[1] *Messori A, Bartoli L, Chiumente M et al.* **The Restricted Mean Survival Time as a Tool for Ranking Comparative Outcomes in a Narrative Review that Evaluates a Network of Randomized Trials: An Example Based on PCSK9 Inhibitors**. American journal of cardiovascular drugs : drugs, devices, and other interventions 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33030677
ABSTRACT
INTRODUCTION: On the basis of two randomized trials, evolocumab and alirocumab have been approved in patients with cardiovascular disease. The evidence on these two agents has been studied through different methods of analysis that span from narrative approaches to network meta-analysis. In the present study, we assessed the performance of a narrative approach combined with the application of the restricted mean survival time (RMST). METHODS: We studied the two pivotal placebo-controlled trials focused on evolocumab and alirocumab. Our original framework of comparative assessment employed the RMST. Our objective was to show that in the context of a narrative review, the RMST can be an efficient although simple tool to make indirect comparisons. The endpoint was event-free survival, expressed in months. RESULTS: For each cohort of patients (13,784 patients administered evolocumab, 9462 patients administered alirocumab, 23,242 controls), we determined the RMST values with 95% confidence intervals (CI) [evolocumab: 33.60 months, 95% CI 33.46-33.74; alirocumab: 34.07 months, 95% CI 33.92-34.22]. These results, along with those of the control groups, were analyzed and interpreted narratively. Univariate statistics were conducted, but no network meta-analysis was performed. CONCLUSION: The experience presented herein indicates that a framework of evidence assessment focused on the RMST is a worthwhile option. Our study is in line with the growing literature that has recently emphasized the methodological advantages of the RMST.

[2] *Meshram NH, Jackson D, Mitchell CC et al.* **Study of the Relationship Between Ultrasound Strain Indices and Cognitive Decline for Vulnerable Carotid Plaque**. Annu Int Conf IEEE Eng Med Biol Soc 2020; 2020:2088-2091.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33018417
ABSTRACT
A relationship between ultrasound strain indices in carotid plaque to cognitive domains of executive and language function are studied in 42 symptomatic and 34 asymptomatic patients. The mean and standard deviation of the percentage stenosis were 72.10 ± 15.19 and 77.41 ± 11.20 for symptomatic and asymptomatic patients respectively. Pearson's correlation between axial, lateral and shear strain indices versus executive and language composite scores was performed.. A significant inverse correlation for both executive and language function for symptomatic patients to strain indices was found. On the other hand, for asymptomatic patients only executive function was inversely correlated with the corresponding strain indices. Our hypothesis that microemboli from vulnerable plaque and possible 'silent strokes' may be responsible for decline in executive function for both symptomatic and asymptomatic patients'. Strokes and transient ischemic attacks may be responsible for further cognitive decline in language function for symptomatic patients.

[3] *Mi S, Wei Z, Xu J et al.* **Detecting Carotid Intima-Media From Small-Sample Ultrasound Images**. Annu Int Conf IEEE Eng Med Biol Soc 2020; 2020:2129-2132.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33018427

ABSTRACT
Cardiovascular diseases are the biggest threat to human being's health all over the world, and carotid atherosclerotic plaque is the leading cause of ischemic cardiovascular diseases. To determine the location and shape of the plaque, it is of great significance to detect the intima-media (IM). In this paper, a new IM detection method based on convolution neural network (IMD-CNN) is proposed for the detection of IM of blood vessels in longitudinal ultrasonic images. In IMD-CNN, firstly the region of interest (ROI) is automatically extracted by morphological processing, then the patch-wise training data are constructed, and finally a simple CNN is trained to detect the IM. The experimental results obtained on 23 images show that the test accuracy of IMD-CNN is over 86% and the performance of IMD-CNN is also visually proved to be effective.

[4] *Pleouras DS, Sakellarios AI, Loukas VS et al.* **Prediction of the development of coronary atherosclerotic plaques using computational modeling in 3D reconstructed coronary arteries**. Annu Int Conf IEEE Eng Med Biol Soc 2020; 2020:2808-2811.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33018590

ABSTRACT
In this work we present a novel method for the prediction and generation of atherosclerotic plaques. This is performed in a two-step approach, by employing first a multilevel computational plaque growth model and second a correlation between the model's results and the 3D reconstructed follow-up plaques. In particular, computer tomography coronary angiography (CTCA) data and blood tests were collected from patients at two time points. Using the baseline data, the plaque growth is simulated using a multi-level computational model which includes: i) modeling of the blood flow dynamics, ii) modeling of low and high density lipoproteins and monocytes' infiltration in the arterial wall, and the species reactions during the atherosclerotic process, and iii) modeling of the arterial wall thickening. The correlation between the followup plaques and the simulated plaque density distribution resulted to the extraction of a threshold of the plaque density, that can be used to identify plaque areas.Clinical Relevance- The methodology presented in this work is a first step to the prediction of the plaque shape and location of patients with atherosclerosis and could be used as an additional tool for patient-specific risk stratification.

[5] *Sakellarios AI, Pezoulas VC, Bourantas C et al.* **Prediction of atherosclerotic disease progression combining computational modelling with machine learning**. Annu Int Conf IEEE Eng Med Biol Soc 2020; 2020:2760-2763.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33018578

ABSTRACT
Non-invasive serial computed tomography coronary angiography (CTCA) was acquired from 32 patients and 3D reconstruction of 58 coronary arteries was achieved. The arterial geometries were utilized for blood flow and LDL transport modelling. Navier-Stokes and convection-diffusion equations were employed for simulation of blood flow and LDL transport, respectively. Disease progression was assessed comparing the follow-up and baseline arterial models after co-registration using side branches as anatomical landmarks. A machine learning model for predicting disease progression was built using the Gradient Boosted Trees (GBT) algorithm. The Accuracy, Sensitivity, Specificity and AUC of the developed methodology for predicting lumen area decrease equal was 0.68, 0.56, 0.34 and 0.59, respectively. The best

results were found for the prediction of plaque area increase by 20%, with 0.73, 0.67, 0.86, and 0.76 accuracy, sensitivity, specificity andAUC, respectively. This approach outperforms significantly the predictive capability of models based on binary logistic regression.

[6] *Tsakanikas VD, Siogkas PK, Mantzaris MD et al.* **A deep learning oriented method for automated 3D reconstruction of carotid arterial trees from MR imaging**. Annu Int Conf IEEE Eng Med Biol Soc 2020; 2020:2408-2411.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33018492
ABSTRACT
The scope of this paper is to present a new carotid vessel segmentation algorithm implementing the U-net based convolutional neural network architecture. With carotid atherosclerosis being the major cause of stroke in Europe, new methods that can provide more accurate image segmentation of the carotid arterial tree and plaque tissue can help improve early diagnosis, prevention and treatment of carotid disease. Herein, we present a novel methodology combining the U-net model and morphological active contours in an iterative framework that accurately segments the carotid lumen and outer wall. The method automatically produces a 3D meshed model of the carotid bifurcation and smaller branches, using multispectral MR image series obtained from two clinical centres of the TAXINOMISIS study. As indicated by a validation study, the algorithm succeeds high accuracy (99.1% for lumen area and 92.6% for the perimeter) for lumen segmentation. The proposed algorithm will be used in the TAXINOMISIS study to obtain more accurate 3D vessel models for improved computational fluid dynamics simulations and the development of models of atherosclerotic plaque progression.

[7] *Cesena FHY, Valente VA, Santos RD, Bittencourt MS*. **Cardiovascular Risk and Statin Eligibility in Primary Prevention: A Comparison between the Brazilian and the AHA/ACC Guidelines**. Arquivos brasileiros de cardiologia 2020; 115:440-449.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33027365
ABSTRACT
BACKGROUND: Differences between the updated versions of the Brazilian Guideline on Dyslipidemias and the American Heart Association (AHA)/American College of Cardiology (ACC) Cholesterol Guideline regarding cardiovascular risk stratification and statin eligibility are unknown. OBJECTIVES: To compare cardiovascular risk categorization and statin eligibility based on the Brazilian guideline with those based on the AHA/ACC guideline in primary prevention patients. METHODS: We retrospectively analyzed individuals aged 40-74 years without high-risk conditions, with LDL-c 70 to < 190 mg/dL, not on lipid-lowering drugs, who underwent routine clinical assessment. Cardiovascular risk was stratified according to the Brazilian and the AHA/ACC guidelines. Subjects were considered eligible for statin therapy if LDL-c was at least 30 mg/dL above the target for the cardiovascular risk (Brazilian guideline) or the 10-year atherosclerotic cardiovascular disease risk was ≥7.5% (AHA/ACC guideline). A p-value < 0.05 was considered statistically significant. RESULTS: The study sample consisted of 18,525 subjects (69% male, age 48 ± 6 years). Among subjects considered at intermediate or high risk by the Brazilian guideline, over 80% would be in a lower risk category by the AHA/ACC guideline. Among men, 45% and 16% would be statin eligible by the Brazilian and the AHA/ACC guidelines criteria, respectively (p < 0.001). Among women, the respective proportions would be 16% and 1% (p < 0.001). Eighty-two percent of women and 57% of men

eligible for statins based on the Brazilian guideline criterion would not be eligible according to the AHA/ACC guideline criterion. CONCLUSIONS: Compared with the AHA/ACC guideline, the Brazilian guideline classifies a larger proportion of primary prevention patients into higher-risk categories and substantially increases statin eligibility. (Arq Bras Cardiol. 2020; 115(3):440-449).

[8] *Yavuz F, Kilic S, Kaplan M et al.* **Impact of Atherogenic Indexes in Saphenous Vein Graft Stenosis**. Arquivos brasileiros de cardiologia 2020; 115:538-544.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33027378
ABSTRACT
BACKGROUND: Saphenous vein grafts (SVG) are frequently used in patients that have undergone coronary artery bypass graft (CABG) surgery. Objectives: To evaluate the relationship between atherogenic indexes and SVG stenosis. METHODS: Altogether, 534 patients (27.7% women, mean age 65±8.4 years) that underwent CABG and elective coronary angiography were included in the study. Patients with at least one SVG stenosis ≥50% were allocated to the stenosis group SVG (+) (n=259) and patients without stenosis were categorized as SVG (-) (n=275). Atherogenic index of plasma (AIP) and atherogenic coefficient (AC) were calculated from the patients' routine lipid parameters. The level of significance was $p<0.05$. RESULTS: The number of patients with a history of hypertension (HT), diabetes mellitus (DM), stroke, and heart failure was significantly higher in the SVG (+) group than in the SVG (-) group. Total cholesterol, triglycerides, LDL-C were significantly higher and HDL-C was lower in the SVG (+) group than in the SVG (-) group. AIP ($p<0.001$) and AC ($p<0.001$) were significantly higher in the SVG (+) group than in the SVG (-) group. The receiver operating characteristic (ROC) analysis show that both AIP and AC were better than HDL-C, LDL-C and non-HDL-C at predicting SVG stenosis. In the multivariate analysis, history of DM, HT, stroke, heart failure (HF), number of saphenous grafts, HDL-C, LDL-C, non-HDL-C, AIP and AC were found to be independent risk factors for SVG stenosis. CONCLUSION: AIP and AC were independent predictors of SVG stenosis. Moreover, both AIP and AC have better performance in predicting SVG stenosis than LDL-C, HDL-C and non-HDL-C. (Arq Bras Cardiol. 2020; 115(3):538-544).

[9] *Chattopadhyay A, Kwartler CS, Kaw K et al.* **Cholesterol-Induced Phenotypic Modulation of Smooth Muscle Cells to Macrophage/Fibroblast-like Cells Is Driven by an Unfolded Protein Response**. Arteriosclerosis, thrombosis, and vascular biology 2020:Atvbaha120315164.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33028096
ABSTRACT
OBJECTIVE: Vascular smooth muscle cells (SMCs) dedifferentiate and initiate expression of macrophage markers with cholesterol exposure. This phenotypic switching is dependent on the transcription factor Klf4 (Krüppel-like factor 4). We investigated the molecular pathway by which cholesterol induces SMC phenotypic switching. Approach and Results: With exposure to free methyl-β-cyclodextrin cholesterol, SMCs decrease expression of contractile markers, activate Klf4, and upregulate a subset of macrophage and fibroblast markers characteristic of modulated SMCs that appear with atherosclerotic plaque formation. These phenotypic changes are associated with activation of all 3 pathways of the endoplasmic reticulum unfolded protein response (UPR), Perk (protein kinase RNA-like endoplasmic reticulum kinase), Ire

(inositol-requiring enzyme) 1α, and Atf (activating transcription factor) 6. Blocking the movement of cholesterol from the plasma membrane to the endoplasmic reticulum prevents methyl-β-cyclodextrin cholesterol-induced UPR, Klf4 activation, and upregulation of the majority of macrophage and fibroblast markers. Cholesterol-induced phenotypic switching is also prevented by global UPR inhibition or specific inhibition of Perk signaling. Exposure to chemical UPR inducers, tunicamycin, and thapsigargin is sufficient to induce these same phenotypic transitions. Finally, analysis of published single-cell RNA sequencing data during atherosclerotic plaque formation in hyperlipidemic mice provides preliminary in vivo evidence of a role of UPR activation in modulated SMCs. CONCLUSIONS: Our data demonstrate that UPR is necessary and sufficient to drive phenotypic switching of SMCs to cells that resemble modulated SMCs found in atherosclerotic plaques. Preventing a UPR in hyperlipidemic mice diminishes atherosclerotic burden, and our data suggest that preventing SMC transition to dedifferentiated cells expressing macrophage and fibroblast markers contributes to this decreased plaque burden.

[10] *Cordero A, Santos-Gallego CG, Fácila L et al.* **Estimation of the major cardiovascular events prevention with Inclisiran**. Atherosclerosis 2020; 313:76-80.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33032236
ABSTRACT
BACKGROUND AND AIMS: The ORION 10-11 trials have reported the efficacy of Inclisiran on low-density lipoprotein cholesterol (LDLc) reduction, and also suggested prevention of major cardiovascular events (MACE) incidence. METHODS: We have performed a meta-analysis of the available studies, involving PCSK9 inhibitors or Inclisiran for >6 months, that reported the incidence of MACE. The primary endpoint was MACE incidence, as reported in outcomes-based randomized clinical trials (OB-RCT) and non OB-RCT. Analyses were performed using fixed effect models and fractional polynomial regression. RESULTS: The meta-analysis included a total of 57,431 patients, 1592 treated with Inclisiran and 28,259 with PSCK9 inhibitors (17,244 with evolocumab and 11,015 with alirocumab). Baseline mean LDLc was 104.1 (12.9) mg globally. On-treatment mean LDLc was 40.1 (7.8) mg/dl and mean absolute LDLc reduction was 60.6 (10.3) mg/dl. A total of 5389 MACE were reported, 2482 in patients receiving the study drug and 2907 in patients assigned to placebo. Treatment was associated with OB-RCT and no heterogeneity was observed. The estimation of MACE reduction associated with LDLc reduction, adjusted by age, diabetes, hypertension and baseline LDLc, provided a linear trend in the risk of MACE and LDLc reduction that was linear and all studies fitted properly. CONCLUSIONS: The results of the ORION 10-11 trials are in concordance with results of trials involving treatment with PCSK9 inhibitors. The results of the ORION-4 trial will provide definite evidence on the effects of Inclisiran on MACE reduction.

[11] *Reiner Ž*. **Why might visit-to visit variability of lipoproteins have an effect on cardiovascular events?** Atherosclerosis 2020; 312:99-100.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33036767
ABSTRACT

[12] *Tengryd C, Nielsen SH, Cavalera M et al.* **The proteoglycan mimecan is associated with carotid plaque vulnerability and increased risk of future cardiovascular death**. Atherosclerosis 2020; 313:88-95.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33032238

ABSTRACT

BACKGROUND AND AIMS: A vulnerable plaque is an atherosclerotic plaque that is rupture-prone with a higher risk to cause cardiovascular symptoms such as myocardial infarction or stroke. Mimecan or osteoglycin is a small leucine-rich proteoglycan, important for collagen fibrillogenesis, that has been implicated in atherosclerotic disease, yet the role of mimecan in human atherosclerotic disease remains unknown. METHODS: 196 human atherosclerotic carotid plaques were immunostained for mimecan. Smooth muscle cells, macrophages and intraplaque haemorrhage were also measured with immunohistochemistry. Neutral lipids were stained with Oil Red O and calcium deposits were quantified. Plaque homogenate levels of MCP-1, IL-6 and MIP-1β were measured using a Proximity Extension Assay and MMP-9 levels were measured using Mesoscale. Glycosaminoglycans, collagen and elastin were assessed by colorimetric assays and TGF-β1, β2 and β3 were measured using a multiplex assay. Mimecan gene expression in THP-1 derived macrophages was quantified by qPCR and protein expression in vitro was visualized with immunofluorescence. Cardiovascular events were registered using medical charts and national registers during follow-up. RESULTS: Mimecan correlated positively with plaque area of lipids, macrophages, intraplaque haemorrhage and inversely with smooth muscle cell staining. Mimecan also correlated positively with plaque levels of MMP-9 and MCP-1. Mimecan was upregulated in THP-1 derived macrophages upon stimulation with MCP-1. Patients with high levels of mimecan (above median) had higher risk for cardiovascular death. CONCLUSIONS: This study indicates that mimecan is associated with a vulnerable plaque phenotype, possibly regulated by plaque inflammation. In line, plaque levels of mimecan independently predict future cardiovascular death.

