Literature update week 05 (2019)

[1] *Cardellini M, Rovella V, Scimeca M et al.* **Chronic Kidney Disease Is Linked to Carotid Nodular Calcification, An Unstable Plaque Not Correlated to Inflammation**. Aging and disease 2019; 10:71-81.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30705769
ABSTRACT
The incidence and the different type of carotid calcifications, nodular and non-nodular, and their role in the acute cerebrovascular disease has not yet been defined. Various studies have correlated the presence of specific risk factors, in particular the chronic kidney disease, with the presence of calcification, but not with the type of calcification. Since it is likely that carotid nodular calcifications rather than those with non-nodular aspect may represent a plaque at high risk of rupture, the purpose of our study was to evaluate the role of nodular calcification in the pathogenesis of cerebrovascular syndromes and their possible correlation with specific risk factors. A total of 168 carotid plaques from symptomatic and asymptomatic patients submitted to endarterectomy, whom complete clinical and laboratory assessment of major cardiovascular risk factors was available, were studied. In 21 endarterectomies (5 from symptomatic and 16 from asymptomatic patients) an eruptive calcified nodule, consisting of calcified plates associated to a small amount of fibrous tissue without extracellular lipids and inflammatory cells, was found protruding into the lumen. Nodular calcifications were significantly observed in patients affected by chronic kidney disease (with GFR<60 ml / min / 1.73 m(2)), with a normal lipidic and glycemic profile. On the contrary, non-nodular calcification, mainly correlated to diabetes, were stable lesions. Results of our study suggest that the mechanisms and the clinical significance of carotid atherosclerotic calcification may be different. The nodular calcification could represent a type of unstable plaque, significantly related to chronic kidney disease, without inflammation, morphologically different from the classical vulnerable plaques.

[2] *Riestenberg RA, Furman A, Cowen A et al.* **Differences in statin utilization and lipid lowering by race, ethnicity, and HIV status in a real-world cohort of persons with human immunodeficiency virus and uninfected persons**. American heart journal 2018; 209:79-87.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30685678
ABSTRACT
BACKGROUND: Risks for cardiovascular diseases, including myocardial infarction and stroke, are elevated in people with HIV infection (PWH). However, no trials of statin utilization with clinical cardiovascular disease (CVD) end points have been completed in PWH, and there are sparse real-world data regarding statin use and lipid-lowering effectiveness. We therefore used a unique cohort of PWH and uninfected controls to evaluate (1) differences in statin types used for PWH versus uninfected persons; (2) lipid lowering achieved by statin use for PWH versus uninfected persons; and (3) racial and ethnic disparities in appropriate statin use among PWH and uninfected persons. METHODS: We analyzed a cohort of 5,039 PWH and 10,011 uninfected demographically matched controls who received care at a large urban medical center between January 1, 2000, and May 17, 2017. Medication administration records, prescription data, and validated natural language processing algorithms were used to determine statin utilization. Statins were categorized by generic active ingredient name and intensity (high, moderate, or low). Lipid values collected in routine clinical care were available for analysis. The first set of analyses was restricted to PWH and uninfected matched controls taking statins and compared

(1) differences in statin type and (2) difference in cholesterol levels after versus before statin initiation by HIV status. For the second set of analyses, we first used prevalent CVD risk factors to determine participants with statin indications and then determined how many of these participants were taking statins. We then compared statin utilization among persons with indications for statins by race/ethnic group for PWH and uninfected matched controls using multivariable-adjusted logistic regression. RESULTS: Among people prescribed statins, PWH were more likely than controls to have ever taken pravastatin (34.8% vs 12.3%, P < .001) or atorvastatin (72.2% vs 65.6%, P = .002) and less likely to have ever taken simvastatin (14.2% vs 39.5%, P < .001). Among PWH with indications for statin utilization, 55.7% of whites, 39.4% of blacks, and 45.8% of Hispanics were prescribed statins (P < .001). These differences in statin prescription by race/ethnicity remained significant after adjustment for demographics (including insurance status), cardiovascular risk factors, antiretroviral therapy use, HIV viremia, and CD4 count. These racial/ethnic disparities in statin utilization were less pronounced among uninfected persons. CONCLUSIONS: Among PWH with statin indication(s), blacks and Hispanics were less likely than whites to have been prescribed a statin. These racial/ethnic disparities were less pronounced among uninfected persons. There were significant differences in type of statin used for PWH compared to uninfected matched controls. Future efforts addressing disparities in CVD prevention among PWH are warranted.

