Literature update week 35 (2019)

[1] *Lutski M, Weinstein G, Tanne D, Goldbourt U*. **Angina pectoris severity and late-life frailty among men with cardiovascular disease**. The aging male : the official journal of the International Society for the Study of the Aging Male 2019:1-8.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31446880
ABSTRACT
Objective: We investigated the association between severity of angina pectoris (AP) and subsequent late-life frailty among men with cardiovascular disease (CVD). Method: A subset of 351 men (mean age at baseline 56.7 +/- 6.5 years) who previously participated in the Bezafibrate Infarction Prevention, BIP trial (1990-1997) underwent a neurovascular evaluation as part of the BIP Neurocognitive study 15.0 +/- 3.0 years after baseline (T1) and a frailty evaluation according to Fried 19.9 +/- 1.0 years after baseline (T2). Severity of AP was assessed at baseline of the BIP trial using the Canadian Cardiovascular Society angina classification. We assessed the odds of being in the advanced rank of frailty status (robust, pre-frail, and frail) using ordered logistic regression. Results: Among 351 participants, 134 (38.2%) were classified as pre-frail and 100 (28.5%) as frail. Frailty was found among 42% participants in the AP class >/=2 and among 26% participants in the AP class <2. Adjusting for demographic, health-related and cognitive variables, odds ratio (OR), and 95% confidence interval (95% CI) for advanced rank of frailty was 2.68 (95% CI: 1.29-5.59) comparing AP class >/=2 to AP class <2. Discussion: Among men with CVD, severity of AP should be taken into risk consideration due to its strong association with late-life frailty, particularly among inactive participants and participants with cerebral microvascular damage.

[2] *Bajaj T, Grandhe S, Duong H, Ratnayake SN*. **A rare case of acute pancreatitis due to very severe hypertriglyceridemia treated with subcutaneous insulin and lipid lowering drugs**. AME case reports 2019; 3:26.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31463431
ABSTRACT
The diagnosis of acute pancreatitis in a patient requires the presence of two of the following three criteria: (I) acute onset of persistent, severe; (II) epigastric pain often radiating to the back, elevation in serum lipase or amylase to three times or greater than the upper limit of normal; (III) characteristic radiographic evidence hypertriglyceridemia is a potential cause of acute pancreatitis when levels are greater than 1,000 mg/dL. Very severe hypertriglyceridemia is classified as levels above 2,000 mg/dL. Management includes targeting pancreatitis with intravenous fluids, pain control, and nutritional support. While apheresis with therapeutic plasma exchange is a known option for severe hypertriglyceridemia, we present a rare case with management with intravenous fluids, subcutaneous insulin, statins, and fibrates in a patient with a triglyceride level of 12,234 mg/dL who presented with severe epigastric pain radiating to her back.

[3] *Shek AB, Alieva RB, Kurbanov RD et al.* **Can metformin stabilize PCSK9 level in stable coronary artery disease patients treated with statins?** Archives of medical sciences. Atherosclerotic diseases 2019; 4:e144-e150.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31448346
ABSTRACT

Literature update week 35 (2019)

Introduction: Proprotein convertase subtilisin/kexin type 9 (PCSK9) has emerged as an important marker of cardiovascular risk and a new target for therapeutic interventions. We aimed to study the influence of metformin on the level of circulating PCSK9 in patients with stable coronary artery disease (SCAD) and type 2 diabetes (T2DM) or metabolic syndrome (MetS), receiving moderate doses of statins used in routine clinical practice. Material and methods: The study included 80 patients with T2DM or MetS receiving rosuvastatin for at least three months prior the study. MetS was diagnosed based on the Global Consensus Definition of the International Diabetes Federation (IDF). Serum level of PCSK9 was measured with an ELISA kit. Results: Patients with T2DM or MetS, who took part in the research, were divided into 2 groups - those who received metformin prior the main study (21 patients - 1(st) group) and patients who did not (59 patients - 2(nd) group). Addition of metformin to the 3-month statin therapy of the 2nd group patients, divided into subgroup A (n = 27) with the addition of metformin and subgroup B (n = 29) without one, did not significantly affect the level of lipids. However, the level of circulating PCSK9 in subgroup A patients decreased, compared to subgroup B ($p < 0.01$). At the same time, ongoing metformin and rosuvastatin therapy in the 1(st) group patients was not accompanied by a further decrease of the PCSK9 level. Conclusions: The addition of metformin to ongoing rosuvastatin therapy did not significantly affect serum lipid levels, but stabilized the level of circulating PCSK9, compared with the group without metformin treatment.

[4] *Akers EJ, Nicholls SJ, Di Bartolo BA*. **Plaque Calcification**. Arteriosclerosis, thrombosis, and vascular biology 2019:Atvbaha119311574.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31462089
ABSTRACT
Vascular calcification (VC) is strongly associated with all-cause mortality and is an independent predictor of cardiovascular events. Resulting from its complex, multifaceted nature, targeted treatments for VC have not yet been developed. Lipoproteins are well characterized in the pathogenesis of atherosclerotic plaques, leading to the development of plaque regressing therapeutics. Although their roles in plaque progression are well documented, their roles in VC, and calcification of a plaque, are not well understood. In this review, early in vitro data and clinical correlations suggest an inhibitory role for HDL (high-density lipoproteins) in VC, a stimulatory role for LDL (low-density lipoprotein) and VLDL (very low-density lipoprotein) and a potentially causal role for Lp(a) (lipoprotein [a]). Additionally, after treatment with a statin or PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitor, plaque calcification is observed to increase. With the notion that differing morphologies of plaque calcification associate with either a more stable or unstable plaque phenotype, uncovering the mechanisms of lipoprotein-artery wall interactions could produce targeted therapeutic options for VC.

[5] *Yang KY, Yong CS, Choi HD, Kim JO*. **Diet and lipid-lowering drug use among people with dyslipidemia in Korea**. Asia Pacific journal of clinical nutrition 2019; 28:476-485.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31464394
ABSTRACT
BACKGROUND AND OBJECTIVES: Obesity and diet contribute to the development of hypercholesterolemia; therefore, controlling blood lipid concentration through diet is essential.

To understand the role of diet in controlling blood lipid concentration, we evaluated the food and nutrient intakes, anthropometry, and blood lipid concentrations of adults with dyslipidemia with or without lipid-lowering drug use. METHODS AND STUDY DESIGN: For this crosssectional study, three-year data were obtained from the 6th-7th Korean National Health and Nutrition Examination Survey (2015-2017). Patients with dyslipidemia were categorized as users (1,734) or nonusers (856) of lipidlowering drugs. RESULTS: Age, education level, marital status, self-reported health status, hypertension, diabetes, and alcohol intake were significantly different between users and nonusers ($p<0.05$). Multiple logistic regression analysis revealed a significant association between hypertension and diabetes and blood cholesterol status among users. Total cholesterol, triglycerides, and low-density lipoprotein cholesterol were significantly lower in users than in nonusers. During the study period, intake of saturated fatty acids increased significantly among users and nonusers, and intakes of vitamins A and C decreased significantly with potential detrimental health effects. However, intakes of n-3 fatty acids and dietary fiber significantly increased in users and nonusers with potential health benefits. Intakes of vegetables and fish significantly increased in users. No associations were observed between intakes of nuts, fruits, or vegetables and blood cholesterol status. CONCLUSIONS: Changes in personal behaviors of dyslipidemic patients need reinforcement for effective blood lipid management, particularly for optimal food intake patterns, whether lipid-lowering drug users or nonusers.

