Literature update week 44 (2018)

[1] *Cid-Silva P, Fernandez-Bargiela N, Margusino-Framinan L et al.* **Treatment with tenofovir alafenamide fumarate worsens the lipid profile of HIV-infected patients versus treatment with tenofovir disoproxil fumarate, each coformulated with elvitegravir, cobicistat, and emtricitabine**. Basic & clinical pharmacology & toxicology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30388308
ABSTRACT
Two elvitegravir/cobicistat-based therapies combined with emtricitabine/tenofovir disoproxil fumarate (EVG/c/FTC/TDF) or emtricitabine/tenofovir alafenamide fumarate (EVG/c/FTC/TAF) are currently available for HIV patients. This study evaluated the modifications in the lipid profile of patients who received these treatments in the last three years at our institution. A retrospective observational study in HIV-infected patients who received EVG/c/FTC/TDF or EVG/c/FTC/TAF from January 2015 to January 2018 at a reference hospital in northwestern Spain was carried out. Epidemiological, clinical and immunovirological data were recorded. A statistical analysis was performed using SPSS software. A total of 384 EVG/c-based therapies were initiated during the study period, 151 EVG/c/FTC/TDF and 233 EVG/c/FTC/TAF. A significantly negative influence in all the lipid profile parameters in experienced patients and total cholesterol (TC), and LDL-C in naive patients were observed after 48 weeks of treatment with EVG/c/FTC/TAF, while these parameters remained stable in the EVG/c/FTC/TDF group. During follow-up, a greater proportion of patients had lipid levels above the normal range (63.1% TC, 56.2% LDL-C) and new lipid-modifying drugs were prescribed (11.9%) in the EVG/c/FTC/TAF group. The number of cardiovascular risk factors [OR 1.66 (95% CI 1.01-2.72);p=0.043] was recognised as an independent predictor of lipid-lowering prescription for patients treated with both EVG/c/FTC/TDF and EVG/c/FTC/TAF. For patients treated with EVG/c/FTC/TAF, the mean total cholesterol to HDL ratio in the first 48 weeks of the study treatment was associated with a higher likelihood of lipid-lowering prescription in multivariate analysis [OR 1.6 (95% CI 1.12-2.52);p=0.011]. Significant changes in lipid profile have been observed in patients who have received EVG/c/FTC/TAF. It was necessary to prescribe almost twice the number of lipid-lowering drugs to patients who received EVG/c/FTC/TAF (11.9%) versus EVG/c/FTC/TDF (4.7%).

[2] *Schol-Gelok S, Galema-Boers J, van Gelder T et al.* **No effect of PCSK9 inhibitors on D-dimer and fibrinogen levels in patients with familial hypercholesterolemia**. Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie 2018; 108:1412-1414.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30372843
ABSTRACT
Statins are generally believed to have cardiovascular protective effects independent of low-density lipoprotein-cholesterol (LDL-C) lowering, such as antithrombotic effects characterized by a decrease in D-dimer levels. For the recently introduced Proprotein convertase subtilisin/kexin 9 (PCSK9) inhibitors antithrombotic effects are yet unknown. We determined the effect of starting PCSK9 inhibitors on D-dimer and fibrinogen levels as most robust markers for thrombogenicity in statin-intolerant patients with familial hypercholesterolemia. We determined D-dimer and fibrinogen levels before and after start of evolocumab (n = 19) or alirocumab (n = 11). Baseline median D-dimer levels were 0.34 mg/L (IQR 0.24-0.59 mg/L) and baseline median fibrinogen levels 3.2 g/L (IQR 2.88-3.63 g/L). At follow-up D-dimer levels

(median 0.31 mg/L (IQR 0.25-0.59 mg/L); p = 0.37), and fibrinogen levels (median 3.4 g/L (IQR 2.98-3.62 g/L); p = 0.38) did not change significantly. We therefore conclude PCSK9 inhibitors do not seem to have a profound antithrombotic effect, although a more subtle effect can not been excluded.

[3] *Choudhary MK, Eraranta A, Tikkakoski AJ et al.* **LDL cholesterol is associated with systemic vascular resistance and wave reflection in subjects naive to cardiovascular drugs**. Blood pressure 2018:1-11.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30369274
ABSTRACT
BACKGROUND AND AIM: Low density lipoprotein cholesterol (LDL-C) is a primary risk factor for atherosclerosis, but it is also associated with elevated blood pressure (BP) and future development of hypertension. We examined the relationship between LDL-C and haemodynamic variables in normotensive and never-treated hypertensive subjects. METHODS: We recruited 615 volunteers (19-72 years) without lipid-lowering and BP-lowering medication. Supine haemodynamics were recorded using continuous radial pulse wave analysis, whole-body impedance cardiography, and single channel electrocardiogram. The haemodynamic relations of LDL-C were examined using linear regression analyses with age, sex, body mass index (BMI) (or height and weight as appropriate), smoking status, alcohol use, and plasma C-reactive protein, sodium, uric acid, high density lipoprotein cholesterol (HDL-C), triglycerides, estimated glomerular filtration rate, and quantitative insulin sensitivity check index as the other included variables. RESULTS: The mean (SD) characteristics of the subjects were: age 45 (12) years, BMI 27 (4) kg/m(2), office BP 141/89 (21/13) mmHg, creatinine 74 (14) micromol/l, total cholesterol 5.2 (1.0), LDL-C 3.1 (0.6), triglycerides 1.2 (0.8), and HDL-C 1.6 (0.4) mmol/l. LDL-C was an independent explanatory factor for aortic systolic and diastolic BP, augmentation index, pulse wave velocity (PWV), and systemic vascular resistance index ($p < 0.05$ for all). When central BP was included in the model for PWV, LDL-C was no longer an explanatory factor for PWV. CONCLUSIONS: LDL-C is independently associated with BP via systemic vascular resistance and wave reflection. These results suggest that LDL-C may play a role in the pathogenesis of primary hypertension.