[3] *Schooling CM, Zhao JV*. **How Might Bromodomain and Extra-Terminal (BET) Inhibitors Operate in Cardiovascular Disease?** American journal of cardiovascular drugs : drugs, devices, and other interventions 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30693439
ABSTRACT
Bromodomain and extra-terminal (BET) inhibitors, acting via epigenetic mechanisms, have been developed recently as potential new treatments for cancer, including prostate cancer, and inflammatory conditions. Some BET inhibitors, such as RVX-208, also raise high-density lipoprotein cholesterol (HDL-C) and apolipoprotein A-1 levels. A recent meta-analysis of three small trials (n = 798) found that RVX-208 protected against major adverse cardiovascular events (MACE), raising the question as to whether this protective effect was an artefact, a chance finding, or mediated by HDL-C, anti-inflammatory pathways, or other factors. Notably, the effect of RVX-208 on MACE was largely driven by revascularizations, but fewer interventions in the treatment arm could have arisen accidently from favorable effects of RVX-208 on HDL-C and C-reactive protein influencing decisions about patient care. A larger (n = 2400) trial of RVX-208, BETonMACE (NCT02586155), with a more restricted definition of MACE, excluding hospitalizations, will shortly provide clarity. A successful BETonMACE trial would raise the question as to whether RVX-208 operates via lipids, inflammation, or other means, because several previous HDL-C modulators and anti-inflammatories have not provided effective means of treating cardiovascular disease and reducing overall mortality. Re-conceptualizing cardiovascular disease within the well-established evolutionary biology theory that growth and specifically reproduction trade-off against longevity might provide a more comprehensive explanation. Drivers of the gonadotropic axis, particularly androgens, suppress both HDL-C and the immune system while promoting ischemic heart disease and stroke. As such, any effects of RVX-208 on cardiovascular disease might be the result of reducing androgens, of which higher

HDL-C and reduced inflammation are biomarkers. Notably, several other effective treatments for cardiovascular disease, such as statins and spironolactone, are known anti-androgens. Results of the BETonMACE trial, and corresponding insight about the mechanism of BET inhibitors in cardiovascular disease, are eagerly awaited.

[4] *Zhu X, Zhao P, Lu Y et al.* **Potential injurious effects of the fine particulate PM2.5 on the progression of atherosclerosis in apoE-deficient mice by activating platelets and leukocytes**. Archives of medical science : AMS 2019; 15:250-261.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30697277
ABSTRACT
Introduction: Exposure to the fine particulate matter PM2.5 is strongly associated with atherosclerotic diseases, creating considerable public concern. Nevertheless, the mechanisms have not been fully elucidated. We exposed atherosclerosis-prone apoE-deficient mice to PM2.5 to begin investigating these mechanisms. Material and methods: Thirty-two 8-week-old male apoE(-/-) mice were divided to two groups fed with high-fat diet: a control group instilled with 0.9% saline, and an experimental group instilled with PM2.5 (30 mg/kg/day) for 8 weeks. We measured PM2.5 in whole blood by the ICP-MS method, and lipids and inflammatory factors by standard methods. The whole descending arteries were stained with oil red O; Aortic roots were stained with Movat, Sirius Red and immunohistochemical stains for pathological analysis; Brachiocephalic arteries for scanning electron microscopy, the descending arteries for Q-PCR. Echocardiography was used to evaluate cardiac function. Results: In PM2.5 group, we observed elevated heavy metal components, consistent with higher amounts of platelets in total blood. The PM2.5 group also had elevated serum inflammatory factor levels. Finally, the PM2.5 group showed larger atherosclerotic plaques ($p = 0.0231$), higher numbers of lesion macrophages ($p = 0.0183$), greater injury to endothelial layers with greater adherence of platelets and leukocytes, elevated inflammatory factor levels, the NAD(P)H oxidase subunits p22phox and p47phox ($p = 0.0079$ and $p = 0.0294$), the M1/M2 associated markers IL-6, TNF-alpha ($p = 0.0291$, $p = 0.0286$), iNOS, IL-12 ($p = 0.0122$ and $p = 0.0280$) and arginase-1, and CD206 ($p = 0.0216$ and $p = 0.0317$). Conclusions: PM2.5 exposure activated circulating leukocytes, platelets and associated inflammatory factors, contributing to the progression of atherosclerosis in apoE(-/-) mice.