[6] *Zhang KQ, Tian T, Hu LL et al.* **Effect of probucol on autophagy and apoptosis in the penile tissue of streptozotocin-induced diabetic rats**. Asian journal of andrology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31464204

ABSTRACT

Autophagy and apoptosis have been regarded as important processes in the development of diabetic erectile dysfunction (DMED). Probucol is considered to have anti-apoptotic effects, but its relationship with autophagy has not been reported. The aim of this study was to investigate the effects and mechanisms of probucol on erectile function. Thirty Sprague-Dawley (SD) male rats (12 weeks old) were fasted for 12 h. Twenty SD rats were injected with a single intraperitoneal injection of 60 mg kg(-1) streptozotocin (STZ). Ten rats were given vehicle only and used as a sham group. After 72 h, 20 STZ-treated rats with random blood glucose concentrations consistently greater than 16.7 mmol l(-1) were used as successfully established diabetic rats. The diabetic rats were divided randomly into two groups and treated with a daily gavage of probucol at a dose of 0 or 500 mg kg(-1) for 12 weeks. After treatment, the intracavernous pressure (ICP) was used to measure erectile function upon electrical stimulation of the cavernous nerve. After euthanasia, penile tissue was examined using immunohistochemistry and Western blot to assess the protein levels of B-cell lymphoma-2 (Bcl-2), BCL2-associated X (Bax), microtubule-associated protein light chain 3-II (LC3-II), mammalian target of rapamycin (mTOR), and sequestosome 1 (P62). Caspase-3 activity was measured to determine apoptosis using a caspase-3 assay kit. After 12 weeks of treatment, the erectile function of the probucol group was significantly better than that of the DM group ($P < 0.05$). Bax and LC3-II protein expression and caspase-3 activity were significantly lower in the probucol group than those in the DM group (all $P < 0.05$), while Bcl-2, mTOR, and P62 protein expression

levels were significantly higher than those in the DM group (all P < 0.05). We demonstrated that probucol inhibited apoptosis and autophagy in STZ-induced diabetic rats.

[7] *Nishikido T, Ray KK*. **Targeting PCSK9: Implications for basic science and upcoming challenges**. Br J Pharmacol 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31465540
ABSTRACT
Low-density lipoprotein cholesterol (LDL-C) plays a central role in the progression of atherosclerosis. Statin therapy for lowering LDL-C reduces the risk of atherosclerotic cardiovascular disease and is the recommended first-line treatment for patients with high LDL-C levels. However, some patients are unable to achieve an adequate reduction in LDL-C with statins or are statin intolerant; thus, PCSK9 inhibitors were developed to reduce LDL-C beyond statin therapy. PCSK9 monoclonal antibodies dramatically reduce LDL-C levels and cardiovascular risk, and promising new PCSK9 inhibitors using different mechanisms are currently being developed. The absolute benefit of LDL-C reduction depends on the individual absolute risk and the achieved absolute reduction in LDL-C. Therefore, PCSK9 inhibitors may provide the greatest benefits from further LDL-C reduction for the highest risk patients. Here, we focus on PCSK9-targeted therapies and discuss the challenges of LDL-C reduction for prevention of atherogenic cardiovascular disease.

[8] *Herminghaus A, Laser E, Schulz J et al.* **Pravastatin and Gemfibrozil Modulate Differently Hepatic and Colonic Mitochondrial Respiration in Tissue Homogenates from Healthy Rats**. Cells 2019; 8.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31461874
ABSTRACT
Statins and fibrates are widely used for the management of hypertriglyceridemia but they also have limitations, mostly due to pharmacokinetic interactions or side effects. It is conceivable that some adverse events like liver dysfunction or gastrointestinal discomfort are caused by mitochondrial dysfunction. Data about the effects of statins and fibrates on mitochondrial function in different organs are inconsistent and partially contradictory. The aim of this study was to investigate the effect of pravastatin (statin) and gemfibrozil (fibrate) on hepatic and colonic mitochondrial respiration in tissue homogenates. Mitochondrial oxygen consumption was determined in colon and liver homogenates from 48 healthy rats after incubation with pravastatin or gemfibrozil (100, 300, 1000 muM). State 2 (substrate dependent respiration) and state 3 (adenosine diphosphate: ADP-dependent respiration) were assessed. RCI (respiratory control index)-an indicator for coupling between electron transport chain system (ETS) and oxidative phosphorylation (OXPHOS) and ADP/O ratio-a parameter for the efficacy of OXPHOS, was calculated. Data were presented as a percentage of control (Kruskal-Wallis + Dunn's correction). In the liver both drugs reduced state 3 and RCI, gemfibrozil-reduced ADP/O (complex I). In the colon both drugs reduced state 3 but enhanced ADP/O. Pravastatin at high concentration (1000 microM) decreased RCI (complex II). Pravastatin and gemfibrozil decrease hepatic but increase colonic mitochondrial respiration in tissue homogenates from healthy rats.

[9] *Chelvanambi S, Gupta SK, Chen X et al.* **HIV-Nef Protein Transfer to Endothelial Cells Requires Rac1 Activation and Leads to Endothelial Dysfunction: Implications for Statin Treatment in HIV Patients**. Circulation research 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31451038
ABSTRACT
RATIONALE: Even in antiretroviral therapy (ART) treated patients, HIV continues to play a pathogenic role in cardiovascular diseases. A possible cofactor may be persistence of the early HIV response gene Nef, which we have demonstrated recently to persist in the lungs of HIV+ patients on ART. Previously, we have reported that HIV strains with Nef, but not Nef-deleted HIV strains, cause endothelial proinflammatory activation and apoptosis. OBJECTIVE: To characterize mechanisms through which HIV-Nef leads to the development of cardiovascular diseases using ex vivo tissue culture approaches as well as interventional experiments in transgenic murine models. METHODS AND RESULTS: EV (extracellular vesicles) derived from both peripheral blood mononuclear cells (PBMC) and plasma from HIV+ patient blood samples induced human coronary artery endothelial cells dysfunction. Plasma derived EV from ART+ patients that were HIV-Nef+ induced significantly greater endothelial apoptosis compared to HIV-Nef- plasma EV. Both HIV-Nef expressing T cells and HIV-Nef-induced EV increased transfer of cytosol and Nef protein to endothelial monolayers in a Rac1-dependent manner, consequently leading to endothelial adhesion protein upregulation and apoptosis. HIV-Nef induced Rac1 activation also led to dsDNA breaks in endothelial colony forming cells (ECFC), thereby resulting in ECFC premature senescence and eNOS downregulation. These Rac1 dependent activities were characterized by NOX2-mediated ROS production. Statin treatment equally inhibited Rac1 inhibition in preventing or reversing all HIV-Nef-induction abnormalities assessed. This was likely due to the ability of statins to block Rac1 prenylation as geranylgeranyl transferase inhibitors were effective in inhibiting HIV-Nef-induced ROS formation. Finally, transgenic expression of HIV-Nef in endothelial cells in a murine model impaired endothelium-mediated aortic ring dilation, which was then reversed by 3-week treatment with 5mg/kg atorvastatin. CONCLUSION: Conclusions: These studies establish a mechanism by which HIV-Nef persistence despite ART could contribute to ongoing HIV related vascular dysfunction which may then be ameliorated by statin treatment.

[10] *Haynes R, Valdes-Marquez E, Hopewell JC et al.* **Serious Adverse Effects of Extended-Release Niacin/Laropiprant: Results From the Heart Protection Study 2-Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) Trial**. Clinical therapeutics 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31447131
ABSTRACT
PURPOSE: The Heart Protection Study 2-Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) trial of patients at high risk of vascular disease found that adding extended-release niacin-laropiprant to intensive statin-based LDL-lowering therapy had no benefit on cardiovascular outcomes. However, the trial also identified previously unrecognized serious adverse effects (including new-onset diabetes, bleeding, and infection). Our objective was to explore the safety profile of niacin-laropiprant and examine whether any patients were at lower (or higher) risk of its adverse effects. METHODS: HPS2-THRIVE was a randomized, double-blind trial of niacin-laropiprant (2000/40 mg/d) versus placebo among 25,673 patients

at high risk of vascular disease. Information on all serious adverse events was collected during a median of 3.9 years of study treatment. Effects of niacin-laropiprant on new-onset diabetes, disturbances of diabetes control, bleeding, infection, and gastrointestinal upset were estimated by (1) time after randomization, (2) severity, (3) baseline characteristics, (4) baseline risk of the adverse event of interest, and (5) risk of major vascular event. FINDINGS: The hazard ratio (HR) for new-onset diabetes with niacin/laropiprant was 1.32 (95% CI, 1.16-1.51; P < .001), which corresponded to an absolute excess of 4 people (95% CI, 2-6) developing diabetes per 1000 person-years in the study population as a whole. Among the 8299 participants with diabetes at baseline, the HR for serious disturbances in diabetes control was 1.56 (95% CI, 1.35-1.80), corresponding to an absolute excess of 12 (95% CI, 8-16) per 1000 person-years. The HR was 1.38 (95% CI, 1.17-1.63; P < .001) for serious bleeding, corresponding to an absolute excess of 2 (95% CI, 1-3) per 1000 person-years and 1.22 (95% CI, 1.11-1.34; P < .001) for serious infection, corresponding to an absolute excess of 4 (95% CI, 2-6) per 1000 person-years. The excess risks of these serious adverse events were larger in the first year after starting niacin-laropiprant therapy than in later years (except for the excess of infection, which did not appear to attenuate with time), and the risks of nonfatal and fatal events were similarly increased. The absolute excesses of each of these adverse effects were similar regardless of the baseline risk of the outcome. IMPLICATIONS: Practitioners or patients considering the use of niacin (in addition to, or instead of, a statin) despite the lack of evidence of cardiovascular benefits (at least when added to effective statin therapy) should take account of the significant risks of these serious adverse effects when making such decisions. ClinicalTrials.gov identifier: NCT00461630.