[4] *Athavale D, Chouhan S, Pandey V et al.* **Hepatocellular carcinoma-associated hypercholesterolemia: involvement of proprotein-convertase-subtilisin-kexin type-9 (PCSK9)**. Cancer & metabolism 2018; 6:16.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30386595
ABSTRACT
Background: PCSK9 regulates low-density lipoprotein cholesterol (LDLc) level and has been implicated in hypercholesterolemia. Aberrant plasma lipid profile is often associated with various cancers. Clinically, the relationship between altered serum lipid level and hepatocellular carcinoma (HCC) has been documented; however, the underlying cause and implications of such dyslipidemia remain unclear. Methods: The present study includes the use of HepG2 tumor xenograft model to study the potential role of glucose (by providing 15% glucose via drinking water) in regulating PCSK9 expression and associated hypercholesterolemia. To support in vivo findings, in vitro approaches were used by incubating HCC cells in culture

medium with different glucose concentrations or treating the cells with glucose uptake inhibitors. Impact of hypercholesterolemia on chemotherapy was demonstrated by exogenously providing LDLc followed by appropriate in vitro assays. Results: We observed that serum and hepatic PCSK9 level is decreased in mice which were provided with glucose containing water. Interestingly, serum and tumor PCSK9 level was upregulated in HepG2-tumor-bearing mice having access to water containing glucose. Additionally, elevated LDLc is detected in sera of these mice. In vitro studies indicated that PCSK9 expression was increased by high glucose availability with potential involvement of reactive oxygen species (ROS) and sterol regulatory element binding protein-1 (SREBP-1). Furthermore, it is also demonstrated that pre-treatment of cells with LDLc diminishes cytotoxicity of sorafenib in HCC cells. Conclusion: Taken together, these results suggest a regulation of PCSK9 by high glucose which could contribute, at least partly, towards understanding the cause of hypercholesterolemia in HCC and its accompanied upshots in terms of altered response of HCC cells towards cancer therapy.

[5] *Takafuji Y, Hori M, Mizuno T, Harada-Shiba M*. **Humoral factors secreted from adipose tissue-derived mesenchymal stem cells ameliorate atherosclerosis in Ldlr-/- mice**. Cardiovascular research 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30388208
ABSTRACT
Aims: Atherosclerosis is a chronic inflammatory disease of the vasculature. Mesenchymal stem cells (MSCs) exert immunomodulatory and immunosuppressive effects by secreting humoral factors; however, the intravascular MSC administration presents a risk of vascular occlusion. Here, we investigated both the effect of conditioned medium from cultured MSCs (MSC-CM) on atherosclerosis and the underlying mechanism. Methods and Results: Low-density lipoprotein receptor-deficient (Ldlr-/-) mice were fed a high-fat diet and received intravenous injections of either MSC-CM from adipose tissue-derived MSCs or control medium 2x/week for 13 weeks. MSC-CM treatment decreased the atherosclerotic plaque area in the aorta and aortic root of Ldlr-/- mice by 41% and 30%, respectively, with no change in serum lipoprotein levels. Histopathologically, the MSC-CM treatment decreased the expression of cell adhesion molecules (CAMs) and the accumulation of macrophages on the vascular walls. Extracellular vesicles (EVs) and supernatant (MSC-CM supernatant) were separated from the MSC-CM by ultracentrifugation. In tumour necrosis factor-a-stimulated human aortic endothelial cells (HAOECs), both the MSC EVs and MSC-CM supernatant decreased CAM expression by inhibiting the mitogen-activated protein kinase (MAPK) and nuclear factor-kappa B (NFkappaB) pathways. In macrophages, the MSC-CM supernatant decreased the lipopolysaccharide-induced increases in M1 marker expression by inhibiting both the MAPK and NFkappaB pathways and increased the expression of M2 markers by activating the signal transducer and activator of transcription 3 pathway. In co-culture, inflamed HAOECs pretreated with MSC-CM supernatant and MSC EVs exhibited decreased monocyte adhesion to HAOECs. In addition, the neutralization of hepatocyte growth factor (HGF) in MSC-CM or MSC-CM supernatant attenuated their abilities to suppress monocyte adhesion to HAOECs in co-culture. Conclusion: MSC-CM ameliorated atherosclerosis in Ldlr-/- mice and suppressed CAM expression and macrophage accumulation

in the vascular walls. Humoral factors, including HGF and EVs from MSCs, hold promise as therapeutic agents to reduce the residual risk of coronary artery diseases.

[6] *Park KY, Heo TH*. **Combination therapy with cilostazol and pravastatin improves antiatherogenic effects in LDLR KO mice**. Cardiovascular therapeutics 2018:e12476.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30378752
ABSTRACT
AIMS: Despite the therapeutic efficacy of statins and antiplatelet agents for atherosclerosis, monotherapy with each drug alone is often insufficient to achieve the patient's therapeutic goals. We previously showed that combined statin/antiplatelet agent/anti-TNF agent therapy (pravastatin/sarpogrelate/etanercept) reduces atherosclerotic lesions by inhibiting TNF, an atherogenic cytokine that contributes to the progression of arteriosclerosis. In addition, our previous study showed that combined treatment with pravastatin and cilostazol is effective for reducing TNF-driven inflammation through anti-TNF activity. Therefore, in the present study, we evaluated the additive effects of combined pravastatin and cilostazol therapy on atherosclerotic progression using LDLR KO mice. METHODS: Ten-week-old LDLR KO mice were fed a high-fat, high-cholesterol diet and orally administered pravastatin and cilostazol alone or in combination. Body weight, plasma lipid levels, and the levels of intracellular adhesion molecules and inflammatory cytokines were analyzed. In addition, aortas and aortic roots were stained with Oil Red O, and atherosclerotic plaques were quantified. RESULTS: The atherosclerotic plaques in the combined pravastatin and cilostazol treatment groups were significantly reduced compared to those in each drug monotherapy group. The combination therapy group also showed the downregulation of ICAM-1, MOMA-2, TNF, IL-6, triglyceride, total cholesterol and low-density lipoprotein levels and the upregulation of high-density lipoprotein levels compared to those of the pravastatin- or cilostazol-treated groups. CONCLUSIONS: Our results suggest that combination therapy with pravastatin and cilostazol exerts beneficial effects by decreasing atherosclerotic lesion progression and improving the proinflammatory state in the vascular endothelium. These effects are mediated by the reduction of adhesion molecule expression, immune cell infiltration, and cytokine levels and the antiatherosclerotic modulation of serum cholesterol levels. Therefore, we conclude that combined treatment with pravastatin and cilostazol may be a more effective antiatherosclerotic strategy than treatment with either agent alone.

