gerons D, Bosco Cortez F, Jimenez Lopez G et al.* **Cataracts and statins. A disproportionality analysis using data from VigiBase**. Regulatory toxicology and pharmacology : RTP 2019; 109:104509.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31669197
ABSTRACT
The basis of the association between statin use and cataract has been explored using the World Health Organization (WHO) global database of individual case safety reports (ICSRs) for drug monitoring (VigiBase) through January 2019. The reporting odds ratios (RORs) as a measure of disproportionality for reported cataracts and individual statins have been calculated. Subgroup analyses according statin lipophilicity, sex, and age groups have been performed. Moreover, RORs have been calculated for non-statin lipid lowering drugs. An increased disproportionality have been found for most individual statins lovastatin: [ROR: 14.80, 95% confidence interval (CI): 13.30, 16.46)], atorvastatin (ROR: 3.48, 95% CI 3.19-3.80), pravastatin (ROR: 3.15, 95% CI: 2.54-3.90), rosuvastatin (ROR: 2.90, 95% CI: 2.53-3.31), simvastatin (ROR: 2.27, 95%CI: 1.99-2.60), fluvastatin (ROR: 2.03, 95% CI: 1.33-3.08) and statins (overall) ROR: 3.66, 95% CI:3.46-3.86). Increased disproportionality for cataract and statins (drug-class) have been found regardless of statin lipophilicity, sex and group age (more or less than 65 years old). No disproportionality was found for other lipid-lowering drugs (ezetimibe, fibrates or PCSK9 inhibitors). These findings suggest an increased risk of cataract associated with statins as a

drug-class. Further studies to characterize the risk are advised. Benefits and potential harms should be considered before starting treatment with statins.

[34] *Dornbos P, Jurgelewicz A, Fader KA et al.* **Characterizing the Role of HMG-CoA Reductase in Aryl Hydrocarbon Receptor-Mediated Liver Injury in C57BL/6 Mice**. Scientific reports 2019; 9:15828.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31676775
ABSTRACT
The aryl hydrocarbon receptor (AHR) is a ligand-activated transcription factor. The prototypical ligand of the AHR is an environmental contaminant called 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). TCDD exposure is associated with many adverse health outcomes in humans including non-alcoholic fatty liver disease (NAFLD). Previous studies suggest that AHR ligands alter cholesterol homeostasis in mice through repression of genes involved in cholesterol biosynthesis, such as Hmgcr, which encodes the rate-limiting enzyme of cholesterol biosynthesis called 3-hydroxy-3-methyl-glutaryl coenzyme A reductase (HMGCR). In this study, we sought to characterize the impact of HMGCR repression in TCDD-induced liver injury. C57BL/6 mice were exposed to TCDD in the presence or absence of simvastatin, a competitive inhibitor of HMGCR. Simvastatin exposure decreased TCDD-induced hepatic lipid accumulation in both sexes, but was most prominent in females. Simvastatin and TCDD (S + T) co-treatment increased hepatic AHR-battery gene expression and liver injury in male, but not female, mice. In addition, the S + T co-treatment led to an increase in hepatic glycogen content that coincides with heavier liver in female mice. Results from this study suggest that statins, which are amongst the most prescribed pharmaceuticals, may protect from AHR-mediated steatosis, but alter glycogen metabolism and increase the risk of TCDD-elicited liver damage in a sex-specific manner.

[35] *Nakada Y, Onoue K, Nakano T et al.* **AST-120, an Oral Carbon Absorbent, Protects against the Progression of Atherosclerosis in a Mouse Chronic Renal Failure Model by Preserving sFlt-1 Expression Levels**. Scientific reports 2019; 9:15571.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31666542
ABSTRACT
Soluble Flt-1 (sFlt-1), an endogenous antagonist of the proatherogenic cytokine placental growth factor, is decreased in chronic kidney disease (CKD), leading to atherosclerotic progression. In this study, we investigated the effect of AST-120, an oral carbon adsorbent which can remove uremic toxins, on sFlt-1 expression levels and atherosclerosis progression. Atherosclerotic apolipoprotein E-deficient mice underwent a 5/6 nephrectomy (5/6 NR) or a sham operation (sham) at 8 weeks of age and were then treated or not with oral AST-120 for 12 weeks. sFlt-1 expression levels and the degree of atherosclerosis were assessed at 22 weeks of age in each of the four groups (sham; n = 7, 5/6 NR; n = 10, sham + AST-120: n = 8, 5/6 NR + AST-120; n = 8). The expression levels of sFlt-1 mRNA in the kidney were significantly lower in the 5/6 NR group than in the sham group, but AST-120 treatment prevented this decrease in sFlt-1 levels. Similarly, the atherosclerotic plaque area of the thoracoabdominal aorta was significantly larger in the 5/6 NR group than in the sham group, and AST-120 treatment

prevented this increase in atherosclerosis. AST-120 could, therefore, be used as a therapeutic to treat atherosclerosis in patients with CKD.