[13] *Penson PE, Pirro M, Banach M*. **LDL-C: lower is better for longer-even at low risk**. BMC medicine 2020; 18:320.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33032586

ABSTRACT

BACKGROUND: Low-density lipoprotein cholesterol (LDL-C) causes atherosclerotic disease, as demonstrated in experimental and epidemiological cohorts, randomised controlled trials, and Mendelian randomisation studies. MAIN TEXT: There is considerable inconsistency between existing guidelines as to how to effectively manage patients at low overall risk of cardiovascular disease (CVD) who have persistently elevated levels of LDL-C. We propose a step-by-step practical approach for the management of cardiovascular risks in individuals with low (< 1%) 10-year risk of CVD, and elevated (> 140 mg/dL, 3.6 mmol/L) LDL-C. The strategy proposed is based on the level of adherence to lifestyle interventions (LSI), and in case of non-adherence, stepwise practical management, including lipid-lowering therapy, is recommended to achieve a target LDL-C levels (< 115 mg/dL, 3.0 mmol/L). CONCLUSIONS: Further studies are necessary to answer the questions on the long-term efficacy, safety, and cost-effectiveness of the suggested approach. This is critical, considering the ever-increasing numbers of such low-risk patients seen in clinical practice.

[14] *KN ON, Bennett KE, Mc Hugh SM et al.* **Trends in national pharmaceutical expenditure on diabetes in Ireland 2011-2015: a repeated cross-sectional study**. BMJ open 2020; 10:e037382.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33039996

ABSTRACT

OBJECTIVES: To explore trends in pharmaceutical expenditure on diabetes between 2011 and 2015, describing trends in expenditure on blood glucose-lowering medications and estimating the effect of cost-containment measures implemented during this time. DESIGN: Repeated cross-sectional study of national pharmacy claims data in Ireland. PARTICIPANTS: Patients' dispensed items used in the treatment or management of diabetes. PRIMARY AND SECONDARY OUTCOMES: Total expenditure associated with diabetes was calculated by extracting data on all diabetes-related items dispensed to eligible patients. Costs were categorised into two groups. Diabetes-specific items include items used directly in diabetes treatment (WHO-Anatomical Therapeutic Chemical (ATC): A10, V07, V04) and diabetes-related include all other condition-related items (WHO-ATC: B01, C, H04, N03, N06). The impacts of two specific cost-containment measures, co-payments and reference pricing, were assessed using segmented linear regression analyses of interrupted time-series. RESULTS: Total expenditure varied over the study period, peaking at €216 994 441 in 2012. Expenditure on diabetes-specific items increased steadily by 18% reaching €153 621 477 in 2015, with blood glucose-lowering medications accounting for 73% of this increase. During the same period, expenditure on diabetes-related items decreased by 32% to €50 835 856. The introduction of reference pricing for atorvastatin in November 2013 resulted in immediate costs savings of €2.4 million per yearly quarter (level-change p<0.001). CONCLUSIONS: The increasing expenditure on blood glucose-lowering medications negates the effect of recent cost-containment measures, presenting a significant challenge for the provision of diabetes care. Innovative policies are required to ensure high-quality diabetes care can be provided at an equitable, affordable and sustainable rate.

[15] *Ödesjö H, Björck S, Franzén S et al.* **Adherence to lipid-lowering guidelines for secondary prevention and potential reduction in CVD events in Swedish primary care: a cross-sectional study**. BMJ open 2020; 10:e036920.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33039993

ABSTRACT

OBJECTIVES: The protective effect of lipid-lowering treatment for secondary prevention after coronary heart disease (CHD) has been well documented. Current guidelines recommend a target level for low-density lipoprotein cholesterol (LDL-C) of ≤1.8 mmol/L. The aim was to describe lipid-lowering treatment patterns and to provide an estimate of the potential reductions in cardiovascular disease (CVD) events with improved adherence to guidelines. DESIGN: Cross-sectional. SETTING: Primary care in a large Swedish region. PARTICIPANTS: 37 120 patients with CHD in a Swedish regional primary care quality register (QregPV), by 31 December 2015. PRIMARY AND SECONDARY OUTCOME MEASURES: Proportion of patients on statin treatment and proportion of patients achieving LDL-C ≤1.8 mmol/L. Estimated number of CVD events calculated for (1) current treatment, (2) improved treatment and (3) lowered LDL-C, based on applying rate reductions from meta-analyses of randomised trials to the potentially undertreated population. Risk estimation modelling was based on 52 042 patients in the same register on January 2011 followed for 5 years. RESULTS: Of 37 120 patients, 18% reached LDL-C ≤1.8 mmol/L and 32% were not on statin treatment. Based on individual risks, the estimated number of CVD events in the study group over 5 years was 9209/37 120. If all patients without a statin or with less potent statin treatment

were given atorvastatin 80 mg, an estimated reduction of CVD events by 14% (7901 vs 9209) was seen. If all patients achieved LDL-C ≤1.8 mmol/L, the number of events was estimated to be reduced by 18% (7577 vs 9209). CONCLUSION: One-third of patients with CHD in primary care were not on lipid-lowering treatment. Based on the assumption that included patients would react to statin therapy the same way as the patients in randomised trials, improved adherence to treatment guidelines could lead to a substantial reduction in new CVD events.

[16] *de Jong M, Oskam MJ, Sep SJS et al.* **Sex differences in cardiometabolic risk factors, pharmacological treatment and risk factor control in type 2 diabetes: findings from the Dutch Diabetes Pearl cohort**. BMJ open diabetes research & care 2020; 8.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33023896
ABSTRACT
INTRODUCTION: Sex differences in cardiometabolic risk factors and their management in type 2 diabetes (T2D) have not been fully identified. Therefore, we aimed to examine differences in cardiometabolic risk factor levels, pharmacological treatment and achievement of risk factor control between women and men with T2D. RESEARCH DESIGN AND METHODS: Cross-sectional data from the Dutch Diabetes Pearl cohort were used (n=6637, 40% women). Linear and Poisson regression analyses were used to examine sex differences in cardiometabolic risk factor levels, treatment, and control. RESULTS: Compared with men, women had a significantly higher body mass index (BMI) (mean difference 1.79 kg/m(2) (95% CI 1.49 to 2.08)), while no differences were found in hemoglobin A(1c) (HbA(1c)) and systolic blood pressure (SBP). Women had lower diastolic blood pressure (-1.94 mm Hg (95% CI -2.44 to -1.43)), higher total cholesterol (TC) (0.44 mmol/L (95% CI 0.38 to 0.51)), low-density lipoprotein cholesterol (LDL-c) (0.26 mmol/L (95% CI 0.22 to 0.31)), and high-density lipoprotein cholesterol (HDL-c) sex-standardized (0.02 mmol/L (95% CI 0.00 to 0.04)), and lower TC:HDL ratio (-0.29 (95% CI -0.36 to -0.23)) and triglycerides (geometric mean ratio 0.91 (95% CI 0.85 to 0.98)). Women had a 16% higher probability of being treated with antihypertensive medication in the presence of high cardiovascular disease (CVD) risk and elevated SBP than men (relative risk 0.84 (95% CI 0.73 to 0.98)), whereas no sex differences were found for glucose-lowering medication and lipid-modifying medication. Among those treated, women were less likely to achieve treatment targets of HbA(1c) (0.92 (95% CI 0.87 to 0.98)) and LDL-c (0.89 (95% CI 0.85 to 0.92)) than men, while no differences for SBP were found. CONCLUSIONS: In this Dutch T2D population, women had a slightly different cardiometabolic risk profile compared with men and a substantially higher BMI. Women had a higher probability of being treated with antihypertensive medication in the presence of high CVD risk and elevated SBP than men, and were less likely than men to achieve treatment targets for HbA(1c) and LDL levels.

[17] *Alkhalil M*. **A promising tool to tackle the risk of cerebral vascular disease, the emergence of novel carotid wall imaging**. Brain circulation 2020; 6:81-86.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33033777
ABSTRACT
Stroke is a heterogeneous vascular disease. Carotid artery atherosclerosis is associated with almost one-quarter of ischemic strokes. Moreover, a large percentage of preventable strokes are currently attributed to carotid atherosclerosis. Over the past three decades, the management of carotid artery disease has evolved. The benefits of carotid revascularization

alongside medical therapy have early been recognized. Nonetheless, the debate regarding the optimal strategy is still ongoing, particularly in patients with asymptomatic carotid artery disease. One of the challenges is the use of luminal stenosis to quantify the severity of the carotid artery disease and to guide decision-making regarding invasive revascularization. Characterizing carotid atherosclerotic plaque is a promising tool to identify vulnerable plaque. Certain features such as large lipid core have already been linked to acute vascular events, not only at the plaque level but also to predict systemic cardiovascular events. Recently, a quantitative T2 mapping magnetic resonance imaging technique was developed and validated against histology. The ability to accurately quantify plaque lipid content using this technique opens several new opportunities. In this review articles, we will discuss the current challenges in the management of carotid artery disease and the future roles of T2 mapping to aid therapeutic options. These roles may include how to determine the mode of invasive carotid revascularization in symptomatic patients. Moreover, there may be a rational to use T2 mapping as a risk stratification tool in asymptomatic patients with carotid artery stenosis. It may also provide an opportunity to stage atherosclerosis and identify patients with coronary atherosclerosis who may benefit maximally from intensive lipid interventions.

[18] *Fedoryak O, Arama C, Diarra I et al.* **Association of the rs562556 PCSK9 Gene Polymorphism with Reduced Mortality in Severe Malaria among Malian Children**. Can J Infect Dis Med Microbiol 2020; 2020:9340480.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33029265
ABSTRACT
Recent evidence suggests that proprotein convertase subtilisin/kexin type 9 (PCSK9), a downmodulator of cellular uptake of blood cholesterol, also negatively impacts host immune response to microbial infection. In this study, we investigated whether carrying the loss-of-function (LOF) rs562556 (c.1420 A > G; p.I474 V) PCSK9 single nucleotide polymorphism (SNP) affected the outcome of severe malaria in children. Archival DNA of a cohort of 207 Malian children suffering from severe malaria was genotyped for the rs562556 SNP. Sixty-four children were either heterozygous or homozygous for the minor G allele (carriers); 143 children were homozygous for the common A allele (noncarriers). Among carriers, there was one mortality case (1.6%), compared to 15 cases (10.5%) among noncarriers (p=0.0251), suggesting that the G allele is associated with better survival in severe malaria. Intriguingly, this allele did not negatively segregate with any of the clinical symptoms linked to mortality in this cohort. Studies are needed to determine whether PCSK9 inactivation promotes a protective immune response to malaria infection.

[19] *Peng J, Liu MM, Jin JL et al.* **Association of circulating PCSK9 concentration with cardiovascular metabolic markers and outcomes in stable coronary artery disease patients with or without diabetes: a prospective, observational cohort study**. Cardiovascular diabetology 2020; 19:167.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33023603
ABSTRACT
BACKGROUND: Whether plasma proprotein convertase subtilisin/kexin type 9 (PCSK9) levels is a predictor for cardiovascular outcomes has currently been controversial. No data is currently available regarding the relation of PCSK9 to cardiovascular metabolic markers (CVMMs) and major adverse cardiovascular events (MACEs) in stable coronary artery disease

(CAD) patients with diabetes or without diabetes. METHODS: A total 1225 untreated patients with stable CAD were consecutively enrolled and their baseline plasma PCSK9 levels were determined by ELISA. Patients were divided into high and low PCSK9 groups according to PCSK9 median. All patients followed up for the occurrence of MACEs and received standard therapy after admission. The associations of PCSK9 with CVMMs and MACEs were evaluated. RESULTS: PCSK9 levels were positively correlated with multiple CVMMs including total cholesterol, low-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol and hemoglobin A(1c) at baseline (all $p < 0.05$). During a median follow-up of 3.3 years, 103 (8.4%) events occurred. PCSK9 levels were higher in patients with events compared to those without ($p < 0.05$). The Kaplan-Meier analysis displayed that patients in high PCSK9 group had lower event-free survival than that in low group ($p < 0.05$). Multivariable Cox regression analysis revealed that PCSK9 levels were independently associated with MACEs in diabetic patients (adjusted hazard ratio [HR]: 1.361, 95% confidence interval [CI]: 1.037-1.785, $p < 0.05$). When added the combination of PCSK9 levels and diabetic status to stratifying factors, patients in high PCSK9 group appeared to have extremely high risk of subsequent MACEs with diabetes (adjusted HR: 5.233, 95% CI: 2.546-10.757, $p < 0.01$). CONCLUSIONS: The present study firstly showed that elevated PCSK9 levels were related to multiple CVMMs and MACEs in stable CAD with diabetes, suggesting that plasma PCSK9 measurement could help to identify diabetic patients with CAD at higher cardiovascular risk. More studies may be needed to confirm our findings.

[20] *Wang L, Zheng ZG, Meng L et al.* **Statins induce skeletal muscle atrophy via GGPP depletion-dependent myostatin overexpression in skeletal muscle and brown adipose tissue**. Cell Biol Toxicol 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33034787
ABSTRACT
Myopathy is the major adverse effect of statins. However, the underlying mechanism of statin-induced skeletal muscle atrophy, one of statin-induced myopathy, remains to be elucidated. Myostatin is a negative regulator of skeletal muscle mass and functions. Whether myostatin is involved in statin-induced skeletal muscle atrophy remains unknown. In this study, we uncovered that simvastatin administration increased serum myostatin levels in mice. Inhibition of myostatin with follistatin, an antagonist of myostatin, improved simvastatin-induced skeletal muscle atrophy. Simvastatin induced myostatin expression not only in skeletal muscle but also in brown adipose tissue (BAT). Mechanistically, simvastatin inhibited the phosphorylation of forkhead box protein O1 (FOXO1) in C2C12 myotubes, promoting the nuclear translocation of FOXO1 and thereby stimulating the transcription of myostatin. In differentiated brown adipocytes, simvastatin promoted myostatin expression mainly by inhibiting the expression of interferon regulatory factor 4 (IRF4). Moreover, the stimulative effect of simvastatin on myostatin expression was blunted by geranylgeranyl diphosphate (GGPP) supplementation in both myotubes and brown adipocytes, suggesting that GGPP depletion was attributed to simvastatin-induced myostatin expression. Besides, the capacities of statins on stimulating myostatin expression were positively correlated with the lipophilicity of statins. Our findings provide new insights into statin-induced skeletal muscle atrophy. Graphical headlights 1. Simvastatin induces skeletal muscle atrophy via increasing serum myostatin levels in mice; 2. Simvastatin promotes myostatin expression in both skeletal muscle and brown adipose tissue

through inhibiting GGPP production; 3. The stimulating effect of statins on myostatin expression is positively correlated with the lipophilicity of statins.

[21] *Lima LR, Nascimento LM, Gomes KRO et al.* **[Association between ultra-processed food consumption and lipid parameters among adolescents]**. Ciencia & saude coletiva 2020; 25:4055-4064.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33027399
ABSTRACT
The scope of this study was to analyze the association between ultra-processed food (UPF) consumption and lipid parameters. It was a cross-sectional study performed with high school adolescents. Food consumption was analyzed by means of a 24-hour food recall form, where UPF were identified in line with the NOVA system of food classification. The total cholesterol levels, HDL-c and triglycerides were determined by enzymatic colorimetry and the LDL-c fraction estimated by formula. The Student's t-test or Mann-Whitney was used to compare averages, and linear regression to make associations among the variables. The results show that UPF consumption was more frequent in female adolescents between 17 and 19 years of age, with a family income above two minimum wages and from private schools. It was observed that individuals in the upper third of UPF consumption had a higher energetic, carbohydrate and sodium intake, with a lower intake of proteins and fibers. Moreover, it was found that a higher UPF intake was negatively associated with HDL-c levels and positively associated with triglyceride levels and dyslipidemia. Therefore, UPF is associated with a worsening of the nutritional profile of the diet and contributes to negative changes in the lipid parameters of young individuals.

[22] *Ashraf J, Ali Khan M, Minhaj S et al.* **Statins and Abnormal Liver Function Tests: Is There a Correlation?** Cureus 2020; 12:e10145.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33014643
ABSTRACT
Background Statins or 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitors are one of the most commonly prescribed medications in cardiac patients. Just like any other class of drugs, they have the potential to cause liver injury over time even with judicious use. This drug-induced liver injury (DILI) can be either direct (hepatocellular) or idiosyncratic. As with multiple other hepatic pathologies, DILI may be asymptomatic or clinically silent. Therefore, it is prudent to carry out liver function tests (LFTs) from time to time. LFTs are an inexpensive, noninvasive, and quick first-line investigation to monitor liver status. However, the pattern of liver injury with statin use is not specific and a correlation over time may not be apparent. Aims To evaluate derangement in LFTs over time with respect to statin use and determine if a correlation exists. Methods This was a retrospective observational cohort. All data were collected from the online database of the National Institute of Cardiovascular Diseases (NICVD), Karachi. Patients admitted to the NICVD from July 1, 2018, to December 31, 2018, were eligible for inclusion in the study. Only patients already taking a statin (in any dose) were considered for inclusion. LFTs were recorded from the database at inclusion, post-induction at six and 12 months. Extensive workup was done and great care taken to rule out other diseases that may have affected the LFTs. Results Two hundred and four patients were eventually inducted into the study after a meticulous exclusion process. The male to female ratio was 4:1. The mean duration of statin use before induction into the study

was 19.92±14.34 months. Patients were predominantly using only one of two statins, i.e., rosuvastatin 20mg/day or atorvastatin 40 mg/day. Elevations of LFTs were seen with both drugs throughout the study period. These elevations were almost always <2x the upper limit of normal (ULN); greater elevations were seen with atorvastatin 40 mg/day. The derangement in LFTs persisted and improvement was not seen. Conclusions Statins cause dose-dependent borderline elevations of liver function tests over time. These elevations are clinically and statistically insignificant and should not deter physicians from prescribing or continuing statins.