[7] *Hinkle JW, Relhan N, Flynn HW, Jr.* **Lipemia Retinalis, Macular Edema, and Vision Loss in a Diabetic Patient with a History of Type IV Hypertriglyceridemia and Pancreatitis**. Case reports in ophthalmology 2018; 9:425-430.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30386228
ABSTRACT
Background: Lipemia retinalis is a rare but known complication of elevated serum triglycerides. This case describes the clinical course of a diabetic patient who presented with lipemia retinalis and macular edema, which responded to systemic and local treatments. Case Report: A 40-year-old female with a history of type II diabetes mellitus, hypertriglyceridemia, and pancreatitis presented with decreased vision in the left eye. She had peripapillary and macular

edema, intraretinal hemorrhages, and prominent exudates in the setting of lipemia retinalis due to type IV hypertriglyceridemia. She was treated with serial intravitreal bevacizumab injections for macular edema and systemic lipid lowering therapy, and her visual acuity improved back to baseline. Conclusions: In the setting of lipemia retinalis and hypertriglyceridemia, the current patient developed macular edema and vision loss. The macular edema was treated with intravitreal injections of bevacizumab, and the patient experienced a rapid recovery of visual acuity.

[8] *Cavallari I, Delli Veneri A, Maddaloni E et al.* **Comparison of Lipid-Lowering Medications and Risk for Cardiovascular Disease in Diabetes**. Current diabetes reports 2018; 18:138.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30370486
ABSTRACT
PURPOSE OF THE REVIEW: To summarize available evidence regarding lipid-lowering interventions for the prevention of cardiovascular disease in patients with diabetes. RECENT FINDINGS: Statins and non-statin therapies that act through upregulation of LDL receptor expression are associated with similar cardiovascular risk reduction per decrease in LDL cholesterol. In subjects with diabetes, with or without established cardiovascular disease, each 39 mg/dl reduction in LDL cholesterol observed with statins is associated with a 21% relative reduction in the risk of major coronary events at 5 years. Statins remain the first-line lipid-lowering agents for the management of dyslipidemia in individuals with diabetes; however, the addition of non-statin therapies to lower LDL cholesterol, such as ezetimibe and PCSK-9 inhibitors, to maximally tolerated statin therapy is recommended in patients with atherosclerotic cardiovascular disease and baseline LDL cholesterol over 70 mg/dl. Recent data support even lower LDL cholesterol targets (< 55 mg/dl) to further reduce the risk of cardiovascular events especially in subjects with diabetes and documented cardiovascular disease.

[9] *Mata P, Alonso R, Perez de Isla L*. **Atherosclerotic cardiovascular disease risk assessment in familial hypercholesterolemia: does one size fit all?** Current opinion in lipidology 2018; 29:445-452.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30382952
ABSTRACT
PURPOSE OF REVIEW: Familial hypercholesterolemia is a frequent genetic disease associated with lifelong elevation of LDL-cholesterol and premature atherosclerotic cardiovascular disease (ASCVD). Statins are the cornerstone of treatment. However, with the introduction of novel LDL-cholesterol-lowering therapies, it is necessary to identify familial hypercholesterolemia patients presenting a significantly high residual ASCVD risk. The aim of this review is to provide an update on the recent literature concerning cardiovascular risk stratification including the role of coronary imaging. RECENT FINDINGS: Several factors have shown to be independent predictors of ASCVD in familial hypercholesterolemia. These include clinical scores with cardiovascular risk factors, coronary imaging and novel protein biomarkers. However, the recent introduction of the SAFEHEART risk-equation (SAFEHEART-RE) could allow a more accurate ASCVD risk prediction in familial hypercholesterolemia. SUMMARY: This article highlights the SAFEHEART-RE as a model to predict incident ASCVD in familial

hypercholesterolemia. This equation is a simple and widely applicable tool for use in every clinical setting. Furthermore, coronary atherosclerosis assessed by coronary computed-tomographic angiography (coronary-CTA) is independently associated to the cardiovascular risk estimated according to the SAFEHEART-RE. This equation, as well as coronary-CTA and new biomarkers, could increase individual ASCVD risk stratification and could improve the efficiency and the use of new lipid-lowering therapies in familial hypercholesterolemia.

[10] *Hirakata T, Lee HC, Ohba M et al.* **Dietary omega-3 fatty acids alter the lipid mediator profile and alleviate allergic conjunctivitis without modulating Th2 immune responses**. FASEB journal : official publication of the Federation of American Societies for Experimental Biology 2018:fj201801805R.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30383446
ABSTRACT
Allergic conjunctivitis (AC) is one of the most common ocular surface diseases in the world. In AC, T helper type 2 (Th2) immune responses play central roles in orchestrating inflammatory responses. However, the roles of lipid mediators in the onset and progression of AC remain to be fully explored. Although previous reports have shown the beneficial effects of supplementation of omega-3 fatty acids in asthma or atopic dermatitis, the underlying molecular mechanisms are poorly understood. In this study, a diet rich in omega-3 fatty acids alleviated AC symptoms in both early and late phases without affecting Th2 immune responses, but rather by altering the lipid mediator profiles. The omega-3 fatty acids completely suppressed scratching behavior toward the eyes, an allergic reaction provoked by itch. Although total serum IgE levels and the expression levels of Th2 cytokines and chemokines in the conjunctiva were not altered by omega-3 fatty acids, eosinophil infiltration into the conjunctiva was dramatically suppressed. The levels of omega-6-derived proinflammatory lipid mediators, including those with chemoattractant properties for eosinophils, were markedly reduced in the conjunctivae of omega-3 diet-fed mice. Dietary omega-3 fatty acids can alleviate a variety of symptoms of AC by altering the lipid mediator profile.-Hirakata, T., Lee, H.-C., Ohba, M., Saeki, K., Okuno, T., Murakami, A., Matsuda, A., Yokomizo, T. Dietary omega-3 fatty acids alter the lipid mediator profile and alleviate allergic conjunctivitis without modulating Th2 immune responses.

[11] *Stoekenbroek RM, Kallend D, Wijngaard PL, Kastelein JJ*. **Inclisiran for the treatment of cardiovascular disease: the ORION clinical development program**. Future cardiology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30375244
ABSTRACT
Inclisiran is a novel drug that inhibits PCSK9 synthesis specifically in the liver, harnessing the natural mechanism of RNAi. Phase I and II data show that inclisiran lowers low-density lipoprotein cholesterol levels on average by >50% with a duration of effect that enables twice-yearly dosing. Phases I, II and emerging Phase III data support inclisiran's safety, tolerability and risk-benefit profile. The ongoing ORION program includes Phase III trials that will provide robust evidence of inclisiran's safety and efficacy in individuals at high risk of atherosclerotic cardiovascular disease (ASCVD), including established ASCVD and familial

hypercholesterolemia. In addition, the ORION-4 trial will assess the impact of inclisiran on cardiovascular outcomes in approximately 15,000 ASCVD subjects.