[11] *Panagiotopoulou O, Chiesa ST, Tousoulis D, Charakida M*. **Dyslipidaemias and cardiovascular disease: Focus on the role of PCSK9 inhibitors**. Curr Med Chem 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31453780
ABSTRACT
Genetic, experimental and clinical studies have consistently confirmed that inhibition of proprotein convertase subtilisin/kexin type 9 (PCSK9) can result in significant LDL-C lowering and two fully human PCSK9 mononclonal antibodies have received regulatory approval for use in high-risk patients. Co- administration of PCSK9 with statins has resulted in extremely low LDL-C levels with excellent short-term safety profiles. While results from Phase III clinical trials provided exciting evidence about the role of PCSK9 inhibitors in reducing cardiovascular event rates, their impact on mortality remains less clear. PCSK9 inhibitor therapy can be considered for high risk patients who are likely to experience the largest cardiovascular risk reduction benefit.

[12] *Hirakata T, Yokomizo T, Matsuda A*. **The roles of omega-3 fatty acids and resolvins in allergic conjunctivitis**. Current opinion in allergy and clinical immunology 2019; 19:517-525.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31465315
ABSTRACT
PURPOSE OF REVIEW: Lipids are one of the most important constituents in our body. Advances of lipidomics are elucidating the new roles of various lipid molecules in allergic diseases. For example, some reports showed anti-inflammatory effects of omega-3 fatty acids (FAs), such as docosahexaenoic acid, eicosapentaenoic acid, and their metabolites, on allergic diseases. Here,

we introduce the role of lipid mediators in allergic conjunctivitis mouse model. RECENT FINDINGS: Lipidomics using liquid chromatography-tandem mass spectrometry can profile numerous lipid molecules from small tissue samples such as conjunctival specimens. Lipidomics analysis showed that various inflammatory lipid mediators are produced in the conjunctival tissue of allergic conjunctivitis mouse model. Dietary omega-3 FAs reduced these inflammatory lipid mediators in the conjunctiva and alleviated allergic conjunctivitis symptoms in mouse models. In addition, the roles of specialized proresolving lipid mediators (SPMs) have been reported for allergic inflammation. SUMMARY: Lipid mediators have important roles for the pathophysiology of the allergic diseases including allergic conjunctivitis. Omega-3 FAs and SPMs are expected as new treatment tools for allergic conjunctivitis.

[13] *Patel PN, Patel SM, Bhatt DL*. **Cardiovascular risk reduction with icosapent ethyl**. Current opinion in cardiology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31464773
ABSTRACT
PURPOSE OF REVIEW: Residual risk for atherosclerotic cardiovascular disease (ASCVD) persists even among patients with optimal low-density lipoprotein cholesterol (LDL-C) levels. Randomized trials attempting to modulate other lipids beyond LDL-C have failed to demonstrate significant reductions in ischemic events. RECENT FINDINGS: Mounting evidence suggests that triglyceride elevation is an independent risk factor for ASCVD. Though trials of triglyceride-lowering therapy in the statin era have failed to provide protection from ASCVD events, subgroup analyses have revealed that those with the highest triglycerides at time of enrollment appeared to receive the greatest clinical benefit. REDUCE-IT was a trial that enrolled patients with high triglycerides despite having goal LDL-C levels on statin therapy. Treatment with icosapent ethyl, a highly purified omega-3 fatty acid (OM3FA), eicosapentaenoic acid ethyl ester, provided a 25% relative risk reduction for the primary composite cardiovascular endpoint (hazard ratio 0.75, 95% CI 0.68--0.83; P = 0.00000001), as well as a 30% relative risk reduction in total ischemic events (P = 0.00000000036). SUMMARY: Icosapent ethyl was rigorously shown to decrease residual risk for cardiovascular events, though the benefits seen were likely because of mechanisms beyond mere triglyceride lowering. Clinical application of icosapent ethyl in this cohort of patients with residual risk is urgently needed.

[14] *Silvain J, Kerneis M, Guerin M, Montalescot G*. **Modulation of cholesterol efflux capacity in patients with myocardial infarction**. Current opinion in cardiology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31464772
ABSTRACT
PURPOSE OF REVIEW: Epidemiologic studies consistently demonstrated that patients with coronary artery disease (CAD) and low HDL cholesterol (HDL-C) are more likely to develop major adverse cardiovascular events as compared with those with normal or high HDL. However, several large randomized trials failed to demonstrate that a substantial, pharmacological-based, increase of HDL-C concentrations results in a clinically significant reduction of ischemic outcomes. This has been largely attributed to the fact that, although these drugs are able to raise the HDL-C concentration, they have no effect on HDL-C atheroprotective function. Subsequently, the 'HDL hypothesis' evolved, and the focus shifted from raising the

concentration of HDL-C to raising the reverse cholesterol transport (RCT) function by increasing patients cholesterol efflux capacity (CEC) instead. Indeed, new data suggest that HDL-C metabolism and the ability of the HDL molecule to transport cholesterol from the atherosclerotic plaque to the liver, measured by the CEC, is more important than steady-state HDL-C levels. Modulation of the CEC has become, therefore, a promising therapeutic target in CAD patients. This article reviews the current data on the 'cholesterol efflux hypothesis' and discuss its ability to be modulated has a potential therapeutic target. RECENT FINDINGS: Recent data have demonstrated that impaired serum CEC was associated with increased mortality after a myocardial infarction (MI). Thus, therapeutic intervention aiming to improve CEC and RCT may reduce the risk of recurrent events. Early phase clinical studies targeting CEC showed promising results and a megatrial is ongoing testing the hypothesis that an improved RCT trough a modulation of the CEC can modify patient's prognosis after an acute MI. SUMMARY: The 'cholesterol efflux hypothesis' is now supported by several clinical studies and is being tested with a therapeutic candidate in a megatrial enrolling high-risk patient with MI.

[15] *Liberale L, Camici GG*. **The Role of Vascular Aging in Atherosclerotic Plaque Development and Vulnerability**. Current pharmaceutical design 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31470777
ABSTRACT
The ongoing demographical shift is leading to an unprecedented aging of the population. As a consequence, the prevalence of age-related diseases such as atherosclerosis and its thrombotic complications is set to increase in the near future. Endothelial dysfunction and vascular stiffening characterize arterial aging and set the stage for the development of cardiovascular diseases. Atherosclerotic plaques evolve over time, the extent to which these changes might affect their stability and predispose to sudden complications remains to be determined. Recent advances in imaging technology will allow for longitudinal prospective studies following the progression of plaque burden aimed at better characterizing changes over time associated to plaque stability or rupture. Oxidative stress and inflammation, firmly established driving forces of age-related CV dysfunction, also play an important role in atherosclerotic plaque destabilization and rupture. Several genes involved in lifespan determination are known regulator of redox cellular balance and pre-clinical evidence underline their pathophysiological roles in age-related cardiovascular dysfunction and atherosclerosis. The aim of this narrative review is to examine the impact of aging on arterial function and atherosclerotic plaque development. Furthermore, we report how molecular mechanisms of vascular aging might regulate age-related plaque modifications and how this may help to identify novel therapeutic targets to attenuate the increased risk of CV disease in elderly people.