[5] *Mehta SP, Tiwari AK, Puri R et al.* **Severe hypertriglyceridemia-induced pancreatitis successfully managed with therapeutic plasma exchange: Report from India**. Asian journal of transfusion science 2018; 12:154-156.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30692801
ABSTRACT
Hypertriglyceridemia (HTG) is the third most significant risk factor for acute pancreatitis after gallstones and alcohol. Therapeutic plasma exchange (TPE) has been considered a possible treatment for HTG-induced pancreatitis, especially in severe and refractory cases. Here, we report one such clinical experience with a patient of severe HTG-induced pancreatitis. He was treated with TPE along with intravenous insulin, statins, and fibrates. TPE resulted in immediate relief of symptoms as well as a marked improvement in laboratory values, with 74.5% reduction

in triglycerides after a single session. TPE can be successfully utilized as an adjunct in HTG-induced pancreatitis.

[6] *Taniguti EH, Ferreira YS, Stupp IJV et al.* **Atorvastatin prevents lipopolysaccharide-induced depressive-like behaviour in mice**. Brain research bulletin 2019; 146:279-286.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30690060
ABSTRACT
Clinical and pre-clinical evidences indicate an association between inflammation and depression since increased levels of pro-inflammatory cytokines are associated with depression-related symptoms. Atorvastatin is a cholesterol-lowering statin that possesses pleiotropic effects including neuroprotective and antidepressant actions. However, the putative neuroprotective effect of atorvastatin treatment in the acute inflammation mice model of depressive-like behaviour has not been investigated. In the present study, we aimed to investigate the effect of atorvastatin treatment on lipopolysaccharide (LPS) induced depressive-like behaviour in mice. Mice were treated with atorvastatin (1 or 10 mg/kg, v.o.) or fluoxetine (30 mg/kg, positive control, v.o.) for 7 days before LPS (0.5 mg/kg, i.p.) injection. Twenty four hours after LPS infusion, mice were submitted to the forced swim test, tail suspension test or open field test. After the behavioural tests, mice were sacrificed and the levels of tumour necrosis factor-alpha (TNF-alpha), brain-derived neurotrophic factor (BDNF), glutathione and malondialdehyde were measured. Atorvastatin (1 or 10 mg/kg/day) or fluoxetine treatment prevented LPS-induced increase in the immobility time in the forced swim and tail suspension tests with no alterations in the locomotor activity evaluated in the open field test. Atorvastatin (1 or 10 mg/kg/day) or fluoxetine treatment also prevented LPS-induced increase in TNF-alpha and reduction of BDNF levels in the hippocampus and prefrontal cortex. Treatment with atorvastatin (1 or 10 mg/kg/day) or fluoxetine prevented LPS-induced increase in lipid peroxidation and the reduction of glutathione levels in the hippocampus and prefrontal cortex. The present study suggests that atorvastatin treatment exerted neuroprotective effects against LPS-induced depressive-like behaviour which may be related to reduction of TNF-alpha release, oxidative stress and modulation of BDNF expression.

[7] *Waters DD, Hsue PY*. **Lipid Abnormalities in Persons Living With HIV Infection**. The Canadian journal of cardiology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30704819
ABSTRACT
Lipid abnormalities are prevalent among persons living with HIV infection and contribute to increasing the risk of cardiovascular events. Antiretroviral therapy (ART) is associated with lipid abnormalities, most commonly hypertriglyceridemia, but also increases in low-density lipoprotein cholesterol and total cholesterol. Different classes of ART, and different drugs within classes, have differing effects on lipid levels, but in general newer drugs have more favourable effects compared with older ones. Low-level inflammation and chronic immune activation act on lipids through a variety of mechanisms to make them more atherogenic. As a consequence, risk is higher than would be expected for any given cholesterol level. Clinical outcome trials of cholesterol-lowering therapies have not yet been completed in people living with HIV, so that treatment decisions depend on extrapolation from studies in uninfected

populations. Traditional risk assessment tools underestimate cardiovascular risk in individuals with HIV. Statins are the mainstay of lipid-lowering drug treatment; however, drug-drug interactions with ART must be considered. Simvastatin and lovastatin are contraindicated in patients taking protease inhibitors, and the dose of atorvastatin and rosuvastatin should be limited to 40 mg and 10 mg/d with some ART combinations. Switching from older forms of ART to lipid-friendly newer ones is a useful strategy as long as virologic suppression is maintained, but adding a statin lowers low-density lipoprotein cholesterol more effectively. Studies indicate that lipid abnormalities are not treated as aggressively in individuals living with HIV as they are in uninfected people, making this an opportunity to improve care.