[12] *Ichimura K, Matoba T, Koga JI et al.* **Nanoparticle-Mediated Targeting of Pitavastatin to Small Pulmonary Arteries and Leukocytes by Intravenous Administration Attenuates the Progression of Monocrotaline-Induced Established Pulmonary Arterial Hypertension in Rats**. Int Heart J 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30369578
ABSTRACT
Statins are known to improve pulmonary arterial hypertension (PAH) by their anti-inflammatory and anti-proliferative effects in animal models. However, recent clinical studies have reported that clinically approved statin doses failed to improve clinical outcomes in patients with PAH. We therefore hypothesized that nanoparticle (NP)-mediated targeting of pitavastatin could attenuate the progression of established PAH.We induced PAH by subcutaneously injecting monocrotaline (MCT) in Sprague-Dawley rats. On day 14 after the MCT injection, animals that displayed established PAH on echocardiography were included. On day 17, they were randomly assigned to the following 5 groups: daily intravenous administration of (1) vehicle, (2) fluorescein-isothiocyanate-NP, (3) pitavastatin, (4) pitavastatin-NP, or (5) oral sildenafil. Intravenous NP was selectively delivered to small pulmonary arteries and circulating CD11b-positive leukocytes. On day 21, pitavastatin-NP attenuated the progression of PAH at lower doses than pitavastatin alone. This was associated with the inhibition of monocyte-mediated inflammation, proliferation, and remodeling of the pulmonary arteries. Interestingly, sildenafil attenuated the development of PAH, but had no effects on inflammation or remodeling of the pulmonary arteries. In separate experiments, only treatment with pitavastatin-NP reduced the mortality rate at day 35.NP-mediated targeting of pitavastatin to small pulmonary arteries and leukocytes attenuated the progression of established MCT-induced PAH and improved survival. Therapeutically, pitavastatin-NP was associated with anti-inflammatory and anti-proliferative effects on small pulmonary arteries, which was completely distinct from the vasodilatory effect of sildenafil. Pitavastatin-NP can be a novel therapeutic modality for PAH.

[13] *Lin PY, Lee FY, Wallace CG et al.* **Corrigendum to "The therapeutic effect of rosuvastatin and propylthiouracil on ameliorating high-cholesterol diet-induced rabbit aortic atherosclerosis and stiffness" [Int. J. Cardiol. 227 (2017) 938-949]**. International journal of cardiology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30384978
ABSTRACT

[14] *Munoz-Vega M, Masso F, Paez A et al.* **HDL-Mediated Lipid Influx to Endothelial Cells Contributes to Regulating Intercellular Adhesion Molecule (ICAM)-1 Expression and eNOS Phosphorylation**. International journal of molecular sciences 2018; 19.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30380707
ABSTRACT
Reverse cholesterol transport (RCT) is considered as the most important antiatherogenic role of high-density lipoproteins (HDL), but interventions based on RCT have failed to reduce the risk of

coronary heart disease. In contrast to RCT, important evidence suggests that HDL deliver lipids to peripheral cells. Therefore, in this paper, we investigated whether HDL could improve endothelial function by delivering lipids to the cells. Internalization kinetics using cholesterol and apolipoprotein (apo) AI fluorescent double-labeled reconstituted HDL (rHDL), and human dermal microvascular endothelial cells-1 (HMEC-1) showed a fast cholesterol influx (10 min) and a slower HDL protein internalization as determined by confocal microscopy and flow cytometry. Sphingomyelin kinetics overlapped that of apo AI, indicating that only cholesterol became dissociated from rHDL during internalization. rHDL apo AI internalization was scavenger receptor class B type I (SR-BI)-dependent, whereas HDL cholesterol influx was independent of SR-BI and was not completely inhibited by the presence of low-density lipoproteins (LDL). HDL sphingomyelin was fundamental for intercellular adhesion molecule-1 (ICAM-1) downregulation in HMEC-1. However, vascular cell adhesion protein-1 (VCAM-1) was not inhibited by rHDL, suggesting that components such as apolipoproteins other than apo AI participate in HDL's regulation of this adhesion molecule. rHDL also induced endothelial nitric oxide synthase eNOS S1177 phosphorylation in HMEC-1 but only when the particle contained sphingomyelin. In conclusion, the internalization of HDL implies the dissociation of lipoprotein components and a SR-BI-independent fast delivery of cholesterol to endothelial cells. HDL internalization had functional implications that were mainly dependent on sphingomyelin. These results suggest a new role of HDL as lipid vectors to the cells, which could be congruent with the antiatherogenic properties of these lipoproteins.

[15] *Arora S, Stouffer GA, Kucharska-Newton A et al.* **Fifteen-Year Trends in Management and Outcomes of Non-ST-Segment-Elevation Myocardial Infarction Among Black and White Patients: The ARIC Community Surveillance Study, 2000-2014**. Journal of the American Heart Association 2018; 7:e010203.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30371336

ABSTRACT

Background Standardization of evidence-based medical therapies has improved outcomes for patients with non- ST -segment-elevation myocardial infarction (NSTEMI). Although racial differences in NSTEMI management have previously been reported, it is uncertain whether these differences have been ameliorated over time. Methods and Results The ARIC (Atherosclerosis Risk in Communities) Community Surveillance study conducts hospital surveillance of acute myocardial infarction in 4 US communities. NSTEMI was classified by physician review, using a validated algorithm. From 2000 to 2014, 17 755 weighted hospitalizations for NSTEMI (patient race: 36% black, 64% white) were sampled by ARIC . Black patients were younger (aged 60 versus 66 years), more often female (45% versus 38%), and less likely to have medical insurance (88% versus 93%) but had more comorbidities. Black patients were less often administered aspirin (85% versus 92%), other antiplatelet therapy (45% versus 60%), beta-blockers (85% versus 88%), and lipid-lowering medications (68% versus 76%). After adjustments, black patients had a 24% lower probability of receiving nonaspirin antiplatelets (relative risk: 0.76; 95% confidence interval, 0.71-0.81), a 29% lower probability of angiography (relative risk: 0.71; 95% confidence interval, 0.67-0.76), and a 45% lower probability of revascularization (relative risk: 0.55; 95% confidence interval, 0.50-0.60). No suggestion of a changing trend over time was observed for any NSTEMI therapy (P values for interaction, all

>0.20). Conclusions This longitudinal community surveillance of hospitalized NSTEMI patients suggests black patients have more comorbidities and less likelihood of receiving guideline-based NSTEMI therapies, and these findings persisted across the 15-year period. Focused efforts to reduce comorbidity burden and to more consistently implement guideline-directed treatments in this high-risk population are warranted.