[16] *Rana RB, Jilani K, Shahid M et al.* **Atorvastatin Induced Erythrocytes Membrane Blebbing**. Dose-response : a publication of International Hormesis Society 2019; 17:1559325819869076.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31447619
ABSTRACT
Atorvastatin, an inhibitor of 3-hydroxy-3-methylglutaryl-coenzymeA reductase, is usually used for the treatment of hypercholesterolemia. Besides its pharmacological and side actions, its toxic effects on human nucleus devoid of erythrocytes are still unknown. Eryptosis is an

alternative term used for suicidal erythrocyte death. Membrane blebbing is among the common markers of eryptosis. In this study, eryptotic effect of atorvastatin was investigated by exposing the erythrocytes for 48 hours to different concentrations (1-10 microM) of atorvastatin. The experimental work related to investigation of eryptosis was done by cell size measurement and calcium channel inhibition. As a possible mechanism of eryptosis, atorvastatin-induced oxidative stress was evaluated by determining catalase, glutathione peroxidase, and superoxide dismutase activities. Similarly, necrotic effect of atorvastatin was also determined by hemolytic assay. Results of our study illustrated that the tested doses of atorvastatin may induce oxidative stress as observed by significant reduction in superoxide dismutase, glutathione peroxidase, and catalase activities as well as induce eryptosis, featured by erythrocytes membrane blebbing. The study concluded that induction of oxidative stress by atorvastatin may lead to eryptosis.

[17] *Emami A, Shojaei S, da Silva Rosa SC et al.* **Mechanisms of simvastatin myotoxicity: The role of autophagy flux inhibition**. European journal of pharmacology 2019; 862:172616.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31449810
ABSTRACT
Statins are some of the most widely used drugs worldwide, but one of their major side effects is myotoxicity. Using mouse myoblast (C2C12) and human alveolar rhabdomyosarcoma cell lines (RH30) in both 2-dimensional (2D) and 3-dimensional (3D) cell culture, we investigated the mechanisms of simvastatin's myotoxicity. We found that simvastatin significantly reduced cell viability in C2C12cells compared to RH30cells. However, simvastatin induced greater apoptosis in RH30 compared to C2C12cells. Simvastatin-induced cell death is dependent on geranylgeranyl pyrophosphate (GGPP) in C2C12cells, while in RH30cells it is dependent on both farnesyl pyrophosphate (FPP) and GGPP. Simvastatin inhibited autophagy flux in both C2C12 and RH30cells and inhibited lysosomal acidification in C2C12cells, while autophagy inhibition with Bafilomycin-A1 increased simvastatin myotoxicity in both cell lines. Simvastatin induced greater cell death in RH30cells compared to C2C12 in a 3D culture model with similar effects on autophagy flux as in 2D culture. Overall, our results suggest that simvastatin-induced myotoxicity involves both apoptosis and autophagy, where autophagy serves a pro-survival role in both cell lines. The sensitivity to simvastatin-induced myotoxicity differs between 2D and 3D culture, demonstrating that the cellular microenvironment is a critical factor in regulating simvastatin-induced cell death in myoblasts.

[18] *Shah PK, Lecis D*. **Inflammation in atherosclerotic cardiovascular disease**. F1000Research 2019; 8.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31448091
ABSTRACT
Atherosclerotic cardiovascular disease is a leading cause of death and morbidity globally. Over the past several years, arterial inflammation has been implicated in the pathophysiology of athero-thrombosis, substantially confirming what pathologist Rudolf Virchow had observed in the 19th century. Lipid lowering, lifestyle changes, and modification of other risk factors have reduced cardiovascular complications of athero-thrombosis, but a substantial residual risk remains. In view of the pathogenic role of inflammation in athero-thrombosis, directly targeting

inflammation has emerged as an additional potential therapeutic option; and some early promising results have been suggested by the Canakinumab Anti-inflammatory Thrombosis Outcome Study (CANTOS), in which canakinumab, a fully human monoclonal antibody targeting the pro-inflammatory and pro-atherogenic cytokine interleukin 1 beta, was shown to reduce cardiovascular events.

[19] *Suwaidi JA*. **Hope for primary cardiovascular prevention with the HOPE (Heart Outcomes Prevention Evaluation)-3 trial findings**. Global cardiology science & practice 2016; 2016:e201613.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31463302
ABSTRACT
The HOPE-3 investigators enrolled 12,705 intermediate-risk participants in 21 countries in a 2-by-2 factorial trial. Subjects were randomized to receive a fixed dose of rosuvastatin or placebo, candesartan plus hydrochlorothiazide daily or placebo, and a third group received combination of antihypertensive and statins versus double placebo. The median follow-up was 5.6 years. The combination of antihypertensive and statin therapy was associated with a significantly lower rate of cardiovascular events than dual placebo. Statin therapy alone was also associated with improved outcome, while antihypertensive therapy had no added benefit compared to placebo.

[20] *Al Mahmeed W, Bakir S, Beshyah SA et al.* **Prevalence of Lipid Abnormalities and Cholesterol Target Value Attainment in Patients with Stable and Acute Coronary Heart Disease in the United Arab Emirates**. Heart views : the official journal of the Gulf Heart Association 2019; 20:37-46.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31462957
ABSTRACT
Background: Careful management of lipid abnormalities in patients with coronary heart disease (CHD) or an acute coronary syndrome (ACS) can reduce the risk of recurrent cardiovascular events. The extent of hyperlipidemia in these very high-risk patients in the United Arab Emirates (UAE), along with the treatment strategies employed, is not clear. Methods: The Dyslipidemia International Study II was a multinational observational analysis carried out from 2012 to 2014. Patients were enrolled if they had either stable CHD or an ACS. Patient characteristics, lipid levels, and use of lipid-lowering therapy (LLT) were recorded at enrollment. For the ACS patients, the LLT used during the 4 months' follow-up period was documented, as were any cardiovascular events. Results: A total of 416 patients were recruited from two centers in the UAE, 216 with stable CHD and 200 hospitalized with an ACS. Comorbidities and cardiovascular risk factors were extremely common. A low-density lipoprotein cholesterol level of <70 mg/dl, recommended for patients at very high cardiovascular risk, was attained by 39.3% of the LLT-treated CHD patients and 33.3% of the LLT-treated ACS patients at enrollment. The mean atorvastatin-equivalent daily statin dose was 29 +/- 15 mg for the CHD patients, with 13.7% additionally using ezetimibe. For the ACS patients, the daily dosage was 23 +/- 13 mg at admission, rising to 39 +/- 12 mg by the end of the 4-month follow-up. The use of nonstatin agents was extremely low in this group. Conclusions: Despite LLT being widely used, hyperlipidemia was found to be prevalent in ACS and CHD patients in the UAE. Treatment

strategies need to be significantly improved to reduce the rate of cardiovascular events in these very high-risk patients.

[21] *Hajar R*. **PCSK 9 Inhibitors: A Short History and a New Era of Lipid-lowering Therapy**. Heart views : the official journal of the Gulf Heart Association 2019; 20:74-75.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31462965
ABSTRACT

[22] *Perrone V, Veronesi C, Gambera M et al.* **Treatment with Free Triple Combination Therapy of Atorvastatin, Perindopril, Amlodipine in Hypertensive Patients: A Real-World Population Study in Italy**. High blood pressure & cardiovascular prevention : the official journal of the Italian Society of Hypertension 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31463886
ABSTRACT
INTRODUCTION: Polytherapy is often required to treat the comorbidity of hypertension and hyperlipidemia. Fixed-dose co-formulation, rather than free combinations, simplifies medication taking and also improves adherence to medication, which is the key for a successful management of these conditions. AIM: To determine the number of patients potentially eligible for treatment with triple fixed-dose atorvastatin/perindopril/amlodipine (CTAPA), and to estimate if an unmet medical need exists among CTAPA free combination treated patients. METHODS: This observational retrospective study was based on administrative databases of 3 Italian Local Health Units. The cohort comprised adult patients with at least one prescription of amlodipine and perindopril (either as free combination or co-formulated) and atorvastatin during 2014. Follow-up period started on the date of prescription of the 3 molecules (index date) and lasted 1 year. Adherence to CTAPA was analyzed during follow-up, by using the proportion of days covered (PDC). RESULTS: 2292 patients (9.1 per 10,000 beneficiaries) had a prescription for CTAPA as free combination. Only 1249 (54.5%) were adherent to the therapy (PDC >/= 80%); among them, a small percentage required dosage modification. The number of patients with CTAPA increased during the study period. Discontinuation of drugs prescribed the year before interested 582 patients in 2014, and 522 in 2015. Considering the Italian national population (n = 60,782,668), it was estimated that 69,542 hypertensive patients could be eligible for fixed-dose CTAPA during 2014. CONCLUSIONS: Real-world analysis among patients with free combination therapy can be applied to estimate the eligible population for fixed combination, and to evaluate the appropriateness of their prescriptions. Moreover, fixed-dose CTAPA could effectively improve adherence, which was calculated to be low in the free combination cohort.