[23] *Kilic ID, Fabris E, Kedhi E et al.* **Intra-coronary Imaging for the Evaluation of Plaque Modifications Induced by Drug Therapies for Secondary Prevention**. Current atherosclerosis reports 2020; 22:76.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33025069
ABSTRACT
PURPOSE OF REVIEW: Patients diagnosed with coronary artery disease are at a high risk of subsequent cardiovascular events; therefore, secondary prevention in the form of therapeutic lifestyle changes, and drug therapies is vital. This article aims to review potential application of intra-coronary imaging for the evaluation of plaque modifications, induced by medications for secondary prevention for CAD. RECENT FINDINGS: Intra-coronary imaging provides detailed information on the atherosclerotic plaque which is the primary pathological substrate for the recurrent ischemic cardiovascular events. These modalities can detect features associated with high risk and allow serial in vivo imaging of lesions. Therefore, intravascular imaging tools have been used in landmark studies and played a role in improving our understanding of the disease processes. Changes in size and plaque composition over time can be evaluated by these tools and may help understanding the impact of a treatment. Moreover, surrogate imaging end points can be used when testing new drugs for secondary prevention.

[24] *Sterpetti AV*. **Inflammatory Cytokines and Atherosclerotic Plaque Progression. Therapeutic Implications**. Current atherosclerosis reports 2020; 22:75.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33025148
ABSTRACT
PURPOSE OF THE REVIEW: Inflammatory cytokines play a major role in atherosclerotic plaque progression. This review summarizes the rationale for personalized anti-inflammatory therapy. RECENT FINDINGS: Systemic inflammatory parameters may be used to follow the clinical outcome in primary and secondary prevention. Medical therapy, both in patients with stable cardiovascular disease, or with acute events, may be tailored taking into consideration the level and course of systemic inflammatory mediators. There is significant space for improvement in primary prevention and in the treatment of patients who have suffered from severe cardiovascular events, paying attention to not only blood pressure and cholesterol levels but also including inflammatory parameters in our clinical analysis. The potential exists to alter the course of atherosclerosis with anti-inflammatory drugs. With increased understanding of the specific mechanisms that regulate the relationship between inflammation and atherosclerosis, new, more effective and specific anti-inflammatory treatment may become available.

[25] *Harreiter J, Fadl H, Kautzky-Willer A, Simmons D*. **Do Women with Diabetes Need More Intensive Action for Cardiovascular Reduction than Men with Diabetes?** Current diabetes reports 2020; 20:61.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33033953
ABSTRACT
PURPOSE OF REVIEW: This narrative review makes the case for greater efforts to reduce cardiovascular disease (CVD) risk in women with diabetes. RECENT FINDINGS: In a recent meta-analysis including five CVOTs of diabetes medications with 46,606 subjects, women (vs men) with type 2 diabetes had a higher relative risk for stroke (RR 1.28; 95% CI 1.09, 1.50) and heart failure (1.30; 1.21, 1.40). Prior studies found higher "within-gender" RR for CVD mortality in women with diabetes although men have an absolute higher risk. Women with prior gestational diabetes mellitus (GDM) have a 2-fold higher CVD risk than the background population. Worse CVD and CVD risk factor management in women, as well as lower female therapy adherence, contribute further to these disparities. The mechanism behind this excess risk includes biological, hormonal, socioeconomic, clinical, and behavioral factors that still require further investigation. The need for more intensive CVD reduction in women now includes more attention to screening for both incident diabetes and CVD risk factors among high-risk women.

[26] *Paquin A, Poirier P, Beaudoin J, Piché ME*. **Secondary prevention after CABG: do new agents change the paradigm?** Current opinion in cardiology 2020; 35:664-672.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33038121
ABSTRACT
PURPOSE OF REVIEW: Coronary artery bypass graft (CABG) surgery remains the gold-standard treatment for multivessel and left main coronary artery disease. Despite significant improvement in cardiovascular outcomes, patients undergoing CABG remain at risk for recurrent adverse ischemic events and other cardiovascular outcomes (coronary revascularisation, stroke, cardiac death, etc.). The purpose of this review is to summarize the most recent evidence in pharmacological preventive therapies addressing the residual cardiovascular risk in patients who have undergone CABG. RECENT FINDINGS: Novel cardiovascular pharmacological preventive strategies targeting inflammatory, metabolic and prothrombotic (antiplatelet and anticoagulation) pathways have been recently assessed, with promising results for secondary prevention after CABG. SUMMARY: Secondary prevention is an essential part of postoperative care after CABG. Novel lipid-lowering and glucose-controlling agents suggest a strong and consistent benefit on native coronary artery disease and overall cardiovascular outcomes. The role and the choice of enhanced antiplatelet/anticoagulation/lipid/glucose-modulating therapies following CABG should be better defined and deserves further investigation. Additional studies are required to identify new therapeutic target addressing the specific multifactorial nature of the graft CV disease and identifying the best preventive strategies for long-term graft patency.

[27] *Nicholls SJ, Nelson AJ*. **The fish-oil paradox**. Current opinion in lipidology 2020; 31:356-361.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33027227
ABSTRACT

PURPOSE OF REVIEW: Increasing interest has focused on the potential cardioprotective effects of the omega-3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) on the basis of findings from epidemiology and cohort studies. This review will summarize the findings of contemporary clinical trials of omega-3 fatty acids. RECENT FINDINGS: Although a large clinical trial performed prior to the widespread use of statins demonstrated cardiovascular benefit with fish oils, subsequent studies have failed to reproduce this result. More recent studies have demonstrated a reduction in cardiovascular risk with administration of high-dose EPA, but not a carboxylic acid formulation containing both EPA and DHA or with lower doses of omega-3 fatty acids. SUMMARY: Administration of omega-3 fatty acids differing in either composition or dose produce variable effects on cardiovascular outcomes. This has implications for both the public health and pharmacological approach to cardiovascular prevention.

[28] *Wolska A, Yang ZH, Remaley AT*. **Hypertriglyceridemia: new approaches in management and treatment**. Current opinion in lipidology 2020; 31:331-339.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33027225
ABSTRACT
PURPOSE OF REVIEW: Hypertriglyceridemia (HTG), a form of dyslipidemia characterized by elevated plasma of triglycerides (TG), is associated with an increased risk for acute pancreatitis. Moreover, HTG has recently been shown to be linked to the development of atherosclerotic cardiovascular disease (ASCVD); therefore, there is a great interest in better understanding the pathophysiology of HTG and improving its clinical management. In this review, we briefly describe TG metabolism, recent guidelines for the clinical management of HTG and provide an overview of the current and potential new therapies for HTG. RECENT FINDINGS: Screening patients for HTG is valuable for not only identifying patients with extreme TG elevations, who are at risk for pancreatitis, but also for managing ASCVD risk in patients with more moderate forms of HTG. Therefore, the most recent USA guidelines for cardiovascular diseases recommend using TG as a risk enhancer test, leading to a more aggressive treatment of patients with intermediate risk. Currently, there are several available approaches for reducing plasma TG, which include lifestyle changes, fibrates and omega-3 fatty acid treatment. The addition of eicosapentaenoic acid (EPA) on top of statins has recently been shown to significantly reduce ASCVD events. Nevertheless, there is an unmet need for more effective treatment options. Several new therapies based on newly identified targets in TG metabolism, such as apolipoprotein C-III and angiopoietin-like 3 protein, are currently under development. SUMMARY: The clinical management of HTG is important in the prevention and treatment of acute pancreatitis and also impacts on how ASCVD risk is managed. More work needs to be done to establish the mechanism for the ability of how EPA lowers ASCVD and how to best integrate it with other lipid-lowering therapies. The efficacy and safety of the novel therapies for HTG should be established soon in the ongoing late-stage clinical trials.

[29] *Muñoz AE, Pollarsky F, Marino M et al.* **Safety of Chronic Simvastatin Treatment in Patients with Decompensated Cirrhosis: Many Adverse Events but No Liver Injury**. Digestive diseases and sciences 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33033975
ABSTRACT

BACKGROUND: The high mortality rate of decompensated cirrhosis underlines the need for new treatments. Experimental models of cirrhosis and its reported relationship with atherosclerotic cardiovascular disease have provided data supporting the rational use of statins in these patients. However, little is known about the safety of statins in this setting. AIM: We evaluate the safety of chronic simvastatin treatment in patients with decompensated cirrhosis. METHODS: We conducted a prospective, open, uncontrolled, phase 2a trial in 30 patients with Child-Pugh class A (n = 6), B (n = 22), and C (n = 2) decompensated cirrhosis. The patients received standard treatment throughout the trial plus simvastatin 20 mg/day for 2 weeks and thereafter simvastatin 40 mg/day up to 1 year. RESULTS: Sixteen out of 30 patients (53.3%) showed adverse events, including gastrointestinal toxicity (36.7%), muscle injury (MI) (36.7%), and headache (13.3%). No liver injury was registered. Due to MI alone, simvastatin dosage was reduced in 23.4% of cases and transiently interrupted in 13.3%. Once these adverse events were overcome, simvastatin was resumed until the end of the trial. MI was associated with baseline MELD score > 12 ($p = 0.035$) and with baseline Child-Pugh class C. No MI was associated with final Child-Pugh score ≤ 6 ($p = 0.030$) or final Child-Pugh class A ($p = 0.020$). CONCLUSIONS: Chronic treatment with simvastatin 40 mg/day in patients with decompensated cirrhosis was associated with several adverse events, being MI the only clinically significant one, which appears to be related to the simvastatin dosage and the degree of cirrhosis severity. Noticeably, no liver injury was recorded.

[30] *Ling Y, Tang S, Cao Y, Fu C*. **Relationship between Plasma Lipoprotein-Associated Phospholipase A2 Concentrations and Apolipoprotein in Stable Coronary Artery Disease Patients**. Disease markers 2020; 2020:8818358.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33029257

ABSTRACT

BACKGROUND: Increasing evidence states that the plasma lipoprotein-associated phospholipase A2 (Lp-PLA2) levels and apolipoprotein particles are regarded as the risk maker for cardiovascular heart disease. Nevertheless, the issue about whether Lp-PLA2 is associated with apolipoprotein particles in individuals who have been diagnosed as stable coronary artery disease (CAD) remains largely unexplored. METHOD: All 569 participants engaged in this research, who never took lipid-lowering drugs, had been divided into groups by the coronary angiography (CAG), namely, stable CAD: n = 291; non-CAD: n = 278. The results concerning Lp-PLA2 levels were calculated by Elisa Kit, while apolipoprotein particles were measured by the department of laboratory. RESULTS: The plasma concentration of Lp-PLA2 was remarkably higher in stable CAD group than the non-CAD group (136.0 ± 60.5 ng/mL vs. 113.2 ± 65.6 ng/mL, $P < 0.001$). Pearson correlation analyses explained the plasma Lp-PLA2 concentration was correlated with apoB ($r = 0.390$, $P < 0.001$) and apoB/apoA1 ($r = 0.450$, $P < 0.001$), not associated with apoA1 ($r = -0.099$, $P = 0.101$). Conversely, the association remains unobserved among non-CAD patients except apoA1. Moreover, multiple linear regression revealed the relations between Lp-PLA2 concentrations and apoB ($\beta = 0.390$, $P < 0.001$), as well as apoB/apoA1 ($\beta = 0.450$, $P < 0.001$), but not apoA1 ($\beta = -0.099$, $P = 0.121$). After adjustment for several risk factors regarding CAD, like hypertension, gender, smoking, age, and diabetes mellitus, there had still been positive associations between the Lp-PLA2 concentration and apoB ($\beta = 0.364$, $P < 0.001$), as well as apoB/apoA1 ($\beta = 0.390$, $P < 0.001$). CONCLUSION: The plasma levels of Lp-PLA2 provide positively a key link with apoB,

apoB/apoA-1 among stable CAD, denoting the communication between Lp-PLA2 and apolipoprotein particles in the state of CAD.

[31] *Sane R, Cheung KWK, Kovács P et al.* **Calibrating the in vitro-in vivo correlation for OATP mediated drug-drug interactions with rosuvastatin using static and PBPK models**. Drug metabolism and disposition: the biological fate of chemicals 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33037044
ABSTRACT
Organic anion transporting polypeptide (OATP) 1B1/3 mediated drug-drug interaction (DDI) potential is evaluated in vivo with rosuvastatin (RST) as a probe substrate in clinical studies. We calibrated our assay with RST and estradiol 17-β-D-glucuronide (E217βG)/ cholecystokinin-8 (CCK8) as in vitro probes for qualitative and quantitative prediction of OATP1B-mediated DDI potential for RST. In vitro OATP1B1/1B3 inhibition using E217βG and CCK8 yielded higher AUC ratio (AUCR) values numerically with the static model, but all probes performed similarly from a qualitative cutoff-based prediction, as described in regulatory guidances. However, the magnitudes of DDI were not captured satisfactorily. Considering that clearance of RST is also mediated by gut breast cancer resistance protein (BCRP), inhibition of BCRP was also incorporated in the DDI prediction if the gut inhibitor concentrations were 10 x IC50 for BCRP inhibition. This combined static model closely predicted the magnitude of RST DDI with root mean square error values of 0.767-0.812 and 1.24-1.31, with and without BCRP inhibition, respectively for in vitro-in vivo- correlation of DDI. Physiologically-based pharmacokinetic (PBPK) modeling was also used to simulate DDI between RST and rifampicin, asunaprevir, and velpatasvir. Predicted AUCR for rifampicin and asunaprevir was within 1.5-fold of that observed, whereas that for velpatasvir showed a 2-fold under-prediction. Overall, the combined static model incorporating both OATP1B and BCRP inhibition provides a quick and simple mathematical approach to quantitatively predict the magnitude of transporter-mediated DDI for RST for routine application. PBPK complemented the static model and provides a framework when a dynamic model is needed. Significance Statement Using 22 drugs, we show that a static model for OATP1B1/1B3 inhibition can qualitatively predict potential for DDI using a cut-off based approach as in regulatory guidances. However, consideration of both OATP1B1/3 and gut BCRP inhibition provided a better prediction of the magnitude of the transporter-mediated DDI of these inhibitors with rosuvastatin. Based on these results, we have proposed an empirical mechanistic-static approach for a more reliable prediction of transporter-mediated DDI liability with rosuvastatin that drug development teams can leverage.

[32] *Nashimoto S, Takekawa Y, Takekuma Y et al.* **Transport via Niemann-Pick C1 Like 1 contributes to the intestinal absorption of ubiquinone**. Drug metabolism and pharmacokinetics 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33036883
ABSTRACT
Ubiquinone, which is a component in the electron-transport systems of mitochondria, is essential for various activities related to energy metabolism, but the detailed absorption mechanism of ubiquinone is not clear. On the other hand, Niemann-Pick C1 Like 1 (NPC1L1) is involved in the intestinal absorption of fat-soluble components such as cholesterol. In this study, we investigated whether the intestinal absorption of ubiquinone was transported by

NPC1L1 as is cholesterol. In this study, coenzyme q10 (CoQ10) and coenzyme q9 (CoQ9) were used as models of ubiquinone. The transport activity of ubiquinone was increased significantly in NPC1L1-overexpressed Madin-Darby canine kidney (MDCK) cells compared with that in pMAM2-BSD vector-transfected MDCK cells and the uptake of ubiquinone was decreased in the presence of ezetimibe, an inhibitor of NPC1L1. These results indicate that NPC1L1 mediates the transport of ubiquinone. Furthermore, to clarify the effect of NPC1L1 on the intestinal absorption of CoQ10, emulsified CoQ10 was orally administered to Wistar rats, and the plasma concentration was measured. The plasma concentration of CoQ10 was significantly decreased by coadministration of ezetimibe and CoQ10 compared to that with administration of only CoQ10. This result indicates that the intestinal absorption of CoQ10 is mediated by NPC1L1.

[33] *Paton DM*. **Bempedoic acid: effect of ATP-citrate lyase inhibition on low-density lipoprotein cholesterol and other lipids**. Drugs of today (Barcelona, Spain : 1998) 2020; 56:573-582.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33025951
ABSTRACT
Bempedoic acid is a new, first-in-class oral ATP-citrate lyase (ACLY) inhibitor that has to be converted to its CoA thioester before it inhibits ACLY. This conversion only occurs in the liver and not in skeletal muscle. This may explain why, unlike the statins, bempedoic acid does not cause myalgia. Bempedoic acid given at a dosage of 180 mg orally once daily produces a highly significant reduction in low-density lipoprotein cholesterol (LDL-C), non-high-density lipoprotein cholesterol, total cholesterol, apolipoprotein B and importantly also in high-sensitivity C-reactive protein. It has recently been approved by both the Food and Drug Administration (FDA) and the European Commission for use in adult patients with heterozygous familial hypercholesterolemia or atherosclerotic cardiovascular disease who require additional lowering of LDL-C, and for the treatment of adults with primary hypercholesterolemia (heterozygous familial and nonfamilial) or mixed dyslipidemia, respectively.