[16] *Kim J, Park KT, Jang MJ et al.* **High-Intensity Versus Non-High-Intensity Statins in Patients Achieving Low-Density Lipoprotein Cholesterol Goal After Percutaneous Coronary Intervention**. Journal of the American Heart Association 2018; 7:e009517.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30376751
ABSTRACT
Background Whether use of high-intensity statins is more important than achieving low-density lipoprotein cholesterol (LDL -C) target remains controversial in patients with coronary artery disease. We sought to investigate the association between statin intensity and long-term clinical outcomes in patients achieving treatment target for LDL -C after percutaneous coronary intervention. Methods and Results Between February 2003 and December 2014, 1746 patients who underwent percutaneous coronary intervention and achieved treatment target for LDL -C (<70 mg/dL or >50% reduction from baseline level) were studied. We classified patients into 2 groups according to an intensity of statin prescribed after index percutaneous coronary intervention: high-intensity statin group (atorvastatin 40 or 80 mg, and rosuvastatin 20 mg, 372 patients) and non-high-intensity statin group (the other statin treatment, 1374 patients). The primary outcome was a composite of cardiac death, myocardial infarction, or stroke. Difference in time-averaged LDL -C during follow-up was significant, but small, between the high-intensity statin group and non-high-intensity statin group (59+/-13 versus 61+/-12 mg/dL; P=0.04). At 5 years, patients receiving high-intensity statins had a significantly lower incidence of the primary outcome than those treated with non-high-intensity statins (4.1% versus 9.9%; hazard ratio, 0.42; 95% confidence interval, 0.23-0.79; P<0.01). Results were consistent after propensity-score matching (4.2% versus 11.2%; hazard ratio, 0.36; 95% confidence interval, 0.19-0.69; P<0.01) and across various subgroups. Conclusions Among patients achieving treatment target for LDL -C after percutaneous coronary intervention, high-intensity statins were associated with a lower risk of major adverse cardiovascular events than non-high-intensity statins despite a small difference in achieved LDL -C level.

[17] *Leucker TM, Weiss RG, Schar M et al.* **Coronary Endothelial Dysfunction Is Associated With Elevated Serum PCSK9 Levels in People With HIV Independent of Low-Density Lipoprotein Cholesterol**. Journal of the American Heart Association 2018; 7:e009996.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30371326
ABSTRACT
Background HIV + people are at increased risk of coronary artery disease, but the responsible mechanisms are incompletely understood. Proprotein convertase subtilisin/kexin type 9 (PCSK 9) is traditionally recognized for its importance in cholesterol metabolism; however, recent data suggest an additional, low-density lipoprotein receptor-independent adverse effect on endothelial cell inflammation and function. We tested the hypotheses that PCSK 9 levels are increased and that abnormal coronary endothelial function is related to PCSK 9 serum levels in

HIV + individuals. Methods and Results Forty-eight HIV + participants receiving antiretroviral therapy with suppressed viral replication, without coronary artery disease, and 15 age- and low-density lipoprotein cholesterol-matched healthy HIV- subjects underwent magnetic resonance imaging to measure coronary endothelial function, quantified as percentage change in coronary artery cross-sectional area during isometric handgrip exercise, an endothelial-dependent stressor; and blood was obtained for serum PCSK 9 and systemic vascular biomarkers. Data are presented as mean+/-SD. Mean serum PCSK 9 was 65% higher in the HIV + subjects (302+/-146 ng/ mL) than in the HIV - controls (183+/-52 ng/ mL , P<0.0001). Coronary endothelial function was significantly reduced in the HIV + versus HIV - subjects (percentage change in coronary artery cross-sectional area, 2.9+/-9.6% versus 11.1+/-3.7%; P<0.0001) and inversely related to PCSK 9 (R=-0.51, P<0.0001). Markers of endothelial activation and injury, P-selectin and thrombomodulin, were also significantly increased in the HIV + subjects; and P-selectin was directly correlated with serum PCSK 9 (R=0.31, P=0.0144). Conclusions Serum PCSK 9 levels are increased in treated HIV + individuals and are associated with abnormal coronary endothelial function, an established measure of vascular health.

[18] *Lowenstern AM, Li S, Navar AM et al.* **Measurement of Low-Density Lipoprotein Cholesterol Levels in Primary and Secondary Prevention Patients: Insights From the PALM Registry**. Journal of the American Heart Association 2018; 7:e009251.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30371214

ABSTRACT

Background The 2013 American College of Cardiology/American Heart Association Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults recommended testing low-density lipoprotein cholesterol (LDL -C) to identify untreated patients with LDL -C >/=190 mg/dL, assess lipid-lowering therapy adherence, and consider nonstatin therapy. We sought to determine whether clinician lipid testing practices were consistent with these guidelines. Methods and Results The PALM (Patient and Provider Assessment of Lipid Management) registry enrolled primary and secondary prevention patients from 140 US cardiology, endocrinology, and primary care offices in 2015 and captured demographic data, lipid treatment history, and the highest LDL -C level in the past 2 years. Core laboratory lipid levels were drawn at enrollment. Among 7627 patients, 2787 (36.5%) had no LDL -C levels measured in the 2 years before enrollment. Patients without chart-documented LDL -C levels were more often women, nonwhite, uninsured, and non-college graduates (all P<0.01). Patients without prior lipid testing were less likely to receive statin treatment (72.6% versus 76.0%; P=0.0034), a high-intensity statin (21.5% versus 24.3%; P=0.016), nonstatin lipid-lowering therapy (24.8% versus 27.3%; P=0.037), and had higher core laboratory LDL -C levels at enrollment (median 97 versus 92 mg/dL; P<0.0001) than patients with prior LDL -C testing. Of 166 individuals with core laboratory LDL -C levels >/=190 mg/dL, 36.1% had no LDL -C measurement in the prior 2 years, and 57.2% were not on a statin at the time of enrollment. Conclusions In routine clinical practice, LDL -C testing is associated with higher-intensity lipid-lowering treatment and lower achieved LDL -C levels.