[23] *Choi S, Snider AJ*. **Diet, lipids and colon cancer**. International review of cell and molecular biology 2019; 347:105-144.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31451212
ABSTRACT
Dietary fat is digested and absorbed in the small intestine and can then be utilized as an energy source and/or as a reservoir for other bioactive lipid species. Excessive dietary fat has been implicated in the induction and/or aggravation of several diseases, including colorectal cancer

(CRC). Diets with high fat content have been shown to exacerbate CRC through regulation of intestinal inflammation and proliferation, as well as alteration of bile acid pools, microbiota, and bioactive lipid species. This chapter will investigate the effects of dietary fat on CRC development and pathobiology, and possible mechanisms for specific lipid species in those processes.

[24] *Genest J, Belanger AM, Sidhu MS*. **How the Cow Ate the CABG: Aim Low, Live Longer?** Journal of the American College of Cardiology 2019; 74:1187-1189.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31466615
ABSTRACT

[25] *Goodman SG, Aylward PE, Szarek M et al.* **Effects of Alirocumab on Cardiovascular Events After Coronary Bypass Surgery**. Journal of the American College of Cardiology 2019; 74:1177-1186.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31466614
ABSTRACT
BACKGROUND: Patients with acute coronary syndrome (ACS) and history of coronary artery bypass grafting (CABG) are at high risk for recurrent cardiovascular events and death. OBJECTIVES: This study sought to determine the clinical benefit of adding alirocumab to statins in ACS patients with prior CABG in a pre-specified analysis of ODYSSEY OUTCOMES (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab). METHODS: Patients (n = 18,924) 1 to 12 months post-ACS with elevated atherogenic lipoprotein levels despite high-intensity statin therapy were randomized to alirocumab or placebo subcutaneously every 2 weeks. Median follow-up was 2.8 years. The primary composite endpoint of major adverse cardiovascular events (MACE) comprised coronary heart disease death, nonfatal myocardial infarction, ischemic stroke, or unstable angina requiring hospitalization. All-cause death was a secondary endpoint. Patients were categorized by CABG status: no CABG (n = 16,896); index CABG after qualifying ACS, but before randomization (n = 1,025); or CABG before the qualifying ACS (n = 1,003). RESULTS: In each CABG category, hazard ratios (95% confidence intervals) for MACE (no CABG 0.86 [0.78 to 0.95], index CABG 0.85 [0.54 to 1.35], prior CABG 0.77 [0.61 to 0.98]) and death (0.88 [0.75 to 1.03], 0.85 [0.46 to 1.59], 0.67 [0.44 to 1.01], respectively) were consistent with the overall trial results (0.85 [0.78 to 0.93] and 0.85 [0.73 to 0.98], respectively). Absolute risk reductions (95% confidence intervals) differed across CABG categories for MACE (no CABG 1.3% [0.5% to 2.2%], index CABG 0.9% [-2.3% to 4.0%], prior CABG 6.4% [0.9% to 12.0%]) and for death (0.4% [-0.1% to 1.0%], 0.5% [-1.9% to 2.9%], and 3.6% [0.0% to 7.2%]). CONCLUSIONS: Among patients with recent ACS and elevated atherogenic lipoproteins despite intensive statin therapy, alirocumab was associated with large absolute reductions in MACE and death in those with CABG preceding the ACS event. (ODYSSEY OUTCOMES: Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab; NCT01663402).

[26] *Cestari RN, Rocha A, Marques MP et al.* **Simultaneous analysis of the total plasma concentration of atorvastatin and its five metabolites and the unbound plasma concentration of atorvastatin: Application in a clinical pharmacokinetic study of single oral dose**. Journal of

chromatography. B, Analytical technologies in the biomedical and life sciences 2019; 1126-1127:121766.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31450089
ABSTRACT
Atorvastatin (ATV) and its two active metabolites, o-hydroxy atorvastatin acid (o-OH-ATV) and p-hydroxy atorvastatin acid (p-OH-ATV) are responsible for its HMG-CoA (3-hydroxy-3-methylglutaryl-coenzyme-A) reductase inhibitory activity, while its corresponding inactive lactone forms (LAC) are related to the manifestation of myopathy. The present study reports the development and validation of a method for the simultaneous analysis of ATV and its five metabolites (o-OH-ATV, p-OH-ATV, ATV-LAC, o-OH-ATV-LAC, p-OH-ATV-LAC) as total plasma concentration and ATV as unbound plasma concentration using UPLC-MS/MS. The method was applied in a pharmacokinetic study following administration of a single oral 20, 40 or 80mg ATV dose in healthy volunteers (n=15). ATV and its five metabolites were separated on a C18 column using as mobile phase a mixture of 0.2% formic acid and acetonitrile (55:45, v/v) at a flow of 0.4mL/min. The method showed linearity from 25pg/mL to 200ng/mL plasma as total concentration and from 6.25pg to 25ng/mL plasma ultrafiltrate as ATV unbound concentration. The coefficients of variation and the relative standard errors of the accuracy and precision analyses were <15%. The method allowed quantification of plasma concentrations of ATV and its five metabolites up to 36h after 20, 40 or 80mg ATV administration. The pharmacokinetic parameters dose normalized to 20mg are presented as follow (n=15, mean): unbound fraction 9.38%, maximum plasma concentration 9.52ng/mL, time to reach maximum plasma concentration 0.98h, apparent total clearance 742.90L/h, apparent distribution volume 9005L, and AUC metabolite/ATV ratios 0.06 for p-OH-ATV, 0.94 for o-OH-ATV, 1.43 for ATV-LAC, 0.25 for p-OH-ATV-LAC and 1.75 for o-OH-ATV-LAC. In conclusion, the methods for simultaneous analysis of ATV and its five metabolites as total plasma concentration and ATV as the unbound plasma concentration showed sensitivity, linearity, precision and accuracy compatible with application in pharmacokinetic studies of single oral dose of 20, 40 or 80mg ATV.

[27] *Shukla AK, Mehani R*. **Safety and efficacy of alirocumab: A meta analysis of 12 randomized controlled trials**. Journal of family medicine and primary care 2019; 8:2249-2257.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31463238
ABSTRACT
Background and Objective: Hypercholesterolemia is one of the major risk factor for atherosclerotic coronary heart disease, especially coronary heart disease. Most effective class of medications for prevention of cardiovascular events and LDL-C reduction are the statins. Approximately only one fourth of these high risk patients had achieved LDL-C levels <70 mg/dL with statins. Monoclonal antibody targeting PCSK9 is a novel class of drug used in the treatment of Hypercholesterolemia. Alirocumab is one such human monoclonal antibody directed against PCSK9. Binding of PCSK9 to the LDL-R on the hepatocytes promotes LDL-R degradation. Inhibition of PCSK9 binding to LDL-R leads to increased number of LDL-Rs to clear LDL, thus decreasing LDL-C levels. The purpose of this systematic study is to assess the safety and efficacy of Alirocumab in adults with hypercholesterolemia and Familial hypercholesterolemia. Materials and Methods: We searched Medline, PubMed Central database, Google scholar, EBSCO, Wiley library, conference proceedings and Clinical trials.gov registry through March

2017. Phase 3 randomized, controlled trials (RCTs) using Alirocumab in adults with hypercholesterolemia and Familial Hypercholesterolemia were selected. Results: In twelve RCTs comprising of 6019 patients included in the meta-analysis, significant favorable changes in LDL-C and HDL-C were found. Limitations: Results were derived from study level data rather than patient level data. Conclusions: Alirocumab substantially reduced the LDL-C level by over 50 %, increased the HDL-C level, and resulted in favorable changes in other lipids.