[34] *Feng JL, Qin X*. **Lipid-lowering medication use and cancer-specific survival among endometrial or lung cancer patients: an Australian nationwide cohort study**. Eur J Clin Pharmacol 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33030570
ABSTRACT
PURPOSE: Inconsistent results of lipid-lowering medications (LLMs) on improved cancer survival need more investigations. We tested the hypothesis that adherence to the drug would be associated with a lower cancer-specific mortality in a homogeneous population who has ever used the drug. METHODS: Utilising data from the Australian Cancer database, linked to the Pharmaceutical Benefits Scheme data and the National Death Index, we identified two separate cohorts of 4519 and 3083 women patients with newly diagnosed endometrial and lung cancer respectively between 2003 and 2013. Adherence to this drug was calculated by proportion of days covered. Cox regression models with time-varying covariates were used to estimate the multivariable-adjusted cause-specific hazard ratios (HRs) and 95% confidence intervals (CIs) for the association of adherence to LLMs, statins, lipophilic and hydrophilic statins, and cancer-specific mortality. RESULTS: Each 10% increase in 1-year adherence to

LLMs reduced cancer-specific mortality among women with endometrial cancer (adjusted HR=0.93, 95% CI 0.90-0.96) or lung cancer (adjusted HR=0.95, 95% CI 0.93-0.97). The inverse associations remained unchanged in different subgroup analyses. The reductions in lung cancer mortality were not apparent for women who adhered to lipophilic statins albeit better endometrial cancer survival appeared in the lipophilic statin group and borderline statistical improvement in the hydrophilic statin group. CONCLUSIONS: Among LLM users, adherence to this drug is inversely associated with reduced cancer-specific mortality. Together with previous evidence, randomised controlled trials are called for to confirm whether LLMs could be considered as an adjuvant treatment to improve prognosis.

[35] *Ferrari F, Martins VM, Rocha VZ, Santos RD*. **Advances with lipid-lowering drugs for pediatric patients with familial hypercholesterolemia**. Expert opinion on pharmacotherapy 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33016816
ABSTRACT
INTRODUCTION: Familial hypercholesterolemia (FH) is a frequent genetic disorder characterized by elevated LDL-cholesterol (LDL-C) and early onset of atherosclerosis. AREAS COVERED: The authors provide an overview of the pediatric FH scenario, with emphasis on the role of statins as the preferred pharmacological therapy, discussing their potential benefits, as well as adverse effects, and the remaining uncertainties about their use in this population. They also comment on other lipid lowering therapies. EXPERT OPINION: Statin therapy is recommended after the ages of 8-10 years old for heterozygous FH patients and can reduce LDL-C by 24-50% depending on drug type and dosage. For more severe cases, higher doses and adjuvant therapies like ezetimibe may be necessary and treatment should be started at diagnosis, as is the case of homozygous FH. Statins reduce progression of subclinical vascular disease and may reduce early cardiovascular events. The available evidence indicates safety of statins in children with no apparent harms related to growth, sexual maturation, steroid hormones, glucose levels, cognitive function, or muscle and liver problems, in comparison with placebo. Newer treatments like lomitapide, PCSK9 inhibitors, bempedoic acid and evinacumab need to be adequately evaluated in pediatric FH patients with more severe dyslipidemia.

[36] *Jin B, Lin H, Yuan J et al.* **Abdominal Adiposity and Total Body Fat as Predictors of Cardiometabolic Health in Children and Adolescents With Obesity**. Frontiers in endocrinology 2020; 11:579.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33013688
ABSTRACT
Objective: We aimed to assess the role of adipose tissue distribution in cardiometabolic risk (in particular insulin sensitivity) in a population of children and adolescents with obesity. Methods: In this cross-sectional study, participants were 479 children and adolescents with obesity (322 boys and 157 girls) aged 3 to 18 years attending the Children's Hospital at Zhejiang University School of Medicine (Hangzhou, China). Clinical assessments included anthropometry, body composition (DXA scans), carotid artery ultrasounds, and OGTT. Insulin sensitivity was assessed using the Matsuda index. Participants were stratified into groups by sex and pubertal stage. Key predictors were DXA-derived android-to-gynoid-fat ratio (A/G) and total body fat percentage (TBF%). Results: Irrespective of sex and pubertal stage, there was a strong

association between increasing A/G (i.e., greater abdominal adiposity) and lower insulin sensitivity. In multivariable models, every 0.1 increase in A/G was associated with a reduction in insulin sensitivity in prepubertal boys [-29% (95% CI -36%, -20%); p < 0.0001], pubertal boys [-13% (95% CI -21%, -6%); p = 0.001], and pubertal girls [-16% (95% CI -24%, -6%); p = 0.002]. In contrast, TBF% was not associated with insulin sensitivity when A/G was adjusted for, irrespective of pubertal stage or sex. In addition, every 0.1 increase in A/G was associated with increased likelihood of dyslipidemia in prepubertal boys [adjusted odds ratio (aOR) 1.62 (95% CI 1.05, 2.49)], impaired glucose tolerance in pubertal boys [aOR 1.64 (95% CI 1.07, 2.51)] and pubertal girls [aOR 1.81 (95% CI 1.10, 2.98)], and odds of NAFLD in both prepubertal [aOR 2.57 (95% CI 1.56, 4.21)] and pubertal [aOR 1.69 (95% CI 1.18, 2.40)] boys. In contrast, higher TBF% was only associated with higher fasting insulin and ALT in pubertal boys, being also predictive of NAFLD in this group [aOR 1.15 per percentage point (95% CI 1.06, 1.26)], but was not associated with the likelihood of other cardiometabolic outcomes assessed in any group. Conclusions: A/G is a much stronger independent predictor of cardiometabolic risk factors in children and adolescents with obesity in China, particularly glucose metabolism.

[37] *Silva GM, França-Falcão MS, Calzerra NTM et al.* **Role of Renin-Angiotensin System Components in Atherosclerosis: Focus on Ang-II, ACE2, and Ang-1-7**. Front Physiol 2020; 11:1067.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33013457
ABSTRACT
Atherosclerosis is the leading cause of vascular disease worldwide and contributes significantly to deaths from cardiovascular complications. There is a remarkably close relationship between atherosclerotic plaque formation and the activation of renin-angiotensin system (RAS). However, depending on which RAS pathway is activated, pro- or anti-atherogenic outcomes may be observed. This brief review focuses on the role of three of the most important pieces of RAS axis, angiotensin II (Ang-II), angiotensin converting enzyme type 2 (ACE2), and angiotensin 1-7 (Ang-1-7) and their involvement in atherosclerosis. We focused on the effects of these molecules on vascular function and inflammation, which are important determinants of atherogenesis. Furthermore, we highlighted potential pharmacological approaches to treat this disorder.

[38] *de Vries E, Bolier R, Goet J et al.* **Fibrates for itch (FITCH) in fibrosing cholangiopathies: a double blind, randomized, placebo-controlled trial**. Gastroenterology 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33031833
ABSTRACT
BACKGROUND AND AIMS: Pruritus may seriously impair quality of life in patients with cholestatic diseases such as primary or secondary sclerosing cholangitis (PSC, SSC) and primary biliary cholangitis (PBC). Pharmacological strategies show limited efficacy and can provoke serious side effects. We hypothesized that bezafibrate, a broad peroxisome proliferator-activated receptor (PPAR) agonist, relieves cholestasis-associated itch by alleviating hepatobiliary injury. The aim of this investigator-initiated FITCH trial ("Fibrates for cholestatic ITCH") was to assess effects of bezafibrate on pruritus in patients with PSC, PBC and SSC. METHODS: Patients with moderate to severe pruritus (>5 out of 10 on visual

analogue scale (VAS)) due to PSC, PBC or SSC were recruited for this double-blind, randomized, placebo-controlled trial between 2016 and 2019. Patients received once-daily bezafibrate (400mg) or placebo for 21 days. The primary endpoint was >50% reduction of pruritus (VAS; intention-to-treat). RESULTS: 70 of 74 randomized patients completed the trial (95%; 44 PSC, 24 PBC, 2 SSC). For the primary endpoint, bezafibrate led in 45% (41% PSC, 55% PBC), placebo in 11% to >50% reduction of severe or moderate pruritus (p=0.003). For secondary endpoints, bezafibrate reduced morning (p=0.01 vs. placebo) and evening (p=0.007) intensity of pruritus (VAS) and improved the validated 5D-itch-questionnaire (p=0.002 vs. placebo). Bezafibrate also reduced serum alkaline phosphatase (-35%, p=0.03 vs. placebo) correlating with improved pruritus (VAS, p=0.01) suggesting reduced biliary damage. Serum bile acids and autotaxin activity remained unchanged. Serum creatinine levels tended to mildly increase (3% bezafibrate, 5% placebo, p=0.14). CONCLUSION: Bezafibrate is superior to placebo in improving moderate to severe pruritus in patients with PSC and PBC. TRIAL REGISTRATION: Netherlands Trial Register, ID: NTR5436 (3 August 2015), ClinicalTrials.gov ID: NCT02701166 (2 March 2016).

[39] *Kaddoura R, Orabi B, Salam AM*. **PCSK9 Monoclonal Antibodies: An Overview**. Heart views : the official journal of the Gulf Heart Association 2020; 21:97-103.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33014302
ABSTRACT
PCSK9 monoclonal antibodies are novel lipid-lowering therapy that have been extensively studied in patients with hypercholesterolemia either as monotherapy or as an add-on to other LLTs. PCSK9 monoclonal antibodies have significantly reduced the low-density lipoprotein cholesterol (LDL-C) plasma level resulting in a better LDL-C goal attainment. The commercially available PCSK9 monoclonal antibodies, alirocumab and evolocumab, have demonstrated reductions in major adverse cardiovascular events such as myocardial infarction, stroke, unstable angina, and the need for coronary revascularization but not mortality. PCSK9 monoclonal antibodies have demonstrated a favorable safety profile. The most reported side effects are mild injection site with no causal relationship proven between the inhibition of PCSK9 and neurocognitive or glycemic adverse events. In this overview, the efficacy and safety of PCSK9 monoclonal antibodies in the treatment of primary and familial hypercholesterolemia will be discussed.

[40] *Shehab A, Bhagavathula AS*. **Statin Therapy and Low-Density Lipoprotein Cholesterol Reduction after Acute Coronary Syndrome: Insights from the United Arab Emirates**. Heart views : the official journal of the Gulf Heart Association 2020; 21:80-87.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33014300
ABSTRACT
BACKGROUND AND AIMS: Attaining guideline-recommended low-density lipoprotein cholesterol (LDL-C) goals (<70 mg/dl or ≥ 50% reduction) with statin therapy remains suboptimal after an acute coronary syndrome (ACS). This study aimed to assess the level of lipid-lowering therapy (LLT) utilization and achievement of LDL-C targets after ACS hospitalization in the United Arab Emirates (UAE). METHODS: A retrospective, observational, longitudinal database analysis of Emirati patients with ACS or stable coronary heart disease was evaluated from January 2015 to June 2018. Patients were divided based on whether or not they were treated with LLT at index hospitalization with ACS. LDL-C target level

achievement was assessed according to the 2013 American College of Cardiology/American Heart Association and European Society of Cardiology/European Atherosclerosis Society guidelines. RESULTS: A total of 3,066 patients (mean age 65.5 ± 14 years) met the inclusion criteria. Overall, 58.1% (n = 1782) of the patients in the cohort were on LLT during the ACS hospitalization. At discharge, the mean LDL-C level was 84.8 ± 39.0 mg/dl, and 28%, 21%, and 9% received high-, moderate-, and low-intensity statins, respectively. At 6 months (n = 2046; 66.7%), 27.7% and 16.7% achieved an LDL-C of <70 mg/dl and 70-100 mg/dl, respectively. The highest level of LDL-C reduction by 50% within 6 months was observed among patients using moderate-intensity statin (37.2%). CONCLUSION: A large proportion of Emirati patients were not on LLT after ACS, and the rate of LDL-C target value attainment was extremely poor (27.7%). Optimal statin utilization by closely implementing the guidelines in the UAE is recommended.

[41] *Vavuranakis MA, Jones SR, Cardoso R et al.* **«The role of Lipoprotein(a) in cardiovascular disease; Current concepts and future perspectives»**. Hellenic journal of cardiology : HJC = Hellenike kardiologike epitheorese 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33039574
ABSTRACT
High lipoprotein(a) [Lp(a)] levels are associated with the development of atherosclerotic cardiovascular disease (ASCVD) and with calcific aortic valve stenosis (CAVS) both observationally and causally from human genetic studies. The mechanisms are not well characterized but likely involve its role as a carrier of oxidized phospholipids (OxPLs), which are known to be increased in pro-inflammatory states, to induce pro-inflammatory changes in monocytes leading to plaque instability, and to impair vascular endothelial cell function, a driver of acute and recurrent ischemic events. In addition, Lp(a) itself has prothrombotic activity. Current lipid lowering strategies do not sufficiently lower Lp(a) serum levels. Lp(a)-specific lowering drugs, targeting apolipoprotein(a) synthesis, lower Lp(a) by up to 90% and are being evaluated in ongoing clinical outcome trials. This review summaries the current knowledge on the associations of Lp(a) with ASCVD and CAVS, the current role of Lp(a) assessment in the clinical setting, as well as emerging Lp(a) specific lowering therapies.

[42] *Machado-Lima A, López-Díez R, Iborra RT et al.* **RAGE Mediates Cholesterol Efflux Impairment in Macrophages Caused by Human Advanced Glycated Albumin**. International journal of molecular sciences 2020; 21.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33019603
ABSTRACT
We addressed the involvement of the receptor for advanced glycation end products (RAGE) in the impairment of the cellular cholesterol efflux elicited by glycated albumin. Albumin was isolated from type 1 (DM1) and type 2 (DM2) diabetes mellitus (HbA1c > 9%) and non-DM subjects (C). Moreover, albumin was glycated in vitro (AGE-albumin). Macrophages from Ager null and wild-type (WT) mice, or THP-1 transfected with siRNA-AGER, were treated with C, DM1, DM2, non-glycated or AGE-albumin. The cholesterol efflux was reduced in WT cells exposed to DM1 or DM2 albumin as compared to C, and the intracellular lipid content was increased. These events were not observed in Ager null cells, in which the cholesterol efflux and lipid staining were, respectively, higher and lower when compared to WT cells. In WT, Ager, Nox4 and Nfkb1, mRNA increased and Scd1 and Abcg1 diminished after treatment with

DM1 and DM2 albumin. In Ager null cells treated with DM-albumin, Nox4, Scd1 and Nfkb1 were reduced and Jak2 and Abcg1 increased. In AGER-silenced THP-1, NOX4 and SCD1 mRNA were reduced and JAK2 and ABCG1 were increased even after treatment with AGE or DM-albumin. RAGE mediates the deleterious effects of AGE-albumin in macrophage cholesterol efflux.

[43] *Nguyen LT, Saad S, Chen H, Pollock CA*. **Parental SIRT1 Overexpression Attenuate Metabolic Disorders Due to Maternal High-Fat Feeding**. International journal of molecular sciences 2020; 21.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33027895
ABSTRACT
Maternal obesity can contribute to the development of obesity and related metabolic disorders in progeny. Sirtuin (SIRT)1, an essential regulator of metabolism and stress responses, has recently emerged as an important modifying factor of developmental programming. In this study, to elucidate the effects of parental SIRT1 overexpression on offspring mechanism, four experimental groups were included: (1) Chow-fed wild-type (WT)-dam × Chow-fed WT-sire; (2) High-fat diet (HFD)-fed WT-dam × Chow-fed WT-sire; (3) HFD-fed hemizygous SIRT1-transgenic (Tg)-dam × Chow-fed WT-sire; and (4) HFD-fed WT dam × Chow-fed Tg-sire. Our results indicate that Tg breeders had lower body weight and fat mass compared to WT counterparts and gave birth to WT offspring with reductions in body weight, adiposity and hyperlipidaemia compared to those born of WT parents. Maternal SIRT1 overexpression also reversed glucose intolerance, and normalised abnormal fat morphology and the expression of dysregulated lipid metabolism markers, including SIRT1. Despite having persistent hepatic steatosis, offspring born to Tg parents showed an improved balance of hepatic glucose/lipid metabolic markers, as well as reduced levels of inflammatory markers and TGF-β/Smad3 fibrotic signalling. Collectively, the data suggest that parental SIRT1 overexpression can ameliorate adverse metabolic programming effects by maternal obesity.

[44] *Bhuiyan N, Kang JH, Papalia Z et al.* **Assessing the stress-buffering effects of social support for exercise on physical activity, sitting time, and blood lipid profiles**. J Am Coll Health 2020:1-7.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33026309
ABSTRACT
OBJECTIVE: This study tested the hypothesized stress-buffering effects of social support on physical activity, sitting time, and blood lipid profiles. PARTICIPANTS: 537 college students. METHODS: College students volunteered to self-report stress, social support for exercise, physical activity and sitting time, and provided blood samples to assess lipid profiles in this cross-sectional study. RESULTS: Lower stress was associated with higher vigorous physical activity ($\beta = -0.1$, $t = -2.9$, $p = .004$). Higher social support was associated with higher moderate ($\beta = 0.2$, $t = 2.0$, $p = .042$), vigorous ($\beta = 0.5$, $t = 5.4$, $p < .001$), and total ($\beta = 0.1$, $t = 3.2$, $p = .001$) physical activity, and lower sitting time on weekdays ($\beta = -0.1$, $t = -3.3$, $p = .001$) and weekends ($\beta = -0.2$, $t = -3.6$, $p < .001$). Social support moderated the association between stress and sitting time on weekdays. CONCLUSIONS: Stress reduction and fostering social support may be important strategies for promoting physical activity and reducing sedentary behaviors in college students. Additional strategies are needed to buffer the deleterious effects of stress.