[19] *Tuteja S, Qu L, Vujkovic M et al.* **Genetic Variants Associated With Plasma Lipids Are Associated With the Lipid Response to Niacin**. Journal of the American Heart Association 2018; 7:e03488.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30371334
ABSTRACT
Background Niacin is a broad-spectrum lipid-modulating drug, but its mechanism of action is unclear. Genome-wide association studies have identified multiple loci associated with blood lipid levels and lipoprotein (a). It is unknown whether these loci modulate response to niacin. Methods and Results Using data from the AIM - HIGH (Atherothrombosis Intervention in Metabolic Syndrome with Low HDL /High Triglycerides and Impact on Global Health Outcomes) trial (n=2054 genotyped participants), we determined whether genetic variations at validated loci were associated with a differential change in plasma lipids and lipoprotein (a) 1 year after randomization to either statin+placebo or statin+niacin in a variant-treatment interaction model. Nominally significant interactions (P<0.05) were found for genetic variants in MVK , LIPC , PABPC 4, AMPD 3 with change in high-density lipoprotein cholesterol; SPTLC 3 with change in low-density lipoprotein cholesterol; TOM 1 with change in total cholesterol; PDXDC 1 and CYP 26A1 with change in triglycerides; and none for lipoprotein (a). We also investigated whether these loci were associated with cardiovascular events. The risk of coronary disease related death was higher in the minor allele carriers at the LIPC locus in the placebo group (odds ratio 2.08, 95% confidence interval 1.11-3.90, P=0.02) but not observed in the niacin group (odds ratio 0.89, 95% confidence interval 0.48-1.65, P=0.7); P-interaction =0.02. There was a greater risk for acute coronary syndrome (odds ratio 1.85, 95% confidence interval 1.16-2.77, P=0.02) and revascularization events (odds ratio 1.64, 95% confidence interval 1.2-2.22, P=0.002) in major allele carriers at the CYP 26A1 locus in the placebo group not seen in the niacin group. Conclusions Genetic variation at loci previously associated with steady-state lipid levels displays evidence for lipid response to niacin treatment. Clinical Trials Registration URL: https://www.clinicaltrials.gov . Unique identifier: NCT00120289.

[20] *Vallejo-Vaz AJ, Ginsberg HN, Davidson MH et al.* **Lower On-Treatment Low-Density Lipoprotein Cholesterol and Major Adverse Cardiovascular Events in Women and Men: Pooled Analysis of 10 ODYSSEY Phase 3 Alirocumab Trials**. Journal of the American Heart Association 2018; 7:e009221.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30371190
ABSTRACT
Background In statin trials, men and women derived similar relative risk reductions in cardiovascular events per 39 mg/ dL low-density lipoprotein cholesterol (LDL -C) reduction. We explored whether lower LDL -C levels and greater LDL -C percentage reductions than those achieved with statins are associated with reduced major adverse cardiovascular event (MACE) rates in women as well as men. Methods and Results Data pooled from 10 phase 3 ODYSSEY randomized trials (n=4983) comparing alirocumab with control (placebo/ezetimibe) were assessed for association between 39 mg/dL lower on-treatment LDL -C and percentage LDL -C change from baseline, and MACE risk by sex, using multivariable Cox regression. Mean baseline LDL -C was 135 mg/dL (women) and 121 mg/dL (men). Average on-treatment LDL -C levels with alirocumab, ezetimibe, and placebo were 71, 114, and 134 mg/dL, respectively, in women

(n=1882) and 52, 93, and 122 mg/dL, respectively, in men (n=3090). Overall, 36.5% and 58.7% of women and men, respectively, achieved on-treatment LDL -C <50 mg/dL. Each 39 mg/dL lower LDL -C was associated with a 33% and 22% lower risk of MACE in women (P=0.0209) and men (P=0.0307), respectively, with no significant between-sex difference (P for heterogeneity=0.4597). Results were similar when analyzed per 50% LDL -C reduction, 24% (P=0.1094) and 29% (P=0.0125) lower MACE risk in women and men, respectively (P for heterogeneity=0.7499). Alirocumab was generally well tolerated in both sexes. Conclusions The present analysis reinforces the notion that both sexes derive a similar cardiovascular benefit from LDL -C lowering. Although women had slightly higher on-treatment LDL -C than men, both sexes showed a similar lower MACE risk with lower LDL -C.

[21] *Firouzi A, Kazem Moussavi A, Mohebbi A et al.* **Comparison between rosuvastatin and atorvastatin for the prevention of contrast-induced nephropathy in patients with STEMI undergoing primary percutaneous coronary intervention**. Journal of cardiovascular and thoracic research 2018; 10:149-152.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30386535
ABSTRACT
Introduction: There is some controversy over the efficacy of statins for the prevention of contrastinduced nephropathy (CIN). There have also been reports on varying efficacies of different statins. Hence, in this study the efficacy of atorvastatin and rosuvastatin for the prevention of CIN was assessed. Methods: This single-blind randomized clinical trial was performed on 495 random patients with myocardial infarction with ST-segment elevation undergoing primary percutaneous coronary intervention (PCI) in a training referral hospital in 2015. Patients were randomly assigned to receive either atorvastatin 80 mg at admission and daily or rosuvastatin 40 mg at admission and daily. CIN was defined based on serum creatinine elevation after 48 hours from the PCI. Results: The incidence of CIN was observed in 63 patients (21.4%) After 48 hours from primary PCI. Of those, 17% (n = 50) were grade 1 CIN, while 4.4% (n = 13) were grade 2 CIN. There was no significant difference between rosuvastatin group compared with atorvastatin group, regarding the CIN grading (P = 0.14). Conclusion: Our results indicate that atorvastatin and rosuvastatin have similar efficacy for the prevention of CIN.

[22] *Cheng Y, Sun T, Yin C et al.* **Downregulation of PTEN by sodium orthovanadate protects the myocardium against ischemia/reperfusion injury after chronic atorvastatin treatment**. Journal of cellular biochemistry 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30368869
ABSTRACT
Acute statin treatment has been reported to be critical in protecting the cardiac cells against ischemia/reperfusion injury by activating PI3K/Akt signal pathway. In vitro rat myocardial ischemia/reperfusion model, chronic statin treatment led to upregulation of phosphatase and tensin homolog (PTEN). This has been potentially indicated the correlation in PTEN and protective effect of statin on myocardium. In this current study, we evaluated the role of sodium orthovanadate a nonspecific inhibitor to PTEN and its correlation with atorvastatin on protecting myocardium against ischemia/reperfusion injury. We found a long-term statin treatment could increase the PTEN level, and this process was counteracted in the presence of

sodium orthovanadate. However, the phosphotyrosine level was not affected by this statin. Besides, this process was mediated by Akt signaling since phosphorylated Akt level was altered by statin and sodium orthovanadate treatment. In a conclusion, this study showed a potential mechanism underlying PTEN-induced attenuation in long-term statin's therapeutic effect, which provided the new insight into the synergic role of PTEN and atorvastatin in protecting cardiac cells against ischemia/reperfusion injury.