[28] *Baumgartner S, Ras RT, Trautwein EA et al.* **Plasma oxyphytosterol concentrations are not associated with CVD status in Framingham Offspring Study participants**. Journal of lipid research 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31455614
ABSTRACT
Dietary plant sterols, such as campesterol and sitosterol, reduce plasma cholesterol concentrations, but any relationship to plaque development and cardiovascular disease remains unclear. Some epidemiologic studies have suggested that elevated plasma plant sterol concentrations are atherogenic - including the Framingham Offspring Study that identified a positive association between plant sterol concentrations and CVD status. We hypothesized that this suggested atherogenicity relates to the oxidation status of plant sterols (i.e., concentrations of plasma oxyphytosterols). Therefore, in the Framingham Offspring Study Cohort, we measured plasma oxyphytosterol concentrations in 144 patients with documented CVD and/or more than 50% carotid stenosis and 383 matched controls. We analyzed plasma oxyphytosterol concentrations by GC-MS/MS and performed conditional logistic regression analysis to determine associations between plasma plant sterol or oxyphytosterol concentrations and CVD status. We found that higher total cholesterol (TC)-standardized campesterol concentrations (odds ratio [OR], 2.36; 95% CI, 1.60-3.50) and higher sitosterol concentrations (OR, 1.47; 95% CI, 1.09-1.97) were significantly associated with increased CVD risk, as in the earlier study. However, the sum of absolute oxyphytosterol concentrations (OR, 0.99; 95% CI, 0.81-1.21) and the sum of TC-standardized oxyphytosterol concentrations (OR, 0.98; 95% CI, 0.80-1.19) were not associated with an increased CVD risk. Results were comparable for individual absolute and TC-standardized oxycampesterol and oxysitosterol concentrations. Plasma non-oxidized TC-standardizedsitosterol and campesterol concentrationsshowed weak or no correlations with oxyphytosterol concentrations, while all individual plasma concentrations of oxyphytosterol correlated with each other. In conclusion, circulating plasma oxyphytosterols are not associated with CVD risk in the Framingham Offspring Study.

[29] *Ajdidi A, Sheehan G, Abu Elteen K, Kavanagh K*. **Assessment of the in vitro and in vivo activity of atorvastatin against Candida albicans**. Journal of medical microbiology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31460860
ABSTRACT
Aim. The aim of this work was to characterize the response of Candida albicans to atorvastatin, and to assess its in vivo antifungal capability.Methodology. The effect of atorvastatin on the growth and viability of C. albicans was assessed. The ability of the statin to alter cell permeability was quantified by measuring amino acid and protein leakage. The response of C. albicans to atorvastatin was assessed using label-free quantitative proteomics. The in vivo

antifungal activity of atorvastatin was assessed using Galleria mellonella larvae infected with C. albicans.Results. Atorvastatin inhibited the growth of C. albicans. The atorvastatin-treated cells showed lower ergosterol levels than the controls, demonstrated increased calcofluor staining and released elevated quantities of amino acids and protein. Larvae infected with C. albicans showed a survival rate of 18.1+/-4.2 % at 144 h. In contrast, larvae administered atorvastatin (9.09 mg kg(-1)) displayed a survival rate of 60.2+/-6.4 % (P<0.05). Label-free quantitative proteomics identified 1575 proteins with 2 or more peptides and 465 proteins were differentially abundant (P<0.05). There was an increase in the abundance of enzymes with oxidoreductase and hydrolase activity in atorvastatin-treated cells, and squalene monooxygenase (4.52-fold increase) and lanosterol synthase (2.84-fold increase) were increased in abundance. Proteins such as small heat shock protein 21 (-6.33-fold) and glutathione peroxidase (-2.05-fold) were reduced in abundance.Conclusion. The results presented here indicate that atorvastatin inhibits the growth of C. albicans and is capable of increasing the survival of G. mellonella larvae infected with C. albicans.

[30] *Sil S, Dagur RS, Liao K et al.* **Strategies for the use of Extracellular Vesicles for the Delivery of Therapeutics**. Journal of neuroimmune pharmacology : the official journal of the Society on NeuroImmune Pharmacology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31456107
ABSTRACT
Extracellular vesicles (EVs) are nanosized, membrane-bound vesicles released from eukaryotic and prokaryotic cells that can transport cargo containing DNA, RNA, lipids and proteins, between cells as a means of intercellular communication. Although EVs were initially considered to be cellular debris deprived of any essential biological functions, emerging literature highlights the critical roles of EVs in the context of intercellular signaling, maintenance of tissue homeostasis, modulation of immune responses, inflammation, cancer progression, angiogenesis, and coagulation under both physiological and pathological states. Based on the ability of EVs to shuttle proteins, lipids, carbohydrates, mRNAs, long non-coding RNAs (lncRNAs), microRNAs, chromosomal DNA, and mitochondrial DNA into target cells, the presence and content of EVs in biofluids have been exploited for biomarker research in the context of diagnosis, prognosis and treatment strategies. Additionally, owing to the characteristics of EVs such as stability in circulation, biocompatibility as well as low immunogenicity and toxicity, these vesicles have become attractive systems for the delivery of therapeutics. More recently, EVs are increasingly being exploited as conduits for delivery of therapeutics for anticancer strategies, immunomodulation, targeted drug delivery, tissue regeneration, and vaccination. In this review, we highlight and discuss the multiple strategies that are employed for the use of EVs as delivery vehicles for therapeutic agents, including the potential advantages and challenges involved. Graphical abstract.

[31] *Lorza-Gil E, Garcia-Arevalo M, Favero BC et al.* **Diabetogenic effect of pravastatin is associated with insulin resistance and myotoxicity in hypercholesterolemic mice**. Journal of translational medicine 2019; 17:285.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31455371
ABSTRACT

BACKGROUND: HMG-CoA reductase inhibitors (statins) are cholesterol-lowering drugs widely used to treat hypercholesterolemia and prevent cardiovascular disease. Statins are generally well tolerated, but adverse reactions may occur, particularly myopathy and new onset of diabetes. The exact mechanism of statin-induced myopathy and diabetes has not been fully elucidated. We have previously shown that treatment of hypercholesterolemic (LDLr(-/-)) mice with pravastatin for 2 months decreased pancreatic islet insulin secretion and increased oxidative stress and cell death, but no glucose intolerance was observed. The purpose of the current work was to study long-term pravastatin effects on glucose homeostasis, insulin sensitivity, muscle protein turnover and cell viability. METHODS: LDLr(-/-) mice were treated with pravastatin for 3, 6 and 10 months. Glucose tolerance, insulin resistance and glucose-stimulated insulin secretion were evaluated. The rates of protein synthesis and degradation were determined in gastrocnemius muscle after 10 months of treatment. Insulin signalling, oxidative stress and cell death were analysed in vitro using C2C12 myotubes. RESULTS: After 6 and 10 months of treatment, these mice became glucose intolerant, and after 10 months, they exhibited marked insulin resistance. Reduced islet glucose-stimulated insulin secretion was observed after the 3rd month of treatment. Mice treated for 10 months showed significantly decreased body weight and increased muscle protein degradation. In addition, muscle chymotrypsin-like proteasomal activity and lysosomal cathepsin were markedly elevated. C2C12 myotubes exposed to increasing concentrations of pravastatin presented dose-dependent impairment of insulin-induced Akt phosphorylation, increased apoptotic markers (Bax protein and cleaved caspase-3) and augmented superoxide anion production. CONCLUSIONS: In addition to reduced insulin secretion, long-term pravastatin treatment induces insulin resistance and muscle wasting. These results suggest that the diabetogenic effect of statins is linked to the appearance of myotoxicity induced by oxidative stress, impaired insulin signalling, proteolysis and apoptosis.

[32] *Ray KK, Corral P, Morales E, Nicholls SJ*. **Pharmacological lipid-modification therapies for prevention of ischaemic heart disease: current and future options**. Lancet 2019; 394:697-708.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31448741

ABSTRACT

Atherosclerosis and its clinical manifestation as ischaemic heart disease remains a considerable health burden. Given that many factors contribute to ischaemic heart disease, a multifactorial approach to prevention is recommended, starting with lifestyle advice, smoking cessation, and control of known cardiovascular risk factors, such as blood pressure and lipids. Within the lipid profile, the principal target is lowering LDL cholesterol, firstly with lifestyle interventions and subsequently with pharmacological therapy. Statins are the recommended first-line pharmacological treatment. Some individuals might require further lowering of LDL cholesterol or be unable to tolerate statins. Additional therapies targeting different pathways in cholesterol metabolism are now available, ranging from small molecules taken orally, to injectable therapies. Examples include ezetimibe, which targets Niemann-Pick C1-like protein, and monoclonal antibodies that target PCSK9. Phase 3 trials have also been completed for bempedoic acid (targeting ATP-citrate lyase) and inclisiran (an interference RNA-based therapeutic targeting hepatic PCSK9 synthesis). In addition to LDL cholesterol, mendelian randomisation studies support a causal role for lipoprotein(a) and triglycerides in ischaemic

heart disease. In this Series paper, we appraise currently available and emerging therapies for lowering LDL cholesterol, lipoprotein(a), and triglycerides for prevention of ischaemic heart disease.