[45] *Kojima K, Hiro T, Koyama Y et al.* **High Wall Shear Stress Is Related to Atherosclerotic Plaque Rupture in the Aortic Arch of Patients with Cardiovascular Disease: A Study with Computational Fluid Dynamics Model and Non-Obstructive General Angioscopy**. Journal of atherosclerosis and thrombosis 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33012739
ABSTRACT
AIMS: Wall shear stress (WSS) has been considered a major determinant of aortic atherosclerosis. Recently, non-obstructive general angioscopy (NOGA) was developed to visualize various atherosclerotic pathologies, including in vivo ruptured plaque (RP) in the aorta. However, the relationship between aortic RP and WSS distribution within the aortic wall is unclear. This study aimed to investigate the relationship between aortic NOGA-derived RP and the stereographic distribution of WSS by computational fluid dynamics (CFD) modeling using three-dimensional computed tomography (3D-CT) angiography. METHODS: We investigated 45 consecutive patients who underwent 3D-CT before coronary angiography and NOGA during coronary angiography. WSS in the aortic arch was measured by CFD analysis based on the finite element method using uniform inlet and outlet flow conditions. Aortic RP was detected by NOGA. RESULTS: Patients with a distinct RP showed a significantly higher maximum WSS value in the aortic arch than those without aortic RP (56.2±30.6 Pa vs 36.2±19.8 Pa, p=0.017), no significant difference was noted in the mean WSS between those with and without aortic RP. In a multivariate logistic regression analysis, the presence of a maximum WSS value more than a specific value was a significant predictor of aortic RP (odds ratio 7.21, 95% confidence interval 1.78-37.1, p=0.005). CONCLUSIONS: Aortic RP detected by NOGA was strongly associated with a higher maximum WSS in the aortic arch derived by CFD using 3D-CT. The maximum WSS value may have an important role in the underlying mechanism of not only aortic atherosclerosis, but also aortic RP.

[46] *Okada T, Sumida M, Ohama T et al.* **Development and Clinical Application of an Enzyme-Linked Immunosorbent Assay for Oxidized High-Density Lipoprotein**. Journal of atherosclerosis and thrombosis 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33028763
ABSTRACT
AIMS: HDL particles have various anti-atherogenic functions, whereas HDL from atherosclerotic patients was demonstrated to be dysfunctional. One possible mechanism for the formation of dysfunctional HDL is the oxidation of its components. However, oxidized HDLs (Ox-HDLs) remain to be well investigated due to lack of reliable assay systems. METHODS: We have developed a novel sandwich enzyme-linked immunosorbent assay (ELISA) for Ox-HDL by using the FOH1a/DLH3 antibody, which can specifically recognize oxidized phosphatidylcholine, a major component of HDL phospholipid (HDL-PL). We defined forced oxidation of 1 mg/L HDL-PL as 1 U/L Ox-HDL. We assessed serum Ox-HDL levels of normolipidemic healthy subjects (n=94) and dyslipidemic patients (n=177). RESULTS: The coefficients of variation of within-run and between-run assays were 12.5% and 13.5%. In healthy subjects, serum Ox-HDL levels were 28.5±5.0 (mean±SD) U/L. As Ox-HDL levels were moderately correlated with HDL-PL (r=0.59), we also evaluated the Ox-HDL/HDL-PL ratio, which represents the proportion of oxidized phospholipids in HDL particles. In dyslipidemic patients, Ox-HDL levels were highly variable and ranged from 7.2 to 62.1U/L, and were extremely high (50.4±13.3U/L) especially in patients with hyperalphalipoproteinemia due to

cholesteryl ester transfer protein deficiency. Regarding patients with familial hypercholesterolemia, those treated with probucol, which is a potent anti-oxidative and anti-hyperlipidemic drug, showed significantly lower Ox-HDL (16.2±5.8 vs. 30.2±5.4, $p < 0.001$) and Ox-HDL/HDL-PL ratios (0.200±0.035 vs. 0.229±0.031, p=0.015) than those without probucol. CONCLUSION: We have established a novel sandwich ELISA for Ox-HDL, which might be a useful and easy strategy to evaluate HDL functionality, although the comparison study between this Ox-HDL ELISA and the assay of HDL cholesterol efflux capacity remains to be done. Our results indicated that probucol treatment may be associated with lower Ox-HDL levels.

[47] *Kulik A, Abreu AM, Boronat V, Ruel M*. **Impact of lipid levels and high-intensity statins on vein graft patency after CABG: Midterm results of the ACTIVE trial**. Journal of cardiac surgery 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33025656
ABSTRACT
BACKGROUND: High-dose atorvastatin did not improve 1-year vein graft patency in the recent Aggressive Cholesterol Therapy to Inhibit Vein Graft Events trial. However, it remains unknown whether high-intensity statins may impact graft disease in the years that follow. METHODS: In the trial, patients (N = 173) were randomized to receive atorvastatin 10 or 80 mg for 1 year after coronary bypass surgery (CABG). Beyond 1 year, the choice of statin was left to the patient's physician. In this study of participants who agreed to follow-up (N = 76), low-density lipoprotein (LDL) levels were measured and graft patency was assessed 3 years after surgery. RESULTS: The rate of vein graft disease 3 years after surgery was not significantly reduced with atorvastatin 80 mg during the first postoperative year or the use of open-label high-intensity statin thereafter (p = NS). However, a trend was observed between higher LDL levels during the first postoperative year and a greater incidence of vein graft disease at 3 years (p = .12). Among patients who had LDL levels more than 90 mg/dl in the first year after CABG, 38.5% had vein graft disease at 3 years, compared to 19.0% for those with LDL levels less than 90 mg/dl (p = .15). Higher mean LDL levels during the first postoperative year were associated with a higher rate of vein disease 3 years after surgery both at the graft level (p = .03) and at the patient level (p = .03) in multivariate analysis. CONCLUSIONS: Higher LDL levels during the first postoperative year were associated with significantly greater vein graft disease 3 years after CABG.

[48] *Kim M, Lee SP, Kwak S et al.* **Impact of age on coronary artery plaque progression and clinical outcome: A PARADIGM substudy**. Journal of cardiovascular computed tomography 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33032975
ABSTRACT
BACKGROUND: The association of age with coronary plaque dynamics is not well characterized by coronary computed tomography angiography (CCTA). METHODS: From a multinational registry of patients who underwent serial CCTA, 1153 subjects (61 ± 5 years old, 61.1% male) were analyzed. Annualized volume changes of total, fibrous, fibrofatty, necrotic core, and dense calcification plaque components of the whole heart were compared by age quartile groups. Clinical events, a composite of all-cause death, acute coronary syndrome, and any revascularization after 30 days of the initial CCTA, were also analyzed. Random forest

analysis was used to define the relative importance of age on plaque progression. RESULTS: With a 3.3-years' median interval between the two CCTA, the median annual volume changes of total plaque in each age quartile group was 7.8, 10.5, 10.8, and 12.1 mm(3)/year and for dense calcification, 2.5, 4.6, 5.4, and 7.1 mm(3)/year, both of which demonstrated a tendency to increase by age (p-for-trend = 0.001 and < 0.001, respectively). However, this tendency was not observed in any other plaque components. The annual volume changes of total plaque and dense calcification were also significantly different in the propensity score-matched lowest age quartile group versus the other age groups as was the composite clinical event (log-rank p = 0.003). In random forest analysis, age had comparable importance in the total plaque volume progression as other traditional factors. CONCLUSIONS: The rate of whole-heart plaque progression and dense calcification increases depending on age. Age is a significant factor in plaque growth, the importance of which is comparable to other traditional risk factors. CLINICAL TRIAL REGISTRATION: URL: http://www.clinicaltrials.gov. Unique identifiers: NCT02803411.

[49] *Taglieri N, Ghetti G, Bruno AG et al.* **Optical coherence tomography assessment of macrophages accumulation in non-ST-segment elevation acute coronary syndromes**. Journal of cardiovascular medicine (Hagerstown, Md.) 2020; 21:860-865.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33017123
ABSTRACT
AIMS: To investigate in patients with non-ST-segment elevation acute coronary syndrome (NSTE-ACS) the prevalence and the features of optical coherence tomography (OCT)-detected macrophages accumulation in culprit plaques as compared with nonculprit plaques (NCP). METHODS: The study is a post-hoc analysis of a prospective study aimed at evaluating the relationship between aortic inflammation as assessed by F-fluorodeoxyglucose-PET and features of coronary plaque vulnerability as assessed by OCT. We enrolled 32 patients with first NSTE-ACS who successfully underwent three-vessel OCT. RESULTS: The median age was 65 (54-72) years and 27 patients (84%) were men. Culprit plaques were clinically defined. Overall, the rate of lipid plaques and lipid plaques containing macrophages were 6.4 and 4.2 per patient, respectively. Culprit plaques had a smaller minimal luminal area, a higher extension of lipid component and a thinner fibrous cap than NCPs. Macrophages accumulations were more likely found in culprit plaque (84 vs. 61%, P=0.015) in which they had also a higher circumferential extension. On univariable analysis, macrophages accumulation extension had a higher association with culprit plaques (odds ratio=4.42; 95% confidence interval; 2.54-9.15, P<0.001) than the mere presence of macrophages accumulation (odds ratio=3.36; 95% confidence interval; 1.30-8.66, P=0.012). Culprit plaques with thrombus had a lower distance between macrophages accumulation and the luminal surface than culprit plaque with no thrombus (0.06 vs. 0.1mm; P=0.04). CONCLUSION: In patients with NSTE-ACS, macrophages accumulations are more likely present in culprit plaque in which they disclose also a greater extension compared with those observed in NCP. The distance between macrophages accumulation and the luminal surface is lower in thrombotic culprit plaque than that in nonthrombotic culprit plaque.

[50] *Li Y, Chen S, Zhao T, Li M*. **Serum IL-36 cytokines levels in type 2 diabetes mellitus patients and their association with obesity, insulin resistance, and inflammation**. Journal of clinical laboratory analysis 2020:e23611.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33034926

ABSTRACT

BACKGROUND: The interleukin (IL)-36 cytokines include IL-36α, IL-36β, IL-36γ, and IL-36Ra. Little was known about their roles in type 2 diabetes mellitus (T2DM). METHODS: The study included 40 T2DM patients and 42 healthy control subjects. The anthropometric and biochemical measurements were performed using automatic biochemical analyzer, high-performance liquid chromatography, and electrochemiluminescence immunoassay. Circulating IL-36α, IL-36γ, IL-36Ra, and IL-17 levels were determined by enzyme-linked immunosorbent assay. RESULTS: Serum IL-36α, IL-36γ, and IL-17 levels in T2DM patients were significantly higher than those in controls, whereas serum IL-36Ra levels in T2DM patients were lower. Correlation analysis showed that serum IL-36α was positively correlated with high sensitivity C-reactive protein. Serum IL-36α was negatively correlated with IL-36Ra. Serum IL-17 was negatively correlated with low-density lipoprotein cholesterol. CONCLUSIONS: This study demonstrated that T2DM patients displayed increased IL-36α and IL-36γ expression and decreased IL-36Ra expression. Moreover, the inflammatory cytokine levels were directly proportional to the inflammation and blood lipid levels. Our results suggest that IL-36 cytokines may be a new target for the diagnosis or treatment of T2DM.

[51] *Sun CJ, Brisson D, Gaudet D, Ooi TC*. **Relative effect of hypertriglyceridemia on non-HDLC and apolipoprotein B as cardiovascular disease risk markers**. Journal of clinical lipidology 2020.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33032940

ABSTRACT

BACKGROUND: Non-high density lipoprotein cholesterol (non-HDLC) represents the cholesterol in triglyceride-rich lipoproteins (TRL) and low-density lipoproteins (LDL). Apolipoprotein B (apoB) reflects the number of TRL and LDL particles. In hypertriglyceridemia (HTG), there is triglyceride (TG) enrichment of TRLs, and also a substantial increase of cholesterol in larger TRLs that considerably augments the non-HDLC value. Therefore, in HTG, non-HDLC could increase disproportionately with respect to apoB. OBJECTIVE: We aimed to compare the relative effect of the full range of mild, moderate, and severe HTG on the status of non-HDLC and apoB as cardiovascular disease (CVD) risk markers. METHODS: Analysis of lipid profile data from 4347 patients in a Lipid Clinic cohort with baseline fasting lipid profiles documented prior to starting lipid-lowering medications. The correlation between non-HDLC and apoB was assessed in intervals of increasing TG. Non-HDLC and apoB were analyzed at each TG level using comparative CVD risk equivalent categories and assessed for divergence and discordance. RESULTS: With increasing TG levels: (1) the correlation between non-HDLC and apoB diminished progressively, (2) non-HDLC levels increased continuously, whereas apoB levels plateaued after an initial increase up to TG of ~ 4.0-5.0 mmol/L (~354-443 mg/dL), (3) there was divergence in the stratification of non-HDLC and apoB into CVD risk equivalent categories. CONCLUSIONS: Non-HDLC and apoB should not be viewed as interchangeable CVD risk markers in the presence of severe HTG. This has never been tested. With increasing HTG severity, discordance between non-HDLC and apoB can cause clinically important divergence in CVD risk categorization.

[52] *Underberg JA, Cannon CP, Larrey D et al.* **Long-term safety and efficacy of lomitapide in patients with homozygous familial hypercholesterolemia: Five-year data from the**

Lomitapide Observational Worldwide Evaluation Registry (LOWER). Journal of clinical lipidology 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33023859
ABSTRACT
BACKGROUND: Lomitapide is a lipid-lowering agent indicated as adjunct therapy for homozygous familial hypercholesterolemia (HoFH) in adults. OBJECTIVE: The Lomitapide Observational Worldwide Evaluation Registry is an international, observational registry assessing long-term safety, tolerability, and effectiveness of lomitapide. METHODS: This analysis examines 5-year data from the registry up to February 28, 2019. RESULTS: At lomitapide initiation, enrolled patients (N = 187) were a mean ± SD age of 52.2 ± 15.3 years with a mean ± SD low-density lipoprotein cholesterol (LDL-C) measurement of 232.0 ± 94.9 mg/dL. Exposure duration was up to 5.9 years (median, 1.98 years), and median dose was 10 mg (range, 5 mg QOD to 40 mg QD). After treatment, there was a mean 33% reduction in LDL-C (45% in patients remaining on lomitapide), 65.4% achieved LDL-C <100 mg/dL, and 41.1% achieved LDL-C <70 mg/dL. At year 4, the absolute mean change from baseline in LDL-C was -70.6 ± 76.21 mg/dL. Adverse events (AEs) occurred in 75.7% of patients, treatment-related AEs in 54.6%, and serious AEs in 22.2%; 23.2% of patients discontinued because of an AE. Events of special interest included gastrointestinal (13.5%), hepatic (15.1%), major adverse cardiovascular events (10.8%, resulting in 5 deaths), tumors (2.2%), and 4 pregnancies in 3 of 32 women of childbearing potential. CONCLUSION: The efficacy and safety of lomitapide are consistent with phase III trial data despite using a much lower median dose of 10 mg vs 40 mg in phase III. No new safety signals were identified. The incidence of AEs, serious AEs, and aminotransferase alanine transaminase elevations was lower than that seen in the phase III trial, potentially related to the lower median dose.

[53] *Lee J, Lee SH, Kim H et al.* **Low-density lipoprotein cholesterol reduction and target achievement after switching from statin monotherapy to statin/ezetimibe combination therapy: Real-world evidence**. Journal of clinical pharmacy and therapeutics 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33026659
ABSTRACT
WHAT IS KNOWN AND OBJECTIVES: This study investigated the additional low-density lipoprotein cholesterol (LDL-C) reductions and target (LDL-C < 100 mg/dL) achievement rates in patients after switching from statin monotherapy to statin/ezetimibe combination therapy, in clinical practice. METHODS: This retrospective study used data recovered from the electronic medical record systems of two tertiary care medical centres for patients treated between 2015 and 2017. Patients prescribed statin/ezetimibe combination therapy after switching from statin monotherapy were enrolled. The observed LDL-C reductions and the percentage of patients achieving LDL-C levels of <100 mg/dL, after 3 months of treatment, were assessed relative to baseline values. RESULTS AND DISCUSSION: A total of 4252 patients with prescriptions for statin/ezetimibe combination therapy were enrolled. Changing from statin monotherapy to the combination therapy resulted in additional LDL-C level reductions of 31.0-41.0% (all intensity groups, P < .01). Similarly, 88.3-91.1% of the enrolled patients successfully achieved LDL-C levels of <100 mg/dL (all intensity groups, P < .01). A subgroup analysis of patients with baseline LDL-C levels ≥ 100 mg/dL showed that switching from moderate- or high-intensity statin monotherapy to a rosuvastatin/ezetimibe combination showed greater LDL-C reductions than did switching to an atorvastatin/ezetimibe combination, within the same statin intensity

groups. WHAT IS NEW AND CONCLUSION: The present study provides real-world evidence of the LDL-C reduction benefits associated with statin/ezetimibe combinations in the clinical practice setting. The results also demonstrate that if statin monotherapy does not effectively help patients reach their target LDL-C goals, changing to a statin/ezetimibe combination prescription may show enhanced LDL-C-lowering effects and improve the likelihood of achieving LDL-C targets, in real practice.