[8] *Huang R, Mills K, Romero J et al.* **Comparative effects of lipid lowering, hypoglycemic, antihypertensive and antiplatelet medications on carotid artery intima-media thickness progression: a network meta-analysis**. Cardiovascular diabetology 2019; 18:14.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30700294

ABSTRACT

BACKGROUND: Carotid artery intima-media thickness (cIMT) progression is a surrogate marker of atherosclerosis with a high predictive value for future CVD risk. This study evaluates the comparative efficacies of lipid lowering, hypoglycemic, antihypertensive and antiplatelet medications on cIMT progression. METHODS: We conducted a network meta-analysis (NMA) to evaluate the relative efficacies of several drug classes in modifying cIMT progression. After a literature search in several electronic databases, studies were selected by following predetermined eligibility criteria. An inverse variance-heterogeneity model was used for NMA. Sensitivity analyses were performed to check the reliability of the overall NMA, and transitivity analyses were performed to examine the effects of modifiers on the NMA outcomes. RESULTS: Data were taken from 47 studies (15,721 patients; age: 60.2 years [95% confidence interval (CI) 58.8, 61.6]; BMI: 27.2 kg/m(2) [95% CI 26.4, 28.0]; and gender: 58.3% males [95% CI 48.3, 68.3]). Treatment duration was 25.8 months [95% CI 22.9, 28.7]. Of the 13 drug classes in the network, treatment with phosphodiesterase III inhibitors was the most effective in retarding annual mean cIMT against network placebo (weighted mean difference (WMD) - 0.059 mm [95% CI - 0.099, - 0.020) followed by the calcium channel blockers (WMD - 0.055 mm [95% CI - 0.099, 0.001]) and platelet adenosine diphosphate inhibitors (WMD - 0.033 mm [95% CI - 0.058, 0.008]). These 3 drug classes also attained the same positions when the NMA was conducted by using first-year changes in mean cIMT. In transitivity analyses, longer treatment duration, higher body mass index (BMI), and a higher baseline cIMT were found to be independently associated with a lesser reduction in annual mean cIMT. However, in a multivariate analysis with these 3 modifiers, none of these factors was significantly associated with annual change in mean cIMT. In the placebo group, age was inversely associated with annual change in mean cIMT independently. CONCLUSION: Phosphodiesterase III inhibitors and calcium channel blockers are found more effective than other drug classes in retarding cIMT progression. Age, BMI, and baseline cIMT may have some impact on these outcomes.

[9] *Tong XK, Trigiani LJ, Hamel E*. **High cholesterol triggers white matter alterations and cognitive deficits in a mouse model of cerebrovascular disease: benefits of simvastatin**. Cell death & disease 2019; 10:89.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30692517

ABSTRACT

Transgenic mice overexpressing transforming growth factor-beta1 (TGF mice) display impaired cerebrovascular reactivity, cerebral hypoperfusion and neurovascular uncoupling, but no overt cognitive deficits until old age. Cardiovascular diseases are a major risk factor for vascular cognitive impairment and dementia (VCID). We investigated the impact of a high cholesterol diet (HCD) on cerebrovascular and cognitive function in adult (6 months) and aged (12 months) TGF mice, together with the potential benefit of simvastatin (SV), an anti-cholesterol drug with pleiotropic effects, in adult mice. HCD increased blood, but not brain, cholesterol levels in treated mice, which SV did not reduce. In WT mice, HCD induced small, albeit significant, impairment in endothelium-dependent dilatory function. In TGF mice, HCD worsened the established brain vessel dilatory dysfunction in an age-dependent manner and increased the number of string vessels in the white matter (WM), alterations respectively normalized and significantly countered by SV. HCD triggered cognitive decline only in TGF mice at both ages, a deficit prevented by SV. Concurrently, HCD upregulated galectin-3 immunoreactivity in WM microglial cells, a response significantly reduced in SV-treated TGF mice. Grey matter astrogliosis and microgliosis were not affected by HCD or SV. In the subventricular zone of adult HCD-treated TGF mice, SV promoted oligogenesis and migration of oligodendrocyte progenitor cells. The results demonstrate that an underlying cerebrovascular pathology increases vulnerability to cognitive failure when combined to another risk factor for dementia, and that WM alterations are associated with this loss of function. The results further indicate that myelin repair mechanisms, as triggered by SV, may bear promise in preventing or delaying cognitive decline related to VCID.