[33] *Roshandel G, Khoshnia M, Poustchi H et al.* **Effectiveness of polypill for primary and secondary prevention of cardiovascular diseases (PolyIran): a pragmatic, cluster-randomised trial**. Lancet 2019; 394:672-683.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31448738
ABSTRACT
BACKGROUND: A fixed-dose combination therapy (polypill strategy) has been proposed as an approach to reduce the burden of cardiovascular disease, especially in low-income and middle-income countries (LMICs). The PolyIran study aimed to assess the effectiveness and safety of a four-component polypill including aspirin, atorvastatin, hydrochlorothiazide, and either enalapril or valsartan for primary and secondary prevention of cardiovascular disease. METHODS: The PolyIran study was a two-group, pragmatic, cluster-randomised trial nested within the Golestan Cohort Study (GCS), a cohort study with 50 045 participants aged 40-75 years from the Golestan province in Iran. Clusters (villages) were randomly allocated (1:1) to either a package of non-pharmacological preventive interventions alone (minimal care group) or together with a once-daily polypill tablet (polypill group). Randomisation was stratified by three districts (Gonbad, Aq-Qala, and Kalaleh), with the village as the unit of randomisation. We used a balanced randomisation algorithm, considering block sizes of 20 and balancing for cluster size or natural log of the cluster size (depending on the skewness within strata). Randomisation was done at a fixed point in time (Jan 18, 2011) by statisticians at the University of Birmingham (Birmingham, UK), independent of the local study team. The non-pharmacological preventive interventions (including educational training about healthy lifestyle-eg, healthy diet with low salt, sugar, and fat content, exercise, weight control, and abstinence from smoking and opium) were delivered by the PolyIran field visit team at months 3 and 6, and then every 6 months thereafter. Two formulations of polypill tablet were used in this study. Participants were first prescribed polypill one (hydrochlorothiazide 12.5 mg, aspirin 81 mg, atorvastatin 20 mg, and enalapril 5 mg). Participants who developed cough during follow-up were switched by a trained study physician to polypill two, which included valsartan 40 mg instead of enalapril 5 mg. Participants were followed up for 60 months. The primary outcome-occurrence of major cardiovascular events (including hospitalisation for acute coronary syndrome, fatal myocardial infarction, sudden death, heart failure, coronary artery revascularisation procedures, and non-fatal and fatal stroke)-was centrally assessed by the GCS follow-up team, who were masked to allocation status. We did intention-to-treat analyses by including all participants who met eligibility criteria in the two study groups. The trial was registered with ClinicalTrials.gov, number NCT01271985. FINDINGS: Between Feb 22, 2011, and April 15, 2013, we enrolled 6838 individuals into the study-3417 (in 116 clusters) in the minimal care group and 3421 (in 120 clusters) in the polypill group. 1761 (51.5%) of 3421 participants in the polypill group were women, as were 1679 (49.1%) of 3417 participants in the minimal care group. Median adherence to polypill tablets was 80.5% (IQR 48.5-92.2). During follow-up, 301 (8.8%) of 3417 participants in the minimal care group had major cardiovascular events compared with 202 (5.9%) of 3421 participants in the polypill group (adjusted hazard ratio [HR]

0.66, 95% CI 0.55-0.80). We found no statistically significant interaction with the presence (HR 0.61, 95% CI 0.49-0.75) or absence of pre-existing cardiovascular disease (0.80; 0.51-1.12; pinteraction=0.19). When restricted to participants in the polypill group with high adherence, the reduction in the risk of major cardiovascular events was even greater compared with the minimal care group (adjusted HR 0.43, 95% CI 0.33-0.55). The frequency of adverse events was similar between the two study groups. 21 intracranial haemorrhages were reported during the 5 years of follow-up-ten participants in the polypill group and 11 participants in the minimal care group. There were 13 physician-confirmed diagnoses of upper gastrointestinal bleeding in the polypill group and nine in the minimal care group. INTERPRETATION: Use of polypill was effective in preventing major cardiovascular events. Medication adherence was high and adverse event numbers were low. The polypill strategy could be considered as an additional effective component in controlling cardiovascular diseases, especially in LMICs. FUNDING: Tehran University of Medical Sciences, Barakat Foundation, and Alborz Darou.

[34] *Mulvihill E, Ardoin S, Thompson SD et al.* **Elevated serum complement levels and higher gene copy number of complement C4B are associated with hypertension and effective response to statin therapy in childhood-onset systemic lupus erythematosus (SLE)**. Lupus science & medicine 2019; 6:e000333.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31448126
ABSTRACT
Objective: Systemic lupus erythematosus (SLE) features high frequency of cardiovascular disease (CVD) and fluctuating complement levels. The clinical trial Atherosclerosis Prevention in Pediatric Lupus Erythematosus (APPLE) aimed to evaluate whether atorvastatin treatment reduced the progression of atherosclerosis in 221 patients with childhood-onset SLE (cSLE), using carotid intima media thickness (CIMT) as surrogates. We leveraged APPLE biorepository and trial data to investigate the relationship between complement and CVD in cSLE. Methods: Gene copy numbers (GCNs) for total C4, C4A and C4B were measured by TaqMan-based real-time PCR and Southern blotting, and analysed with laboratory and clinical parameters through Student's t-test and chi(2) analyses. Effects of total C4, C4A and C4B GCNs on the response to placebo or atorvastatin treatment and progression of CIMT were examined by regression analyses. Results: At baseline, C4 protein levels strongly correlated with GCNs of total C4 (p=1.8x10(-6)). Each copy of C4 gene increased mean serum C4 by 3.28 mg/dL. Compared with those without hypertension (N=142), individuals with hypertension demonstrated significantly elevated serum levels for C4 and C3 at baseline and serially (C4: P=5.0x10(-25); C3: P=5.84x10(-20)). Individuals with >/=2 C4B genes had 2.5 times the odds of having hypertension (p=0.016) and higher diastolic blood pressure (p=0.015) compared with those with C4B deficiency. At the study end, subjects with >/=2 C4B and atorvastatin treatment had significantly slower increase in CIMT compared with those treated with placebo (p=0.018). Conclusions: cSLE with hypertension had elevated serum levels of C4 and C3 and higher GCN of C4B; cSLE with >/=2 C4B genes would benefit from statins therapy to prevent atherosclerosis.

[35] *Mangge H, Almer G*. **Immune-Mediated Inflammation in Vulnerable Atherosclerotic Plaques**. Molecules (Basel, Switzerland) 2019; 24.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31450823

ABSTRACT

Atherosclerosis is a chronic long-lasting vascular disease leading to myocardial infarction and stroke. Vulnerable atherosclerotic (AS) plaques are responsible for these life-threatening clinical endpoints. To more successfully work against atherosclerosis, improvements in early diagnosis and treatment of AS plaque lesions are required. Vulnerable AS plaques are frequently undetectable by conventional imaging because they are non-stenotic. Although blood biomarkers like lipids, C-reactive protein, interleukin-6, troponins, and natriuretic peptides are in pathological ranges, these markers are insufficient in detecting the critical perpetuation of AS anteceding endpoints. Thus, chances to treat the patient in a preventive way are wasted. It is now time to solve this dilemma because clear results indicate a benefit of anti-inflammatory therapy per se without modification of blood lipids (CANTOS Trial, NCT01327846). This fact identifies modulation of immune-mediated inflammation as a new promising point of action for the eradication of fatal atherosclerotic endpoints.

[36] *Van Laecke S*. **Lipid lowering and risk of haemorrhagic stroke in CKD**. Nature reviews. Nephrology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31467442
ABSTRACT

[37] *Soheili M, Salami M*. **Letter to the editor concerning coenzyme Q10 supplementation improves acute outcomes of stroke in rats pretreated with atorvastatin**. Nutritional neuroscience 2019:1.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31455160
ABSTRACT

[38] *A ISS, C AB, A JS*. **Changes in Plasma Free Fatty Acids Associated with Type-2 Diabetes**. Nutrients 2019; 11.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31466350
ABSTRACT

Type 2 diabetes mellitus (T2DM) is associated with increased total plasma free fatty acid (FFA) concentrations and an elevated risk of cardiovascular disease. The exact mechanisms by which the plasma FFA profile of subjects with T2DM changes is unclear, but it is thought that dietary fats and changes to lipid metabolism are likely to contribute. Therefore, establishing the changes in concentrations of specific FFAs in an individual's plasma is important. Each type of FFA has different effects on physiological processes, including the regulation of lipolysis and lipogenesis in adipose tissue, inflammation, endocrine signalling and the composition and properties of cellular membranes. Alterations in such processes due to altered plasma FFA concentrations/profiles can potentially result in the development of insulin resistance and coagulatory defects. Finally, fibrates and statins, lipid-regulating drugs prescribed to subjects with T2DM, are also thought to exert part of their beneficial effects by impacting on plasma FFA concentrations. Thus, it is also interesting to consider their effects on the concentration of FFAs in plasma. Collectively, we review how FFAs are altered in T2DM and explore the likely downstream physiological and pathological implications of such changes.