[36] *Rajan MR, Sotak M, Barrenas F et al.* **Comparative analysis of obesity-related cardiometabolic and renal biomarkers in human plasma and serum**. Scientific reports 2019; 9:15385.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31659186
ABSTRACT
The search for biomarkers associated with obesity-related diseases is ongoing, but it is not clear whether plasma and serum can be used interchangeably in this process. Here we used high-throughput screening to analyze 358 proteins and 76 lipids, selected because of their relevance to obesity-associated diseases, in plasma and serum from age- and sex-matched lean and obese humans. Most of the proteins/lipids had similar concentrations in plasma and serum, but a subset showed significant differences. Notably, a key marker of cardiovascular disease PAI-1 showed a difference in concentration between the obese and lean groups only in plasma. Furthermore, some biomarkers showed poor correlations between plasma and serum, including PCSK9, an important regulator of cholesterol homeostasis. Collectively, our results show that the choice of biofluid may impact study outcome when screening for obesity-related biomarkers and we identify several markers where this will be the case.

[37] *Singh AB, Liu J*. **Berberine decreases plasma triglyceride levels and upregulates hepatic TRIB1 in LDLR wild type mice and in LDLR deficient mice**. Scientific reports 2019; 9:15641.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31666640
ABSTRACT
TRIB1 is a GWAS locus associated with plasma cholesterol and triglycerides (TG) levels. In mice, liver-specific overexpression of TRIB1 lowers plasma lipid levels. Berberine (BBR) is a natural lipid lowering drug that reduces plasma LDL-cholesterol (LDL-C), total cholesterol (TC) and TG in hyperlipidemic patients and in mice by mechanisms involving upregulation of hepatic LDL receptor (LDLR). Here, we demonstrated that BBR treatment reduced plasma LDL-C, TC and TG in LDLR wildtype (WT) mice fed a high fat and high cholesterol diet and it only lowered TG in LDLR WT mice fed a normal chow diet. In hypercholesterolemic LDLR deficient mice (Ldlr(-/-)), BBR treatment reduced plasma TG levels by 51% compared to the vehicle control without affecting plasma cholesterol levels. Hepatic gene expression analysis revealed that Trib1 mRNA levels were significantly elevated by BBR treatment in all three mouse models and increases of Trib1 mRNA expression were associated with reduced expression of lipogenic genes including Cebpa, Acc1 and Scd1. In vitro studies further demonstrate that BBR induces TRIB1 mRNA expression by a transcriptional mechanism via ERK signaling pathway. These new findings warrant future in vivo studies to determine the causal role of Trib1 in BBR-mediated TG lowering independent of LDLR regulation.

[38] *Sundboll J, Larsen AP, Veres K et al.* **Cardiovascular event rates and trajectories of LDL-cholesterol levels and lipid-lowering therapy in patients with atherosclerotic cardiovascular disease: A population-based cohort study**. Thrombosis research 2019; 183:124-130.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31677592

ABSTRACT
BACKGROUND: An understanding of cardiovascular event rates and low-density lipoprotein cholesterol (LDL-C) levels and trajectories in patients with atherosclerotic cardiovascular disease is needed to evaluate treatment goals and adherence to guidelines. METHODS: We conducted a population-based cohort study in the North and Central Denmark Regions. Patients with prevalent atherosclerotic cardiovascular disease (myocardial infarction, non-hemorrhagic stroke, or peripheral artery disease) during 2006-2009 were identified. All patients received lipid-lowering therapy (statins or ezetimibe) and had LDL-C levels >/=1.8mmol/L at baseline (January 1, 2010). We followed patients for 6years until a primary composite outcome of cardiovascular death, myocardial infarction, non-hemorrhagic stroke, hospitalization for unstable angina, or coronary revascularization. Additionally, we characterized changes in LDL-C levels and use of statins during follow-up. RESULTS: The study included 10,772 patients (median age 69.2years, 60.4% male). The overall event rate for the primary outcome was 62.7 (95% confidence interval: 59.2-66.2) per 1000 person-years. This event rate was higher among men than among women and increased with age and baseline LDL-C levels. Approximately 25% of patients with LDL-C measurements during follow-up achieved LDL-C levels below 1.8mmol/L. Of the approximately two-thirds of patients using statins at the end of follow-up, nearly all patients (97%) received high-intensity therapy. CONCLUSIONS: In this population of patients with atherosclerotic cardiovascular disease, we found high cardiovascular event rates, which increased with baseline LDL-C levels. Although most patients were on high-intensity statin therapy at end of follow-up, only one-quarter reached the guideline-recommended target LDL-C level</=1.8mmol/L.

[39] *Ye XZ, Huang SS, Liu J et al.* **[High serum cholesterol: a novel risk factor for thyroid associated ophthalmopathy?]**. Zhonghua nei ke za zhi 2019; 58:823-825.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31665858

ABSTRACT
This study was aimed to investigate the association between dyslipidemia and thyroid associated ophthalmopathy (TAO). We evaluated the relationship between dyslipidemia and TAO in 218 patients with Graves' disease (GD) and found that the serum total cholesterol (TC) and low density lipoprotein cholesterol (LDL-C) in the GD subjects with TAO (n=110) were significantly increased [(5.32+/-1.39) mmol/L vs. (3.18+/-2.12) mmol/L, (2.98+/-0.75) mmol/L vs. (1.25+/-0.98) mmol/L] than those in the GD subjects without TAO (n=108). TC and LDL-C were positively correlated with the Clinical disease activity score (CAS) [TC (r=0.7, P=0.03),LDL-C (r=0.82, P=0.03)], and the levels of TC (OR=2.56, P=0.02) and LDL-C(OR=2.01, P=0.015) were positively associated with TAO. These suggested that high serum cholesterol level is a novel risk factor for TAO, and management of blood lipids should be included in the treatment of TAO.