[23] *Zhaolin Z, Jiaojiao C, Peng W et al.* **OxLDL induces vascular endothelial cell pyroptosis through miR-125a-5p/TET2 pathway**. Journal of cellular physiology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30370524
ABSTRACT
Pyroptosis participates in the formation and development of atherosclerosis (As) by promoting inflammatory factor release and is closely related to the stability of atherosclerotic plaque. MicroRNAs can regulate the expression of target genes at the posttranscriptional level. Previous studies have shown that miR-125a-5p increases in hyperlipidemic-hyperglycemic conditions and is involved in apoptosis, but its specific role in pyroptosis and As remains unclear. We propose that miR-125a-5p may be implicated in oxidized low-density lipoprotein (oxLDL)-induced vascular endothelial cells (VECs) pyroptosis and therefore conducted the current study. We observed that miR-125a-5p can inhibit tet methylcytosine dioxygenase 2 (TET2) expression at the posttranscription level, resulting in abnormal DNA methylation, mitochondrial dysfunction, and increased reactive oxygen species production, activated nuclear factor-kappaB that induces activation of inflammasome and maturation, release of proinflammatory cytokines interleukin (IL)-1beta and IL-18, and pyroptosis. Given the role of VECs in vascular physiology, oxLDL-induced VEC pyroptosis may promote the development of As. Our current study reveals a novel pathway associated with pyroptosis program regulation, which comprises miR-125a-5p and TET2 in VECs. Modulation of their expression levels may serve as a potential target for therapeutic strategies of As.

[24] *Anggadiredja K, Ufamy N, Amalia L et al.* **Ameliorating Effects of Four-Week Fiber-Multivitamin Combination Treatment on Low-Density Lipoprotein Cholesterol, Total Cholesterol, and Apolipoprotein B Profiles in Hypercholesterolemic Participants**. Journal of dietary supplements 2018:1-11.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30380357
ABSTRACT
Hyperlipidemia is one of the leading causes of death and requires lipid-lowering treatment to reduce morbidity and mortality. Effective and safe alternative and adjunctive therapies could be beneficial for patients with hyperlipidemia. To assess the effect of a fiber-multivitamin combination product on the lipid parameters low-density lipoprotein cholesterol (LDL-c), high-density lipoprotein cholesterol (HDL-c), total cholesterol (TC), triglyceride (TG), and apolipoprotein B (Apo B) in patients with hypercholesterolemia, we conducted a double-blind, randomized, parallel-group study. Forty-one out of 50 randomized hypercholesterolemic participants recruited between August 2016 and March 2018 completed the trial. The participants were assigned to receive either test product (treatment group, n = 20) or placebo (placebo group, n = 21) for 4 weeks following a 6-week dietary intervention (based on

education from a dietitian) run-in period. The primary outcome was LDL-c levels and the secondary outcomes were HDL-c, TC, TG, and Apo B levels. All of the outcomes were measured at baseline and week 4 after the completion of run-in period. Participants in both groups had similar LDL-c levels (142 +/- 15.7 vs. 143 +/- 19.3 mg/dL). After 4 weeks of exposure to test product, participants in the treatment group demonstrated a 17.25 +/- 22.26 reduction in LDL-c ($p < .05$ vs. placebo). This improvement in LDL-c was accompanied by amelioration in TC and Apo B levels, without any detrimental effects on HDL and TG concentration. Results of the present study suggest that fiber-vitamin combination has potential to be used as an adjunct therapy for the management of hypercholesterolemia.

[25] *Ghosh M, Galman C, Rudling M, Angelin B*. **Erratum: Influence of physiological changes in endogenous estrogen on circulating PCSK9 and LDL cholesterol**. Journal of lipid research 2018; 59:2253.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30385517
ABSTRACT

[26] *Ghorbani P, Smith TKT, Fullerton MD*. **Does prenylation predict progression in NAFLD?** The Journal of pathology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30374976
ABSTRACT
Non-alcoholic fatty liver disease (NAFLD) often develops in concert with related metabolic diseases like obesity, dyslipidemia and insulin resistance. Prolonged lipid accumulation and inflammation can progress to non-alcoholic steatohepatitis (NASH). Although factors associated with the development of NAFLD are known, the triggers for the progression of NAFLD to NASH are poorly understood. Recent findings published in The Journal of Pathology reveal the possible regulation of NASH progression by metabolites of the mevalonate pathway. Mevalonate can be converted into the isoprenoids farnesyldiphosphate (FPP) and geranylgeranyl diphosphate (GGPP). GGPP synthase (GGPPS), the enzyme that converts FPP to GGPP, is dysregulated in humans and mice during NASH. Both FPP and GGPP can be conjugated to proteins through prenylation, modifying protein function and localization. Deletion or knockdown of GGPPS favours FPP prenylation (farnesylation) and augments the function of liver kinase B1, an upstream kinase of AMP-activated protein kinase (AMPK). Despite increased AMPK activation, livers in Ggpps-deficient mice on a high-fat diet poorly oxidize lipids due to mitochondrial dysfunction. Although work from Liu et al. provides evidence as to the potential importance of the prenylation portion of the mevalonate pathway during NAFLD, future studies are necessary to fully grasp any therapeutic or diagnostic potential. This article is protected by copyright. All rights reserved.

[27] *Rezvani-Sharif A, Tafazzoli-Shadpour M, Avolio A*. **Progressive changes of elastic moduli of arterial wall and atherosclerotic plaque components during plaque development in human coronary arteries**. Medical & biological engineering & computing 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30374700
ABSTRACT

Stiffness of the arterial wall and atherosclerotic plaque components is a determinant of the stress field within plaques, which has been suggested to be an indicator of plaque vulnerability. The diversity and inhomogeneous structure of atherosclerotic lesions complicate the characterization of plaque components. In the present study, stiffness of the arterial wall and atherosclerotic plaque components in human coronary arteries was examined in early and developed atherosclerotic lesions. The force-spectroscopy mode of the atomic force microscope and histological examination were used for determination of elastic moduli at specified locations within samples. Fibrous cap (E = 14.1 +/- 3.8 kPa) showed lower stiffness than the fibrous tissue beneath the lipid pool (E = 17.6 +/- 3.2 kPa). Calcification zones (E = 96.1 +/- 18.8 kPa) and lipid pools (E = 2.7 +/- 1.8 kPa) were the stiffest and softest components of atherosclerotic lesions, respectively. The increase of media stiffness (%44.8) and reduction of the elastic modulus of the internal elastic lamina (%28.9) was observed in coronary arteries. Moreover, significant differences were observed between the stiffness of medial layer in diseased parts and free-plaque segments in incomplete plaques of coronary arteries. Our results can be used for better understanding of remodeling mechanisms of the arterial wall with plaque development. Graphical abstract Stiffness alteration of the arterial wall and atherosclerotic plaque components with plaque development in coronary arteries.