[10] *Kato T, Ushiogi Y, Yokoyama H et al.* **A case of apolipoprotein E Toyonaka and homozygous apolipoprotein E2/2 showing non-immune membranous nephropathy-like glomerular lesions with foamy changes**. CEN case reports 2019.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30701487

ABSTRACT

A 47-year-old Japanese man with mild proteinuria was treated with an ACE inhibitor and antiplatelet agent for 7 years. However, urinary protein levels increased and renal biopsy was performed. Eight out of 20 glomeruli showed global or segmental sclerosis with foamy changes or bubbles, but with a different appearance to typical foam cells or lipoprotein thrombi. "Spike" formation, as observed in membranous nephropathy (MN), was segmentally detected in methenamine silver-stained sections. In an immunofluorescence study, weak linear patterns for IgG and scanty deposits for C3 were observed in glomeruli, but were not specific for immunogenetic MN. An electron microscopy study showed highly dense deposits in the subepithelial, subendothelial, and mesangial areas, in which microbubbles appeared under a higher magnification. Since this case exhibited hypertriglyceridemia and cholesterolemia with high serum apolipoprotein E (apoE) clinically and homozygous apoE2/2 by apoE phenotype and genotype analyses, apoE2 homozygote glomerulopathy was diagnosed and various lipid-lowering agents, e.g., probucol, fenofibrate, and ezetimibe, were administered. However, renal dysfunction gradually developed and peritoneal dialysis was initiated 11 years after the diagnosis. ApoE Toyonaka (Ser197Cys) and homozygous E2/2 were recently identified by direct

DNA sequencing. Therefore, non-immune MN-like lesions may develop with the combination of these apoE mutations.

[11] *Hadjiphilippou S, Ray KK*. **Cholesterol-Lowering Agents**. Circulation research 2019; 124:354-363.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30702991
ABSTRACT
Cardiovascular disease (CVD) remains the leading cause of death worldwide. To date, decades of research has established LDL-C (low-density lipoprotein cholesterol) as a causal factor in the development of atherosclerotic CVD. Statin therapy, supported by a broad evidence base, has demonstrated its superior efficacy in reducing LDL-C and subsequent cardiovascular risk. It therefore currently forms the mainstay of lipid-lowering therapy as recommended by international guidelines. Statin therapy is indicated in the secondary prevention of atherosclerotic CVD, as well as genetic causes of dyslipidemia (such as familial hypercholesterolemia). Although this strategy targets those most at risk, it merely addresses those most susceptible and does not account for the fact that most cardiovascular events occur in those at moderate to low risk. In addition, there is evidence for use in primary prevention such as in those with diabetes mellitus, chronic kidney disease, and high risk of future atherosclerotic CVD as determined by risk prediction calculators. Risk prediction tools, however, are far from perfect and do not accurately account for those at low short-term but high lifelong risk. Considering the log-linear relationship between LDL-C reductions and reductions in risk of atherosclerotic CVD, even in those at very low risk of future events, a clinical question posed is can we and should we shift the entire risk distribution by treating everyone? The present review discusses these issues in more detail outlining arguments for and against each approach.

[12] *Hegele RA, Tsimikas S*. **Lipid-Lowering Agents**. Circulation research 2019; 124:386-404.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30702996
ABSTRACT
Several new or emerging drugs for dyslipidemia owe their existence, in part, to human genetic evidence, such as observations in families with rare genetic disorders or in Mendelian randomization studies. Much effort has been directed to agents that reduce LDL (low-density lipoprotein) cholesterol, triglyceride, and Lp[a] (lipoprotein[a]), with some sustained programs on agents to raise HDL (high-density lipoprotein) cholesterol. Lomitapide, mipomersen, AAV8.TBG.hLDLR, inclisiran, bempedoic acid, and gemcabene primarily target LDL cholesterol. Alipogene tiparvovec, pradigastat, and volanesorsen primarily target elevated triglycerides, whereas evinacumab and IONIS-ANGPTL3-LRx target both LDL cholesterol and triglyceride. IONIS-APO(a)-LRx targets Lp(a).