[54] *Chiou SJ, Liao K, Huang YT et al.* **The synergy between the pay-for-performance scheme and better physician-patient relationship may reduce the risk of retinopathy in patients with type 2 diabetes**. Journal of diabetes investigation 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33025682
ABSTRACT
AIMS/INTRODUCTION: This study investigated whether participation by patients with type 2 diabetes in Taiwan's Pay-for-Performance (P4P) program and maintaining good continuity of care (COC) with their healthcare provider reduced the likelihood of future complications such as retinopathy. MATERIALS AND METHODS: The analysis used longitudinal panel data for newly diagnosed T2DM from the National Health Insurance claims database in Taiwan. Continuity of Care (COC) was measured annually from 2003 to 2013, and was used to allocate the patients to low, medium, and high groups. Cox regression analysis was used with time-dependent (time-varying) covariates in a reduced model (with only P4P or COC), and the full model was adjusted with other covariates. RESULTS: Despite the same significant effects of treatment at primary care, the Diabetes Complications Severity Index scores were significantly associated with the development of retinopathy. After adjusting for these, the hazard ratios (HRs) for developing retinopathy among P4P participants in the low, medium, and high COC groups were 0.594 (95%CI= 0.398-0.898, p = 0.012), 0.676 (95%CI= 0.520-0.867, p = 0.0026), and 0.802 (95%CI=0.603-1.030, p =0.1062), respectively. Thus, patients with low or median COC who participated in the P4P program had a significantly lower risk of retinopathy than those who did not. CONCLUSIONS: Diabetes care requires a long-term relationship between patients and their care providers. Besides encouraging patients to participate in P4P programs, health authorities should provide more incentives for providers or patients to regularly survey patients' lipid profiles and glucose levels and reward the better interpersonal relationship to prevent retinopathy.

[55] *Xiao J, Ren WL, Liang YY et al.* **Effectiveness of Lifestyle and Drug Intervention on Hypertensive Patients: a Randomized Community Intervention Trial in Rural China**. Journal of general internal medicine 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33021715
ABSTRACT
BACKGROUND: Strict medication guidance and lifestyle interventions to manage blood pressure (BP) in hypertensive patients are typically difficult to follow. OBJECTIVE: To evaluate the 1-year effectiveness of lifestyle and drug intervention in the management of rural hypertensive patients. DESIGN: Randomized community intervention trial. PARTICIPANTS: The control group comprised 967 patients who received standard antihypertensive drug intervention therapy from two communities, whereas the intervention group comprised 1945 patients who received antihypertensive drug and lifestyle intervention therapies from four communities in rural China. MAIN MEASURES: Data on lifestyle behaviors and BP

measurements at baseline and 1-year follow-up were collected. A difference-in-difference logistic regression model was used to assess the effect of the intervention. KEY RESULTS: BP control after the 1-year intervention was better than that at baseline in both groups. The within-group change in BP control of 59.3% in the intervention group was much higher than the 25.2% change in the control group ($P < 0.001$). Along with the duration of the follow-up period, systolic and diastolic BP decreased rapidly in the early stages and then gradually after 6 months in the intervention group ($P < 0.001$). In the intervention group, drug therapy adherence was increased by 39.5% (from 48.1% at 1 month to 87.6% at 1 year) ($P < 0.001$), more in women (45.6%) than in men (31.2%; $P < 0.001$). The net effect of the lifestyle intervention improved the rate of BP control by 56.1% (70.8% for men and 44.7% for women). For all physiological and biochemical factors, such as body mass index, waist circumference, lipid metabolism, and glucose control, improvements were more significant in the behavioral intervention group than those in the control group (all $P < 0.001$). CONCLUSION: The addition of lifestyle intervention by physicians or nurses helps control BP effectively and lowers BP better than usual care with antihypertensive drug therapy alone.

[56] *Cheong BYC, Wilson JM, Spann SJ et al.* **Coronary artery calcium scoring: an evidence-based guide for primary care physicians**. Journal of internal medicine 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33016506
ABSTRACT
Primary care physicians often must decide whether statin therapy would be appropriate (in addition to lifestyle modification) for managing asymptomatic individuals with borderline or intermediate risk for developing atherosclerotic cardiovascular disease (ASCVD), as assessed on the basis of traditional risk factors. In appropriate subjects, a simple, noninvasive measurement of coronary artery calcium can help clarify risk. Coronary atherosclerosis is a chronic inflammatory disease, with atherosclerotic plaque formation involving intimal inflammation and repeated cycles of erosion and fibrosis, healing and calcification. Atherosclerotic plaque formation represents the prognostic link between risk factors and future clinical events. The presence of coronary artery calcification is almost exclusively an indication of coronary artery disease, except in certain metabolic conditions. Coronary artery calcification can be detected and quantified in a matter of seconds by noncontrast electrocardiogram-gated low-dose X-ray computed tomography (coronary artery calcium scoring [CACS]). Since the publication of the seminal work by Dr. Arthur Agatston in 1990, a wealth of CACS-based prognostic data has been reported. In addition, recent guidelines from various professional societies conclude that CACS may be considered as a tool for reclassifying risk for atherosclerotic cardiovascular disease in patients otherwise assessed to have intermediate risk, so as to more accurately inform decisions about possible statin therapy in addition to lifestyle modification as primary preventive therapy. In this review, we provide an overview of CACS, from acquisition to interpretation, and summarize the scientific evidence for and the appropriate use of CACS as put forth in current clinical guidelines.

[57] *Cho KH, Jeong MH*. **Clinical Benefit of Statins in Korean Patients with Acute Myocardial Infarction: Experience of the Korea Acute Myocardial Infarction Registry**. J Lipid Atheroscler 2020; 9:362-379.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33024731
ABSTRACT

Statins (3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitor) are among the most important medications for treating patients with acute myocardial infarction (AMI). Herein, we review the clinical benefit and future scope of statin therapy in Korean patients with AMI from the experience of the Korea AMI Registry. Statins are effective and safe in AMI patients, even in those with very low low-density lipoprotein cholesterol (LDL-C). Peri-procedural statin treatment could reduce the incidence of early stent thrombosis in patients with AMI after percutaneous coronary intervention. Reduction of high sensitivity C-reactive protein levels in patients with AMI plays an important role in the beneficial effect of statins on regression and compositional change of coronary plaques. Obtaining ≥50% reduction in LDL-C is associated with better clinical outcomes after AMI, whereas achieving <70 mg/dL LDL-C is not. Statin therapy has positive effects on clinical outcomes in patients with cardiogenic shock, ischemic heart failure, chronic kidney disease, and vasospasm. The combination of high-dose statin plus N-acetyl cysteine is associated with lower incidence of contrast-induced nephropathy in patients who underwent primary percutaneous coronary intervention. Moderate-intensity pitavastatin therapy is associated with a lower incidence of new-onset diabetes mellitus in patients with AMI and has similar clinical outcomes to moderate-intensity atorvastatin and rosuvastatin therapy. Future studies are required to assess the optimal intensity and LDL-C target concerning statin therapy, and the implementation of guidelines based cholesterol lowering practice in Korean patients with AMI.

[58] *Park SJ, Park DH*. **REvisiting Lipids in REtinal Diseases: A Focused Review on Age-related Macular Degeneration and Diabetic Retinopathy**. J Lipid Atheroscler 2020; 9:406-418.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33024733
ABSTRACT
Dyslipidemia refers to an abnormal amount of lipid in the blood, and the total cholesterol level is defined as the sum of high-density lipoprotein cholesterol, low-density lipoprotein (LDL) cholesterol, and very-LDL cholesterol concentrations. In Korea, the westernization of lifestyle habits in recent years has caused an increase in the incidence of dyslipidemia, which is an important risk factor of cardiovascular disease (CVD). Several studies have been conducted on how dyslipidemia affects not only CVD, but also chorioretinal diseases such as age-related macular degeneration (AMD) and diabetic retinopathy. Recently, a pathological model of AMD was proposed under the assumption that AMD proceeds through a mechanism similar to that of atherosclerotic CVD. However, controversy remains regarding the relationship between chorioretinal diseases and lipid levels in the blood, and the effects of lipid-lowering agents. Herein, we summarize the role of lipids in chorioretinal diseases. In addition, the effects of lipid-lowering agents on the prevention and progression of chorioretinal diseases are presented.

[59] *Dargent A, Pais DEBJP, Saheb S et al.* **LDL-apheresis as an alternate method for plasma LPS purification in healthy volunteers, dyslipidemic and septic patients**. Journal of lipid research 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33037132
ABSTRACT
Lipopolysaccharide (LPS) is a key player for innate immunity activation. It is therefore a prime target for sepsis treatment, as antibiotics are not sufficient to improve outcome during septic

shock. Extracorporeal removal method by polymyxin B hemoperfusion (PMX-DHP) is used in Japan, but recent trials failed to show a significant lowering of circulating LPS levels after PMX-DHP therapy. PMX-DHP has a direct effect on LPS molecules. However, LPS is not present in a free form in the circulation, as it is mainly carried by lipoproteins, including low density lipoproteins (LDL). Lipoproteins are critical for physiological LPS clearance, as LPS are carried by low density lipoproteins (LDL) to the liver for elimination. We hypothesized that LDL-apheresis can be an alternate method for LPS removal. We demonstrated first in vitro that LDL apheresis microbeads are almost as efficient as PMX beads to reduce LPS concentration in LPS-spiked human plasma, whereas it is not active in phosphate-buffered saline. We found that PMX was also adsorbing lipoproteins, although less specifically. Then, we found that endogenous LPS of patients treated by LDL-apheresis for familial hypercholesterolemia is also removed during their LDL-apheresis sessions, both with electrostatic-based devices and filtration devices. Finally, LPS circulating in the plasma of septic shock and severe sepsis patients with gram-negative bacteremia was also removed in vitro by LDL adsorption. Overall, these results underline the importance of lipoproteins for LPS clearance, making them a prime target to study and treat endotoxemia-related conditions.

[60] *Zhang X, Chen L, Li S et al.* **Enhancement Characteristics of Middle Cerebral Arterial Atherosclerotic Plaques Over Time and Their Correlation With Stroke Recurrence**. Journal of magnetic resonance imaging : JMRI 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33034113
ABSTRACT
BACKGROUND: The progression of atherosclerotic plaque is a dynamic process; however, the natural evolution process of plaque enhancement on MRI remains unclear. PURPOSE: To evaluate changes in enhancement characteristics of middle cerebral arterial (MCA) atherosclerotic plaques over time using MRI and to explore the relationship between the changes in plaque enhancement and stroke recurrence. STUDY TYPE: Prospective. POPULATION: Fifty-four patients with MCA atherosclerotic plaque underwent initial and follow-up examinations with a median interval of 519 days (range 84-1820 days), including 37 males and 16 patients with recurrent stroke. FIELD STRENGTH/SEQUENCE: Time-of-flight magnetic resonance angiography, diffusion-weighted imaging, T(2) -weighted imaging, pre- and postcontrast T(1) -weighted imaging at 3 T. ASSESSMENT: Clinical characteristics and differences in the changes in plaque enhancement among acute, subacute and chronic stroke groups and the changes in the degree of stenosis and plaque enhancement between the patients with and without recurrent stroke were compared. Risk factors for patients with recurrent stroke were assessed. Intra- and interobserver agreement in initial and the changes in plaque enhancement and stenosis, and the correlation between changes in plaque enhancement and recurrent stroke, were evaluated. STATISTICAL TESTS: Independent-samples t-test, Mann-Whitney U-test, chi-squared test, Spearman correlation, logistic regression and Cohen's kappa test. RESULTS: There were significant differences in the changes in stenosis and plaque enhancement ($P < 0.05$) between the patients with and without recurrent stroke. A significant correlation was observed between the changes in plaque enhancement and stroke recurrence ($r = 0.415$, $P < 0.05$). Multivariate regression analysis showed that a change in plaque enhancement was an independent factor for stroke recurrence after adjusting for confounding factors (odds ratio [OR] = 5.797, $P < 0.05$). There was excellent intra- and interobserver agreement in evaluating plaque enhancement and stenosis. DATA

CONCLUSION: Stable or increased enhancement of MCA plaque was related to recurrent stroke events at follow-up. Change in plaque enhancement on MRI may be an important indicator for predicting recurrent stroke. LEVEL OF EVIDENCE: 2 TECHNICAL EFFICACY STAGE: 2.

[61] *Gura KM, Premkumar MH, Calkins KL, Puder M*. **Fish Oil Emulsion Reduces Liver Injury and Liver transplantation in Children with Intestinal Failure-Associated Liver Disease: A Multicenter Integrated Study**. J Pediatr 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33038344
ABSTRACT
OBJECTIVE: To compare aminotransferase with platelet ratio index (APRI), liver transplantation, and mortality rates between children with intestinal failure-associated liver disease (IFALD) who received fish oil lipid emulsion (FOLE) or soybean oil lipid emulsion (SOLE). STUDY DESIGN: In this multicenter integrated analysis, FOLE recipients (1 g/kg/d) (n=189) were compared with historical controls administered SOLE (up to 3 g/kg/d) (n=73). RESULTS: Compared with SOLE, FOLE recipients had a higher direct bilirubin level at baseline (5.8 vs. 3.0 mg/dL, P < .0001). Among FOLE recipients, 65% experienced cholestasis resolution vs. 16% of SOLE (P<0.0001). APRI scores improved in FOLE (1.235 vs. 0.810 and 0.758, P<0.02) but worsened in SOLE recipients (0.540 vs. 2.564 and 2.098, P≤0.0003) when baseline scores were compared with cholestasis resolution and end of study, respectively. Liver transplantation was reduced in FOLE vs. SOLE (4% vs. 12%, P=0.0245). The probability of liver transplantation in relation to baseline DB was lower in FOLE vs SOLE recipients (1% vs. 9% at DB of 2 mg/dL; 8% vs 35% at DB of 12.87 mg/dL, P=0.0022 for both). Death rates were similar (FOLE vs. SOLE: 10% vs. 14% at DB of 2 mg/dL; 17% vs. 23% at a DB of 12.87 mg/dL, P=0.36 for both). CONCLUSION: FOLE recipients experienced a higher rate of cholestasis resolution, lower APRI, and fewer liver transplants compared with SOLE. This demonstrates that FOLE may be the preferred parenteral lipid emulsion in children with IFALD when DB reaches 2 mg/dL. Trial registration Clinicaltrials.gov: NCT00910104 and NCT00738101.

[62] *Middlekauff HR, William KJ, Su B et al.* **Changes in lipid composition associated with electronic cigarette use**. Journal of translational medicine 2020; 18:379.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33028369
ABSTRACT
BACKGROUND: Electronic cigarette use is on the rise despite a number of reports linking electronic cigarettes with adverse health outcomes. Recent studies have suggested that alterations in lipid signaling may be one mechanism by which electronic cigarettes contribute to lung pulmonary function. Vitamin E acetate, for example, is synthetic form of Vitamin E transported via lipids, found to be associated with electronic cigarette associated lung injury. Lipids are absolutely critical for normal lung physiology and perturbations in a number of lipid pathways have been associated with respiratory illness. Is it conceivable that electronic cigarette use even in seemingly healthy cohorts are associated with alterations in lipid pathways? METHODS: To investigate quantitative alterations in the plasma lipidome associated with electronic cigarette use in healthy we obtained plasma samples from 119 male and female participants with who were either: (1) chronic tobacco cigarette (TC) smokers (> 12 months of self-reported TC use), (2) chronic Electronic cigarette (EC) users (> 12 months

of self-reported EC use), or (3) non-users. We measured quantitative lipid species across different lipid sub-classes from plasma samples using the Sciex Lipidyzer. RESULTS: We found that male and female tobacco and electronic cigarette users had distinct lipidome signatures across a number of lipid species although the vast majority of lipids were unchanged when compared to non-users. Intriguingly, we found that female but not male electronic cigarette users had lower levels of plasmalogens, critical glycerophospholipids secreted by alveoli and required for normal surfactant function. CONCLUSIONS: In summary, our study does not reveal striking changes associated with electronic cigarette use but we observed sex-specific changes in lipids known to be critical for lung function.

[63] *Barankay I, Reese PP, Putt ME et al.* **Effect of Patient Financial Incentives on Statin Adherence and Lipid Control: A Randomized Clinical Trial**. JAMA network open 2020; 3:e2019429.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33034639
ABSTRACT
IMPORTANCE: Financial incentives can improve medication adherence and cardiovascular disease risk, but the optimal design to promote sustained adherence after incentives are discontinued is unknown. OBJECTIVE: To determine whether 6-month interventions involving different financial incentives to encourage statin adherence reduce low-density lipoprotein cholesterol (LDL-C) levels from baseline to 12 months. DESIGN, SETTING, AND PARTICIPANTS: This 4-group, randomized clinical trial was conducted from August 2013 to July 2018 among several large US insurer or employer populations and the University of Pennsylvania Health System. The study population included adults with elevated risk of cardiovascular disease, suboptimal LDL-C control, and evidence of imperfect adherence to statin medication. Data analysis was performed from July 2017 to June 2019. INTERVENTIONS: The interventions lasted 6 months during which all participants received daily medication reminders and an electronic pill bottle. Statin adherence was measured by opening the bottle. For participants randomized to the 3 intervention groups, adherence was rewarded with financial incentives. The sweepstakes group involved incentives for daily adherence. In the deadline sweepstakes group, incentives were reduced if participants were adherent only after a reminder. The sweepstakes plus deposit contract group split incentives between daily adherence and a monthly deposit reduced for each day of nonadherence. MAIN OUTCOMES AND MEASURES: The primary outcome was change in LDL-C level from baseline to 12 months. RESULTS: Among 805 participants randomized (199 in the simple daily sweepstakes group, 204 in the deadline sweepstakes group, 201 in the sweepstakes plus deposit contract group, and 201 in the control group), the mean (SD) age was 58.5 (10.3) years; 519 participants (64.5%) were women, 514 (63.9%) had diabetes, and 273 (33.9%) had cardiovascular disease. The mean (SD) baseline LDL-C level was 143.2 (42.5) mg/dL. Measured adherence at 6 months (defined as the proportion of 180 days with electronic pill bottle opening) in the control group (0.69; 95% CI, 0.66-0.72) was lower than that in the simple sweepstakes group (0.84; 95% CI, 0.81-0.87), the deadline sweepstakes group (0.86; 95% CI, 0.83-0.89), and the sweepstakes plus deposit contract group (0.87; 95% CI, 0.84-0.90) ($P < .001$ for each incentive group vs control). LDL-C levels were measured for 636 participants at 12 months. Mean LDL-C level reductions from baseline to 12 months were 33.6 mg/dL (95% CI, 28.4-38.8 mg/dL) in the control group, 32.4 mg/dL (95% CI, 27.3-37.6 mg/dL) in the sweepstakes group, 33.2 mg/dL (95% CI, 28.1-38.3 mg/dL) in the deadline sweepstakes

group, and 36.5 mg/dL (95% CI, 31.3-41.7 mg/dL) in the sweepstakes plus deposit contract group (adjusted P > .99 for each incentive group vs control). CONCLUSIONS AND RELEVANCE: Compared with the control group, different financial incentives improved measured statin adherence but not LDL-C levels. This result points to the importance of directly measuring health outcomes, rather than simply adherence, in trials aimed at improving health behaviors. TRIAL REGISTRATION: ClinicalTrials.gov Identifier: NCT01798784.