[39] *Macchi C, Sirtori CR, Corsini A et al.* **A NEW DAWN FOR MANAGING DYSLIPIDEMIAS: THE ERA OF RNA-BASED THERAPIES**. Pharmacological research : the official journal of the Italian Pharmacological Society 2019:104413.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31449975
ABSTRACT
The high occurrence of atherosclerotic cardiovascular disease (ASCVD) events is still a major public health issue. Although a major determinant of ASCVD event reduction is the absolute change of low-density lipoprotein-cholesterol (LDL-C), considerable residual risk remains and new therapeutic options are required, in particular, to address triglyceride-rich lipoproteins and lipoprotein(a) [Lp(a)]. In the era of Genome Wide Association Studies and Mendelian Randomization analyses aimed at increasing the understanding of the pathophysiology of ASCVD, RNA-based therapies may offer more effective treatment options. The advantage of oligonucleotide-based treatments is that drug candidates are targeted at highly specific regions of RNA that code for proteins that in turn regulate lipid and lipoprotein metabolism. For LDL-C lowering, the use of inclisiran - a silencing RNA that inhibits proprotein convertase subtilisin/kexin type 9 (PCSK9) synthesis - has the advantage that a single s.c. injection lowers LDL-C for up to 6 months. In familial hypercholesterolemia, the use of the antisense oligonucleotide (ASO) mipomersen, targeting apolipoprotein (apoB) to reduce LDL-C, has been a valuable therapeutic approach, despite unquestionable safety concerns. The availability of specific ASOs lowering lipoprotein (a) [Lp(a)] levels will allow rigorous testing of the Lp(a) hypothesis; by dramatically reducing plasma triglyceride levels, volanesorsen (apoC-III) and angiopoietin-like 3 (ANGPTL3)-LRx will further clarify the causality of triglyceride-rich lipoproteins in ASCVD. The rapid progress to date heralds a new dawn in therapeutic lipidology, but outcome, safety and cost-effectiveness studies are required to establish the role of these new agents in clinical practice.

[40] *Sidell MA, Ghai NR, Reynolds K et al.* **Statins as a free pass: Body mass index and other cardiovascular risk factors among lipid-lowering medication users and nonusers in the California Men's Health Study**. Prev Med 2019; 129:105822.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31470024
ABSTRACT
To lower risk from cardiovascular disease (CVD), national guidelines recommend lifestyle changes followed by use of lipid-lowering medications when appropriate. Previous studies have questioned whether individuals taking these medications are less likely to modify their dietary intake and physical activity, resulting in increased body mass index (BMI). We assessed BMI and CVD clinical risk factors over time between lipid-lowering medication users and nonusers in a diverse cohort of middle-aged and older men. The cohort consisted of 63,357 men who enrolled in the California Men's Health Study between 2002 and 2003 and were not taking lipid-lowering medications at baseline. Lipid-lowering medication use was determined over twelve years of follow-up. BMI and other CVD risk factors were assessed with longitudinal linear mixed effect models adjusting for possible confounders. Overall, lipid-lowering medication users had higher BMI than nonusers ($p<.0001$); however, there was a decrease over time for both groups ($p<.0001$). Total cholesterol, LDL-C, and triglycerides decreased for users and nonusers ($p<.0001$). While HDL-C was higher for nonusers ($p<.05$), over time this measure increased in

both groups (p<.0001). We found no evidence of increases in BMI after initiation of lipid-lowering medication in this cohort. Instead, BMI decreased and several cholesterol-related CVD risk factors improved for lipid-lowering medication users and nonusers. This suggests that men placed on lipid-lowering medications do not view them as a panacea for their increased risk of cardiovascular disease. Instead, they appear to perceive them as one component of a multi-pronged strategy including lifestyle and nutrition as suggested by current guidelines.

[41] *Gobbi CA, Asbert P, Alba PB et al.* **Subclinical markers of atherosclerosis and cardiovascular risk factors in early arthritis**. Revista de la Facultad de Ciencias Medicas (Cordoba, Argentina) 2019; 76:174-179.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31465186
ABSTRACT
Background: Mortality from cardiovascular disease (CVD) is increased in rheumatoid arthritis, not explained by traditional cardiovascular risk factors (CVRF), suggesting a role of inflammation. This process would occur early. The common sonographic markers of subclinical atherosclerosis (SA), are increased carotid intima-media thickness (cIMT) or the presence of carotid atherosclerotic plaque and they are closely related to CVD. Aims: To evaluate sonographic markers and cardiovascular risk factors in early Arthritis (EA). Methods: A case control study of patients with EA, defined by 3 joints swollen with <1 year of evolution, served consecutively from January 2011 to may 2013, matched with healthy controls, by sex, age and cardiovascular risk factors (hypertension, diabetes mellitus, cardiovascular disease -IAM and ACV, dyslipidemia, family history of CVD) was conducted. We studied demographics data, cardiovascular risk factors, carotid ultrasound measuring increased cIMT or the presence of carotid atherosclerotic plaque in Common Carotid Artery (CCA) and Carotid Bulb (BC), laboratory test that included cholesterol, LDL, HDL, triglycerides in mg%, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), anti citrullinated peptide (ACCP), rheumatoid factor (RF), antinuclear antibodies (ANA). EA activity was measured by DAS 28, considering high disease activity (HDA) 5.1; moderate (MDA) from 5.1 to 3.2; and low (LDA) <3.2. Statistics: test Mann-Whitney and chi-square were used, p <0.05 was significant. Results: 25 women, 5 men, average age 43 years (DS 14.7) and 30 controls were included. The average DAS 28 was 4, 8 +/- 1. 8; 47% had HDA, 33%MDA and 20%BDA. Both groups had similar values cIMT CCA (0, 57 +/- 0.10 mm vs. 0.58 +/- 0.15 mm, respectively, P = 0.82) and cIMT BC (0.18mm +/- 0.67 vs 0.62 +/- 0.15 mm respectively, P = 0.47). There were no carotid plaques. The median total cholesterol was 181,5 vs 183,5 (p = 0.35); triglycerides 99 vs 92,5 (p = 0.68); HDL 54,5 vs 52,5 (p = 0.921 and LDL 105 vs 110 (p = 0.27) in EA and controls respectively. The cIMT CCA and CB were not related to RF, ACCP, CRP, DAS 28 and smoking (NS). There was no difference in other cardiovascular risk factors Conclusions: Ultrasound evidence of atherosclerosis subclinical markers was not found in this study, suggesting that this process may occur after a year of diagnosis.

[42] *Hwang SD, Lee JH, Jhee JH et al.* **Effect of Fluvastatin on Cardiovascular Complications in Kidney Transplant Patients: A Systemic Review and Meta-analysis**. Transplantation proceedings 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31447193
ABSTRACT

Literature update week 35 (2019)

BACKGROUND: Hyperlipidemia and cardiovascular disease are risk factors for long-term renal transplant dysfunction. However, no meta-analyses of randomized controlled trials have investigated the effects of statin treatment on graft function in renal transplant recipients. The aim of the present study was to evaluate the effects of statin use on renal transplant patients using a meta-analysis approach. METHODS: We conducted a systematic review and meta-analysis using random effects modeling. We searched the following databases for all studies published through to June 15, 2018: Cochrane Central Register, OVID MEDLINE, Embase, and PubMed. We reviewed all relevant reviews, registered trials, and relevant conference proceedings to compare clinical outcomes and survival between fluvastatin recipients and controls. RESULTS: Five trials with a total of 3725 patients were included. Glomerular filtration rates, graft loss, tacrolimus level, antibody-mediated rejection, T cell-mediated rejection, proteinuria, fungal infection (candida), and patient survival rates did not differ between the fluvastatin and control groups. However, major adverse cardiovascular events were 1.547 times more common in the control group than in the fluvastatin group (P = .001). CONCLUSIONS: Fluvastatin use was associated with a reduction in major adverse cardiac events among kidney transplant patients.