[28] *Adhyaru BB, Jacobson TA*. **Safety and efficacy of statin therapy**. Nature reviews. Cardiology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30375494
ABSTRACT
The 2013 ACC/AHA guidelines on blood cholesterol management were a major shift in the delineation of the main patient groups that could benefit from statin therapy and emphasized the use of higher-intensity statin therapies. In 2016, an expert consensus panel from the ACC recommended the use of nonstatin therapies (ezetimibe and PCSK9 inhibitors) in addition to maximally tolerated statin therapy in individuals whose LDL-cholesterol and non-HDL-cholesterol levels remained above certain thresholds after statin treatment. Given the substantial benefits of statin therapies in both primary and secondary prevention of cardiovascular disease, their long-term safety has become a concern. The potential harmful effects of statin therapy on muscle and liver have been known for some time, but new concerns have emerged regarding the risk of new-onset diabetes mellitus, cognitive impairment and haemorrhagic stroke associated with the use of statins and the risks of achieving very low levels of LDL cholesterol. The increased media attention on the adverse events associated with statins has unfortunately led to statin therapy discontinuation, nonadherence to therapy or concerns about initiating statin therapy. In this Review, we explore the safety of statin therapy in light of the latest evidence and provide clinicians with reassurance about the safety of statins. Overwhelming evidence suggests that the benefits of statin therapy far outweigh any real or perceived risks.

[29] *Rahim F, Sayyah M*. **Effects of atorvastatin on treatment-resistant obsessive-compulsive disorder: A double-blind randomized trial**. Psychiatria polska 2018; 52:719-729.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30368541
ABSTRACT

OBJECTIVES: Obsessive-compulsive disorder (OCD) is a chronic disorder of unknown etiology. An augmentation strategy is an approach for treatment-resistant OCD. This study was planned to assess the effect of atorvastatin on treatment-resistant OCD. METHODS: This 12-week-long double-blind randomized trial was performed on 26 adult patients with treatment-resistant OCD. They were diagnosed with this kind of disorder based on the DSM-IV-TR. The patients were randomized to receive either 10 mg/day atorvastatin or placebo. The Yale-Brown scale was assessed at the baseline and 12 weeks later. RESULTS: There were significant reductions in the obsession subtotal scoreof the Y-BOCS ($p = 0.017$) and the total Y-BOCS score ($p = 0.041$) in the atorvastatin group. Hence, the reduction in the Y-BOCS compulsive score ($p = 0.081$) was not statistically significant. Atorvastatin was generally well tolerated. There was a significant reduction in libido in the atorvastatin group ($p = 0.019$). CONCLUSIONS: The results of this study should be interpreted in the shadow of its restrictions. Some of the restrictions were a limited number of patients in the trial, a 12-week-long time trial, and not measuring NO before and after the study. It is recommended that researchers should consider these items in similar type of studies.

[30] *Bjune K, Wierod L, Naderi S*. **Triciribine increases LDLR expression and LDL uptake through stabilization of LDLR mRNA**. Scientific reports 2018; 8:16174.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30385871
ABSTRACT
Low-density lipoprotein receptor (LDLR) is a key regulator of the metabolism of plasma low-density lipoprotein cholesterol (LDL-C), the elevated levels of which are associated with an increased risk of cardiovascular disease. Therefore, enhancing LDLR expression represents a potent treatment strategy for hypercholesterolemia. Here, we report that in cultured human hepatoma cells, triciribine, a highly selective AKT inhibitor, increases the stability of LDLR mRNA, an event that translates into upregulation of cell-surface LDLR levels and induction of cellular LDL uptake. This effect of triciribine requires ERK activity and is partially dependent on the intervening sequence between the AU-rich elements ARE3 and ARE4 in LDLR 3'UTR. We also show that triciribine downregulates the expression of PCSK9 mRNA and blunts the secretion of its protein. Notably, triciribine was found to potentiate the effect of mevastatin on LDLR protein levels and activity. We also show that primary human hepatocytes respond to triciribine by increasing the expression of LDLR. Furthermore, a pilot experiment with mice revealed that a two-weeks treatment with triciribine significantly induced the hepatic expression of LDLR protein. These results identify triciribine as a novel LDLR-elevating agent and warrant further examination of its potential as a hypocholesterolemic drug either as monotherapy or in combination with statins.

[31] *Shah T, Virani SS*. **Lipid-Lowering Therapies: Risks in Women and Evidence-Based Options**. Texas Heart Institute journal / from the Texas Heart Institute of St. Luke's Episcopal Hospital, Texas Children's Hospital 2018; 45:238-239.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30374235
ABSTRACT

[32] *Takaguri A*. **[Elucidation of a New Mechanism of Onset of Insulin Resistance: Effects of Statins and Tumor Necrosis Factor-alpha on Insulin Signal Transduction]**. Yakugaku Zasshi 2018; 138:1329-1334.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30381640

ABSTRACT
Impaired insulin signaling in adipose tissue and skeletal muscle causes insulin resistance associated with the development of type 2 diabetes. However, the molecular mechanisms underlying insulin resistance remain to be elucidated. In this review, we describe the current understanding of the effects of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) and tumor necrosis factor (TNF)-alpha on insulin signal transduction in adipocytes. First, we determined that atorvastatin inhibits the tyrosine phosphorylation of insulin receptor substrate (IRS)-1 through a decrease in the RhoA-Rho-kinase pathway, resulting in the inhibition of glucose uptake. Second, we found that TNF-alpha induces IRS-1 phosphorylation at serine residues 636/639 and inhibits the tyrosine phosphorylation of IRS-1 through the increase in both extracellular signal-regulated kinase (ERK) and c-jun N-terminal kinase (JNK) phosphorylation. Interestingly, 5-aminoimidazole-4-carboxamide-1-beta-D-ribofuranoside, an AMP-activated protein kinase activator, suppresses TNF-alpha-induced IRS-1 serine phosphorylation at 636/639 and the phosphorylation of ERK by enhancing interactions between ERK and dual-specificity phosphatase-9. These results may be helpful in understanding the mechanisms underlying insulin resistance.