[64] *Alhawari H, Jarrar Y, AlKhatib MA et al.* **The Association of 3-Hydroxy-3-Methylglutaryl-CoA Reductase, Apolipoprotein E, and Solute Carrier Organic Anion Genetic Variants with Atorvastatin Response among Jordanian Patients with Type 2 Diabetes**. Life (Basel) 2020; 10.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33027917
ABSTRACT
Atorvastatin is commonly used among type 2 diabetic (DM2) patients at the University of Jordan Hospital to prevent cardiovascular complication. However, we noticed that there is a wide inter-individual variation in the efficacy and toxicity of atorvastatin. This study aimed to find out the effects of major genetic variants in 3-Hydroxy-3-Methylglutaryl-CoA Reductase (HMGCR), Apolipoprotein E (APOE), and Solute Carrier Organic Anion (SLCO1B1) genes on atorvastatin response among DM2 patients. A sample of 139 DM2 patients on 20 mg of atorvastatin was included in this study. The lipid and glycemic profile and the levels of hepatic enzymes alanine aminotransferase (ALT) and aspartate transaminase were recorded before and after 3 months of atorvastatin treatment. Additionally, the genetic variants HMGCR rs17244841,APOE rs7412 and rs429357, and SLCO1B1 rs2306283 and rs11045818 were genotyped using an Applied Biosystems DNA sequencing method (ABI3730×1). We found that atorvastatin reduced total cholesterol and low-density lipoprotein (LDL) more significantly (p-value < 0.05) in patients with wild genotype than variant alleles APOE rs7412C > T and SLCO1B1 rs2306283A > G. Furthermore, the ALT level was elevated significantly (p-value < 0.05) by 27% in patients with heterozygous SLCO1B1 rs11045818 G/A genotype, while it was not elevated among wild genotype carriers. Additionally, atorvastatin reduced total cholesterol more significantly (p-value < 0.05) in patients with SLCO1B1 rs2306283A and rs11045818G haplotypes and increased ALT levels by 27% (p-value < 0.05) in patients with SLCO1B1 rs2306283G and rs11045818A haplotypes. In conclusion, it was found in this study that APOE rs7412, SLCO1B1 rs2306283, and rs11045818 genotypes can be considered as potential genetic biomarkers of atorvastatin response among DM2 patients of Jordanian Arabic origin. Further clinical studies with larger sample numbers are needed to confirm these findings.

[65] *Heffernan KS, Ranadive SM, Jae SY*. **Exercise as medicine for COVID-19: On PPAR with emerging pharmacotherapy**. Medical hypotheses 2020; 143:110197.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33017906
ABSTRACT
Coronavirus disease 2019 (COVID-19) may have a metabolic origin given strong links with risk factors such as lipids and glucose and co-morbidities such as obesity and type 2 diabetes mellitus. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike protein mediates viral cellular entry via the ACE2 receptor. The cytoplasmic tail of this spike protein is heavily palmitoylated. Emerging studies suggest that SARS-CoV-2 alters lipid metabolism in the lung epithelial cells by modulating peroxisome proliferator-activated receptor alpha

(PPARα), possibly contributing to lipotoxicity, inflammation and untoward respiratory effects. Disruption of this process may affect palmitoylation of SARS-CoV spike protein and thus infectivity and viral assembly. COVID-19 is also increasingly being recognized as a vascular disease, with several studies noting prominent systemic endothelial dysfunction. The pathogenesis of endothelial dysfunction may also be linked to COVID-19-mediated metabolic and inflammatory effects. Herein, exercise will be compared to fenofibrate as a possible therapeutic strategy to bolster resilience against (and help manage recovery from) COVID-19. This paper will explore the hypothesis that exercise may be a useful adjuvant in a setting of COVID-19 management/rehabilitation due to its effects on PPARα and vascular endothelial function.

[66] *Kasemy ZA, Hathout HM, Omar ZA et al.* **Effect of Omega-3 supplements on quality of life among children on dialysis: A prospective cohort study**. Medicine (Baltimore) 2020; 99:e22240.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33019398
ABSTRACT
Children with end stage renal disease (ESRD) are liable to various health disorders that possibly impair their quality of life (QoL). Low dietary intake of Omega-3 fatty acids also called marine n-3 fatty acid (n-3 FA) may be associated with health problems which are among the leading causes of impaired QoL.The objective of this study was to assess the effect of omega-3 Fatty acid (n-3 FA) supplements on quality of life among children on dialysis and to evaluate its use regarding adequacy of dialysis and inflammatory markers.A prospective cohort study was conducted on 31 hemodialysis children. Quality of life was measured for patients and an equal number of matched controls using the PedsQL Inventory where the higher the score the poorer is the quality of life. n-3FA supplementation had been given to the patients for 3 months to study its effects on QoL. Laboratory investigations like hemoglobin, lipid profile, inflammatory markers, and tests for adequacy of dialysis had been carried out.Patients had significantly higher QoL scores (42.22±13.31) than controls (22.70±1.31) (P<.001). Young ages showed higher score of physical functioning (18.23±4.22) than older ones (13.92±6.84) (P=.049). Females had significantly higher total QoL score (25.53±6.61) than males (20.06±7.09) (P=.010). The total QoL score was significantly lower post than pre administration of n-3FA (35.41±10.36 vs 42.22±13.31) (P<.001). Triglycerides and CRP were significantly lower post than pre n-3FA supplementation (160.64±32.55 vs 169.35±31.82) (P<.001) and (10.29±4.39 vs 11.19±4.83) (P=.006) respectively. Means of Kt/V and urea reduction ratio (URR) were significantly higher post (1.37±0.09, 70.0±5.99 respectively) than pre n-3FA (1.31±0.07 and 65.25±6.06 respectively) (P=.005, .001 respectively).Quality of life and adequacy of dialysis get improved after n-3FA supplementation among children on dialysis which encourages its testing for more patients to evaluate its long term effects and support its routine use.

[67] *Xu Y, Wu Y*. **Atorvastatin associated with gamma glutamyl transpeptidase elevation in a hyperlipidemia patient: A case report and literature review**. Medicine (Baltimore) 2020; 99:e22572.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33019469
ABSTRACT

RATIONALE: Atorvastatin is the most common drug used in therapy for cardiovascular diseases. The most common adverse side effects associated with statins are myopathy and hypertransaminasemia. Here, we report a rare case of gamma glutamyl transpeptidase (GGT) elevation induced by atorvastatin. PATIENT CONCERNS: A 47-year-old male was admitted to our hospital with dyslipidemia, he had been taking pitavastatin 2 mg/day for 2 months. The levels of total cholesterol (265.28 mg/dL) and low-density lipoprotein-cholesterol (LDL) (179.15 mg/dL) were also high. DIAGNOSIS: Blood lipid test showed mixed dyslipidemia. INTERVENTION: Atorvastatin 10 mg/day was given to the patient. OUTCOMES: The patient came back to our hospital for blood tests after 4 weeks. Although no symptoms were detectable, the patient's GGT level was markedly elevated (up to 6-fold over normal level) with less marked increases in alkaline phosphatase (ALP) and alanine aminotransferase (ALT). The serum GGT level returned to normal within 6 weeks of cessation of atorvastatin. LESSONS: This is a case of GGT elevation without hyperbilirubinemia, hypertransaminasemiam, or serum creatine phosphokinase (CPK) abnormalities despite an atorvastatin regimen. This case highlights GGT elevation caused by atorvastatin, a rare but serious condition. Clinicians should be aware of these possible adverse effects and monitor liver function tests in patients on statin therapy.

[68] *Bonacina F, Da Dalt L, Catapano AL, Norata GD*. **Metabolic adaptations of cells at the vascular-immune interface during atherosclerosis**. Molecular aspects of medicine 2020:100918.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33032828
ABSTRACT
Metabolic reprogramming is a physiological cellular adaptation to intracellular and extracellular stimuli that couples to cell polarization and function in multiple cellular subsets. Pathological conditions associated to nutrients overload, such as dyslipidaemia, may disturb cellular metabolic homeostasis and, in turn, affect cellular response and activation, thus contributing to disease progression. At the vascular/immune interface, the site of atherosclerotic plaque development, many of these changes occur. Here, an intimate interaction between endothelial cells (ECs), vascular smooth muscle cells (VSMCs) and immune cells, mainly monocytes/macrophages and lymphocytes, dictates physiological versus pathological response. Furthermore, atherogenic stimuli trigger metabolic adaptations both at systemic and cellular level that affect the EC layer barrier integrity, VSMC proliferation and migration, monocyte infiltration, macrophage polarization, lymphocyte T and B activation. Rewiring cellular metabolism by repurposing "metabolic drugs" might represent a pharmacological approach to modulate cell activation at the vascular immune interface thus contributing to control the immunometabolic response in the context of cardiovascular diseases.

[69] *Płatek T, Polus A, Góralska J et al.* **DNA methylation microarrays identify epigenetically regulated lipid related genes in obese patients with hypercholesterolemia**. Molecular medicine (Cambridge, Mass.) 2020; 26:93.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33028190
ABSTRACT
BACKGROUND: Epigenetics can contribute to lipid disorders in obesity. The DNA methylation pattern can be the cause or consequence of high blood lipids. The aim of the study was to investigate the DNA methylation profile in peripheral leukocytes associated with elevated LDL-

cholesterol level in overweight and obese individuals. METHODS: To identify the differentially methylated genes, genome-wide DNA methylation microarray analysis was performed in leukocytes of obese individuals with high LDL-cholesterol (LDL-CH, ≥ 3.4 mmol/L) versus control obese individuals with LDL-CH, < 3.4 mmol/L. Biochemical tests such as serum glucose, total cholesterol, HDL cholesterol, triglycerides, insulin, leptin, adiponectin, FGF19, FGF21, GIP and total plasma fatty acids content have been determined. Oral glucose and lipid tolerance tests were also performed. Human DNA Methylation Microarray (from Agilent Technologies) containing 27,627 probes for CpG islands was used for screening of DNA methylation status in 10 selected samples. Unpaired t-test and Mann-Whitney U-test were used for biochemical and anthropometric parameters statistics. For microarrays analysis, fold of change was calculated comparing hypercholesterolemic vs control group. The q-value threshold was calculated using moderated Student's t-test followed by Benjamini-Hochberg multiple test correction FDR. RESULTS: In this preliminary study we identified 190 lipid related CpG loci differentially methylated in hypercholesterolemic versus control individuals. Analysis of DNA methylation profiles revealed several loci engaged in plasma lipoprotein formation and metabolism, cholesterol efflux and reverse transport, triglycerides degradation and fatty acids transport and β-oxidation. Hypermethylation of CpG loci located in promoters of genes regulating cholesterol metabolism: PCSK9, LRP1, ABCG1, ANGPTL4, SREBF1 and NR1H2 in hypercholesterolemic patients has been found. Novel epigenetically regulated CpG sites include ABCG4, ANGPTL4, AP2A2, AP2M1, AP2S1, CLTC, FGF19, FGF1R, HDLBP, LIPA, LMF1, LRP5, LSR, NR1H2 and ZDHHC8 genes. CONCLUSIONS: Our results indicate that obese individuals with hypercholesterolemia present specific DNA methylation profile in genes related to lipids transport and metabolism. Detailed knowledge of epigenetic regulation of genes, important for lipid disorders in obesity, underlies the possibility to influence target genes by changing diet and lifestyle, as DNA methylation is reversible and depends on environmental factors. These findings give rise for further studies on factors that targets methylation of revealed genes.

[70] *Fernández LP, Merino M, Colmenarejo G et al.* **Metabolic enzyme ACSL3 is a prognostic biomarker and correlates with anticancer effectiveness of statins in non-small cell lung cancer**. Mol Oncol 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33030783

ABSTRACT

Lung cancer is one of the most common cancers, still characterized by high mortality rates. As lipid metabolism contributes to cancer metabolic reprogramming, several lipid metabolism genes are considered prognostic biomarkers of cancer. Statins are a class of lipid-lowering compounds used in treatment of cardiovascular disease that are currently studied for their antitumor effects. However, their exact mechanism of action and specific conditions in which they should be administered remains unclear. Here, we found that simvastatin treatment effectively promoted antiproliferative effects and modulated lipid metabolism-related pathways in non-small cell lung cancer (NSCLC) cells and that the antiproliferative effects of statins were potentiated by overexpression of acyl-CoA synthetase long-chain family member 3 (ACSL3). Moreover, ACSL3 overexpression was associated with worse clinical outcome in patients with high-grade NSCLC. Finally, we found that patients with high expression levels of ACSL3 displayed a clinical benefit of statins treatment. Therefore, our study highlights ACSL3 as a

prognostic biomarker for NSCLC, useful to select patients who would obtain a clinical benefit from statin administration.

[71] *Zenti MG, Lupo MG, De Martin S et al.* **Impact of bariatric surgery-induced weight loss on circulating PCSK9 levels in obese patients**. Nutrition, metabolism, and cardiovascular diseases : NMCD 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33028503
ABSTRACT
BACKGROUND AND AIMS: To investigate the effect of obesity and bariatric-induced weight loss on circulating levels of proprotein convertase subtilisin/kexin 9 (PCSK9) in severely obese patients. METHODS AND RESULTS: In this non-randomized interventional study, we enrolled 36 severely obese patients (BMI 43.7 ± 5.6 kg/m(2)), of which 20 underwent bariatric surgery, and 12 nonobese healthy controls. An oral glucose tolerance test (75-g OGTT) was performed in 31 of these obese patients at baseline (T0) and in 14 patients at 6 months after bariatric surgery (T6) to assess plasma glucose, insulin and PCSK9 levels. Plasma PCSK9 levels were also measured in 18 of these obese patients at T0 during a 2-h hyperinsulinemic-euglycemic clamp (HEC). At T0, PCSK9 levels were higher in obese patients than in controls (274.6 ± 76.7 ng/mL vs. 201.4 ± 53.3 ng/mL) and dropped after bariatric surgery (T6; 205.5 ± 51.7 ng/mL) along with BMI (from 44.1 ± 5.9 kg/m(2) to 33.1 ± 5.6 kg/m(2)). At T6, there was also a decrease in plasma glucose (T0 vs. T6: 6.0 ± 1.8 vs. 5.0 ± 0.5 mmol/L) and insulin (15.7 ± 8.3 vs. 5.4 ± 2.1 mU/L) levels. At T0, plasma PCSK9 levels decreased during OGTT in obese patients, reaching a nadir of 262.0 ± 61.4 ng/mL at 120 min with a hyperinsulinemic peak of 75.1 ± 40.0 mU/L, at 60 min. Similarly, at T0 insulin infusion during 2-h HEC acutely reduced plasma PCSK9 levels in obese patients. The aforementioned OGTT-induced changes in plasma PCSK9 levels were not observed neither in nonobese healthy controls nor in obese patients after bariatric-surgery weight loss. CONCLUSIONS: These results suggest a pivotal role of adipose tissue and insulin resistance on PCSK9 homeostasis in severely obese patients.

[72] *Bradshaw PC, Seeds WA, Miller AC et al.* **COVID-19: Proposing a Ketone-Based Metabolic Therapy as a Treatment to Blunt the Cytokine Storm**. Oxidative medicine and cellular longevity 2020; 2020:6401341.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33014275
ABSTRACT
Human SARS-CoV-2 infection is characterized by a high mortality rate due to some patients developing a large innate immune response associated with a cytokine storm and acute respiratory distress syndrome (ARDS). This is characterized at the molecular level by decreased energy metabolism, altered redox state, oxidative damage, and cell death. Therapies that increase levels of (R)-beta-hydroxybutyrate (R-BHB), such as the ketogenic diet or consuming exogenous ketones, should restore altered energy metabolism and redox state. R-BHB activates anti-inflammatory GPR109A signaling and inhibits the NLRP3 inflammasome and histone deacetylases, while a ketogenic diet has been shown to protect mice from influenza virus infection through a protective γδ T cell response and by increasing electron transport chain gene expression to restore energy metabolism. During a virus-induced cytokine storm, metabolic flexibility is compromised due to increased levels of reactive oxygen species (ROS) and reactive nitrogen species (RNS) that damage, downregulate, or inactivate many

enzymes of central metabolism including the pyruvate dehydrogenase complex (PDC). This leads to an energy and redox crisis that decreases B and T cell proliferation and results in increased cytokine production and cell death. It is hypothesized that a moderately high-fat diet together with exogenous ketone supplementation at the first signs of respiratory distress will increase mitochondrial metabolism by bypassing the block at PDC. R-BHB-mediated restoration of nucleotide coenzyme ratios and redox state should decrease ROS and RNS to blunt the innate immune response and the associated cytokine storm, allowing the proliferation of cells responsible for adaptive immunity. Limitations of the proposed therapy include the following: it is unknown if human immune and lung cell functions are enhanced by ketosis, the risk of ketoacidosis must be assessed prior to initiating treatment, and permissive dietary fat and carbohydrate levels for exogenous ketones to boost immune function are not yet established. The third limitation could be addressed by studies with influenza-infected mice. A clinical study is warranted where COVID-19 patients consume a permissive diet combined with ketone ester to raise blood ketone levels to 1 to 2 mM with measured outcomes of symptom severity, length of infection, and case fatality rate.

[73] *Khatana C, Saini NK, Chakrabarti S et al.* **Mechanistic Insights into the Oxidized Low-Density Lipoprotein-Induced Atherosclerosis**. Oxidative medicine and cellular longevity 2020; 2020:5245308.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33014272
ABSTRACT
Dyslipidaemia has a prominent role in the onset of notorious atherosclerosis, a disease of medium to large arteries. Atherosclerosis is the prime root of cardiovascular events contributing to the most considerable number of morbidity and mortality worldwide. Factors like cellular senescence, genetics, clonal haematopoiesis, sedentary lifestyle-induced obesity, or diabetes mellitus upsurge the tendency of atherosclerosis and are foremost pioneers to definitive transience. Accumulation of oxidized low-density lipoproteins (Ox-LDLs) in the tunica intima triggers the onset of this disease. In the later period of progression, the build-up plaques rupture ensuing thrombosis (completely blocking the blood flow), causing myocardial infarction, stroke, and heart attack, all of which are common atherosclerotic cardiovascular events today. The underlying mechanism is very well elucidated in literature but the therapeutic measures remains to be unleashed. Researchers tussle to demonstrate a clear understanding of treating mechanisms. A century of research suggests that lowering LDL, statin-mediated treatment, HDL, and lipid-profile management should be of prime interest to retard atherosclerosis-induced deaths. We shall brief the Ox-LDL-induced atherogenic mechanism and the treating measures in line to impede the development and progression of atherosclerosis.

[74] *Truong TM, Lipschultz E, Schierer E et al.* **Patient insights on features of an effective pharmacogenomics patient portal**. Pharmacogenetics and genomics 2020; 30:191-200.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33017129
ABSTRACT
OBJECTIVES: We built a novel mock pharmacogenomics web portal to deliver pharmacogenomic information and results to patients. Utilizing a patient focus group, we then sought to understand patient insights on desired features of an effective pharmacogenomics patient portal. METHODS: The mock YourPGx Portal delivered four sample pharmacogenomic results (omeprazole, simvastatin, clopidogrel, and codeine). Patients from our existing

institutional, prospective pharmacogenomics implementation study were recruited to pilot the mock portal and then asked to participate in a focus group discussion led by two facilitators. All patients had been previously genotyped, but none had been directly provided access to their own genotyping results and none had previously used the YourPGx portal. The focus group discussion explored nine domains: (1) factors influencing drug response, (2) concerns about drug effects, (3) understanding of genomics and pharmacogenomics, (4) reasons to undergo pharmacogenomic testing, (5) sources of pharmacogenomic information for patient education, (6) attributes of pharmacogenomic sources of information, (7) considerations about privacy and personal pharmacogenomic information, (8) sharing of pharmacogenomic information, and (9) features of an effective patient portal. RESULTS: The median age of patients (n = 10) was 65.5 years old (range 38-72), 70% female, 50% Caucasian/30% Black, and 60% held a bachelor/advanced degree. When asked about resources for seeking pharmacogenomic information, patients preferred consulting their providers first, followed by self-education, then using information provided by university research organizations. A theme emerged regarding attributes of these sources, namely a desire for understandability and trust. Patients said that the effectiveness of a pharmacogenomics patient portal is improved with use of symbolisms/graphics and clear and concise content. Effective use of colors, quantifying information, consistency, and use of layperson's language were additional important facets. Patients communicated the appeal of secured phone/app-enabled access and said that they would desire linking to their electronic medical records to allow sharing of information with different members of their healthcare team. CONCLUSIONS: Patients named providers as their primary source of pharmacogenomic information, but a pharmacogenomics patient portal that is carefully constructed to incorporate desired features may be a favorable tool to effectively deliver pharmacogenomic information and results to patients.

[75] *Maarouf N, Chen YX, Shi C et al.* **Unlike estrogens that increase PCSK9 levels post-menopause HSP27 vaccination lowers cholesterol levels and atherogenesis due to divergent effects on PCSK9 and LDLR**. Pharmacological research : the official journal of the Italian Pharmacological Society 2020; 161:105222.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33022407
ABSTRACT
AIMS: The estrogen-inducible protein Heat Shock Protein 27 (HSP27) as well as anti-HSP27 antibodies are elevated in healthy subjects compared to cardiovascular disease patients. Vaccination of ApoE(-/-) mice with recombinant HSP25 (rHSP25, the murine ortholog), boosts anti- HSP25 levels and attenuates atherogenesis. As estrogens promote HSP27 synthesis, cellular release and blood levels, we hypothesize that menopause will result in loss of HSP27 atheroprotection. Hence, the rationale for this study is to compare the efficacy of rHSP25 vaccination vs. estradiol (E2) therapy for the prevention of post-menopausal atherogenesis. METHODS AND RESULTS: ApoE(-/-) mice subjected to ovariectomy (OVX) showed a 65 % increase atherosclerotic burden compared to sham mice after 5 weeks of a high fat diet. Relative to vaccination with rC1, a truncated HSP27 control peptide, atherogenesis was reduced by 5-weekly rHSP25 vaccinations (-43 %), a subcutaneous E2 slow release pellet (-52 %) or a combination thereof (-82 %). Plasma cholesterol levels declined in parallel with the reductions in atherogenesis, but relative to rC1/OVX mice plasma PCSK9 levels were 52 % higher in E2/OVX and 41 % lower in rHSP25/OVX mice ($p < 0.0001$ for both). Hepatic LDLR mRNA levels did not change with E2 treatment but increased markedly with rHSP25

vaccination. Conversely, hepatic PCSK9 mRNA increased 148 % with E2 treatment vs. rC1/OVX but did not change with rHSP25 vaccination. In human HepG2 hepatocytes E2 increased PCSK9 promoter activity 303 %, while the combination of [rHSP27 + PAb] decreased PCSK9 promoter activity by 64 %. CONCLUSION: The reduction in post-OVX atherogenesis and cholesterol levels with rHSP25 vaccination is associated with increased LDLR but not PCSK9 expression. Surprisingly, E2 therapy attenuates atherogenesis and cholesterol levels post-OVX without altering LDLR but increases PCSK9 expression and promoter activity. This is the first documentation of increased PCSK9 expression with E2 therapy and raises questions about balancing physiological estrogenic / PCSK9 homeostasis and targeting PCSK9 in women - are there effects beyond cholesterol?

[76] *Chen CY, Huang WS, Chen HC et al.* **Effect of a 90 g/day low-carbohydrate diet on glycaemic control, small, dense low-density lipoprotein and carotid intima-media thickness in type 2 diabetic patients: An 18-month randomised controlled trial**. PloS one 2020; 15:e0240158.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33017456
ABSTRACT
AIM: This study explored the effect of a moderate (90 g/d) low-carbohydrate diet (LCD) in type 2 diabetes patients over 18 months. METHODS: Ninety-two poorly controlled type 2 diabetes patients aged 20-80 years with HbA1c ≥7.5% (58 mmol/mol) in the previous three months were randomly assigned to a 90 g/d LCD r traditional diabetic diet (TDD). The primary outcomes were glycaemic control status and change in medication effect score (MES). The secondary outcomes were lipid profiles, small, dense low-density lipoprotein (sdLDL), serum creatinine, microalbuminuria and carotid intima-media thickness (IMT). RESULTS: A total of 85 (92.4%) patients completed 18 months of the trial. At the end of the study, the LCD and TDD group consumed 88.0±29.9 g and 151.1±29.8 g of carbohydrates, respectively ($p < 0.05$). The 18-month mean change from baseline was statistically significant for the HbA1c (-1.6±0.3 vs. -1.0±0.3%), 2-h glucose (-94.4±20.8 vs. -18.7±25.7 mg/dl), MES (-0.42±0.32 vs. -0.05±0.24), weight (-2.8±1.8 vs. -0.7±0.7 kg), waist circumference (-5.7±2.7 vs. -1.9±1.4 cm), hip circumference (-6.1±1.8 vs. -2.9±1.7 cm) and blood pressure (-8.3±4.6/-5.0±3 vs. 1.6±0.5/2.5±1.6 mmHg) between the LCD and TDD groups ($p<0.05$). The 18-month mean change from baseline was not significantly different in lipid profiles, sdLDL, serum creatinine, microalbuminuria, alanine aminotransferase (ALT) and carotid IMT between the groups. CONCLUSIONS: A moderate (90 g/d) LCD showed better glycaemic control with decreasing MES, lowering blood pressure, decreasing weight, waist and hip circumference without adverse effects on lipid profiles, sdLDL, serum creatinine, microalbuminuria, ALT and carotid IMT than TDD for type 2 diabetic patients.

[77] *Braga TG, Graças Coelho de Souza MD, Menezes M et al.* **Dipeptidyl peptidase-4 activity, lipopolysaccharide, C-reactive protein, glucose metabolism, and gut peptides 3 months after bariatric surgery**. Surgery for obesity and related diseases : official journal of the American Society for Bariatric Surgery 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33036944
ABSTRACT
BACKGROUND: Bariatric surgery induces weight loss, but changes in glucose metabolism, gut peptides, and inflammatory biomarkers still have conflicting results. SETTINGS: University

hospital. OBJECTIVES: We investigated glucose metabolism, gut hormones, and inflammatory profile after bariatric surgery and medical treatment. METHODS: Forty patients with obesity were recruited and were subjected to Roux-en-Y gastric bypass (n = 15; Bariatric Surgery Group - BSG) or received medical care (n = 20; MG). Sleeve gastrectomy was performed in five patients who were excluded from analysis. Glucose, insulin, homeostatic model for the assessment of insulin resistance (HOMA-IR), glucagon-like peptide-1 (GLP-1), glucose-dependent insulinotropic peptide (GIP), glucagon, ghrelin, dipeptidyl peptidase-4 (DPP-4) activity, circulating lipopolysaccharide (LPS), LPS-binding protein (LPB) and high-sensitivity C-reactive protein (hs-CRP) were evaluated before and three months after each treatment. Except for HOMA-IR, hs-CRP, and LBP, all variables were assessed at fasting and 30- and 60-minutes after a standard meal. RESULTS: After 3 months, both groups lost weight. However, BSG had a more extensive reduction than MG (respectively, 17.6% vs. 4.25%; $P < 0.01$). Except for LPS levels, higher on BSG than MG (1.38 ± 0.96 vs. 0.83 ± 0.60 EU/ml, $P < 0.01$), groups were similar before treatment. In respect to metabolic/hormonal changes, the BSG showed higher glucose, insulin, GLP-1, and GIP levels at 30-min and also GLP-1 at 30- and 60-minutes. DPP-4 activity, HOMA-IR, and fasting LBP did not change. LPS levels at 60-minutes decreased after surgery in the BSG. hs-CRP decreased on BSG compared to MG. CONCLUSIONS: Bariatric surgery resulted in more extensive effects on glucose metabolism, gut hormones, and inflammation.

[78] *Kurnaz Gömleksiz Ö, Karaali Z, Buğra Z et al.* **[Investigation of metabolic effects of CETP gene rs289714 variation in coronary artery patients: A case-control study]**. Turk Kardiyoloji Dernegi arsivi : Turk Kardiyoloji Derneginin yayin organidir 2020; 48:673-682.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33034581

ABSTRACT

OBJECTIVE: The aim of this study was to investigate the effects of the CETP gene rs289714 polymorphism on the serum lipid profile and other metabolic parameters in Turkish patients with coronary artery disease (CAD). METHODS: The CETP rs289714 variant was examined in 104 patients with CAD and 77 controls using the polymerase chain reaction-restriction fragment length polymorphism method. RESULTS: The CETP rs289714 genotype and allele distribution was not statistically different between the groups ($p>0.05$). The body mass index (BMI) values in men with CAD were higher in patients with the G allele compared with those carrying the AA genotype ($p=0.05$). Logistic regression analysis showed that the G allele in male CAD patients was a risk factor for a BMI of ≥ 27 kg/m2 (odds ratio: 0.269, 95% confidence interval: 0.075–0.966; $p=0.044$). The G allele in female patients was associated with lower HDL-C levels than the AA genotype ($p=0.049$). CONCLUSION: The results suggest that the CETP rs289714 polymorphism may cause risk for the development of CAD due to its effects on high-density lipoprotein cholesterol values in female patients and BMI in male patients.

[79] *Dakin HA, Farmer A, Gray AM, Holman RR*. **Economic Evaluation of Factorial Trials: Cost-Utility Analysis of the Atorvastatin in Factorial With Omega EE90 Risk Reduction in Diabetes 2 × 2 × 2 Factorial Trial of Atorvastatin, Omega-3 Fish Oil, and Action Planning**. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research 2020; 23:1340-1348.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33032778

ABSTRACT
OBJECTIVES: We applied principles for conducting economic evaluations of factorial trials to a trial-based economic evaluation of a cluster-randomized 2 × 2 × 2 factorial trial. We assessed the cost-effectiveness of atorvastatin, omega-3 fish oil, and an action-planning leaflet, alone and in combination, from a UK National Health Service perspective. METHODS: The Atorvastatin in Factorial With Omega EE90 Risk Reduction in Diabetes (AFORRD) Trial randomized 800 patients with type 2 diabetes to atorvastatin, omega-3, or their respective placebos and randomized general practices to receive a leaflet-based action-planning intervention designed to improve compliance or standard care. The trial was conducted at 59 UK general practices. Sixteen-week outcomes for each trial participant were extrapolated for 70 years using the United Kingdom Prospective Diabetes Study Outcomes Model v2.01. We analyzed the trial as a 2 × 2 factorial trial (ignoring interactions between action-planning leaflet and medication), as a 2 × 2 × 2 factorial trial (considering all interactions), and ignoring all interactions. RESULTS: We observed several qualitative interactions for costs and quality-adjusted life-years (QALYs) that changed treatment rankings. However, different approaches to analyzing the factorial design did not change the conclusions. There was a ≥99% chance that atorvastatin is cost-effective and omega-3 is not, at a £20 000/QALY threshold. CONCLUSIONS: Atorvastatin monotherapy was the most cost-effective combination of the 3 trial interventions at a £20 000/QALY threshold. Omega-3 fish oil was not cost-effective, while there was insufficient evidence to draw firm conclusions about action planning. Recently-developed methods for analyzing factorial trials and combining parameter and sampling uncertainty were extended to estimate cost-effectiveness acceptability curves within a 2x2x2 factorial design with model-based extrapolation.

[80] *Yin HM, He X, Shan Y et al.* **[Research of SIRT1 on promoting the proliferation, migration and lipid metabolism of nasopharyngeal carcinoma]**. Zhonghua Er Bi Yan Hou Tou Jing Wai Ke Za Zhi 2020; 55:934-943.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33036508

ABSTRACT
Objective: To analyze the differential expression of silent information regulator transcript-1 (SIRT1) in tissues and cells of nasopharyngeal carcinoma (NPC), to explore the effects of SIRT1 on the proliferation and migration of NPC cells, as well as the effects on and mechanisms of lipid metabolism in NPC cells. Methods: Experimental subjects: In this study, tissue specimens were obtained from patients who visited the Department of Otolaryngology and performed nasopharyngeal tissue biopsy in the Affiliated Hospital of Nantong University from 2019 to 2020. Among them, 6 cases were male, 6 cases were female, age range: 27-72 years old, including 7 cases of NPC diagnosed by pathology and 5 cases of normal nasopharyngeal mucosa. Experimental methods and outcome measures: Western Blot and quantitative real time polymerase chain reaction (qRT-PCR) were used to detect the protein and mRNA levels of SIRT1. CNE2 cell line was selected for subsequent experiments. Cell viability and migratory ability were evaluated by CCK8, wound healing and Transwell assays respectively. Animal xenograft tumor model was used to explore the role of SIRT1 inhibitor Ex527 on tumor growth in nude mice. Oil red and Bodipy were used to stain intracellular lipids. For the mechanical investigation, the interactions between SIRT1 and hypoxia inducible factor-1α (HIF-1α) were analyzed by immunoprecipitation (IP) and chromatin immunoprecipitation (ChIP). Finally, statistical analysis was performed by SPSS 26.0 software, $P<0.05$ was

considered statistically significant. Results: The levels of SIRT1 protein (1.005±0.168) and mRNA (5.829±2.395) in NPC tissues were higher than those in normal nasopharyngeal mucosa (0.181±0.042,1.995±1.605). Differences were statistically significant (t values were 6.438 and 2.759, both $P<0.05$). The mRNA and protein levels of CNE1, CNE2, 5-8F and 6-10B cell lines were also higher than those in normal nasopharynx epithelial cell line NP69. Besides, overexpression of SIRT1 correlated with the proliferation and migration of NPC cells. The tumorigenesis ability of nude mice in the Ex527 group was lower than that in the control group. The low SIRT1 expression reduced the protein level of the key enzymes of liposynthesis in NPC cells, improved the expression of lipolysis enzymes, while HIF-1α overexpression promoted lipid synthesis enzymes in NPC cells. SIRT1 inhibited HIF-1α transcription by enhancing deacetylation levels. The binding ability of HIF-1α to SIRT1 promoter regions decreased when NPC cells were hypoxic. Conclusions: SIRT1 promotes the proliferation, migration and lipid metabolism of nasopharyngeal carcinoma cells, which might be expected to provide new theoretical basis for prognosis judgment and gene therapy.