[13] *Price NL, Rotllan N, Zhang X et al.* **Specific Disruption of Abca1 Targeting Largely Mimics the Effects of miR-33 Knockout on Macrophage Cholesterol Efflux and Atherosclerotic Plaque Development**. Circulation research 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30707082
ABSTRACT

RATIONALE: Inhibition of miR-33 reduces atherosclerotic plaque burden, but miR-33 deficient mice are predisposed to the development of obesity and metabolic dysfunction. The pro-atherogenic effects of miR-33 are thought to be in large part due to its repression of macrophage cholesterol efflux, through targeting of ATP Binding Cassette Subfamily A Member 1 (Abca1). However, targeting of other factors may also be required for the beneficial effects of miR-33 and currently available approaches have not allowed researchers to determine the specific impact of individual miRNA target interactions in vivo. OBJECTIVE: In this work, we sought to determine how specific disruption of Abca1 targeting by miR-33 impacts macrophage cholesterol efflux and atherosclerotic plaque formation in vivo. METHODS AND RESULTS: We have generated a novel mouse model with specific point mutations in the miR-33 binding sites of the Abca1 3'UTR, which prevents targeting by miR-33. Abca1 binding site mutant (Abca1(BSM)) mice had increased hepatic ABCA1 expression, but did not show any differences in body weight or metabolic function after high fat diet feeding. Macrophages from Abca1(BSM) mice also had increased ABCA1 expression, as well as enhanced cholesterol efflux and reduced foam cell formation. Moreover, LDLR deficient animals transplanted with bone marrow from Abca1(BSM) mice had reduced atherosclerotic plaque formation, similar to mice transplanted with bone marrow from miR-33 knockout mice. CONCLUSIONS: Although the more pronounced phenotype of miR-33 deficient animals suggests that other targets may also play an important role, our data clearly demonstrate that repression of ABCA1 is primarily responsible for the pro-atherogenic effects of miR-33. This work shows for the first time that disruption of a single miRNA/target interaction can be sufficient to mimic the effects of miRNA deficiency on complex physiologic phenotypes in vivo and provides an approach by which to assess the impact of individual miRNA targets.

[14] *Ridker PM*. **Anticytokine Agents**. Circulation research 2019; 124:437-450.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30702995

ABSTRACT

The recognition that atherosclerosis is a complex chronic inflammatory disorder mediated through both adaptive and innate immunity has led to the hypothesis that anticytokine therapies targeting specific IL (interleukin) signaling pathways could serve as powerful adjuncts to lipid lowering in the prevention and treatment of cardiovascular disease. Cytokines involved in human atherosclerosis can be broadly classified as proinflammatory and proatherogenic (such as IL-1, IL-6, and TNF [tumor necrosis factor]) or as anti-inflammatory and antiatherogenic (such as IL-10 and IL-1rA). The recent CANTOS (Canakinumab Anti-Inflammatory Thrombosis Outcomes Study) has shown that specific targeting of IL-1beta can significantly reduce cardiovascular event rates without lipid or blood pressure lowering. In CANTOS, the magnitude of benefit of this cytokine-targeted approach to atherosclerosis treatment was associated to the magnitude of reduction of the central signaling cytokine IL-6 and the downstream clinical biomarker high-sensitivity CRP (C-reactive protein). By contrast, in the recent CIRT (Cardiovascular Inflammation Reduction Trial), low-dose methotrexate neither reduced IL-1beta, IL-6, or high-sensitivity CRP nor lowered cardiovascular event rates. Taken together, these 2 contemporary trials provide proof of principle that focused cytokine inhibition, not broad-spectrum anti-inflammatory therapy, is likely to be crucial for atheroprotection. This review provides an overview of cytokines in atherosclerosis, the potential benefits and risks

associated with targeted anticytokine therapies, and a look to the future of clinical practices addressing residual inflammatory risk.

[15] *Rosenson RS, Hegele RA, Koenig W*. **Cholesterol-Lowering Agents**. Circulation research 2019; 124:364-385.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30702994
ABSTRACT
Loss-of-function variants in PCSK9 (proprotein convertase subtilisin-kexin type 9) are associated with lower lifetime risk of atherosclerotic cardiovascular disease) events. Confirmation of these genetic observations in large, prospective clinical trials in participants with atherosclerotic cardiovascular disease has provided guidance on risk stratification and enhanced our knowledge on hitherto unresolved and contentious issues concerning the efficacy and safety of markedly lowering LDL-C (low-density lipoprotein cholesterol). PCSK9 has a broad repertoire of molecular effects. Furthermore, clinical trials with PCSK9 inhibitors demonstrate that reductions in atherosclerotic cardiovascular disease events are more effective in patients with recent myocardial infarction, multiple myocardial infarctions, multivessel coronary artery disease, and lower extremity arterial disease. The potent LDL-C lowering efficacy of PCSK9 inhibitors provides the opportunity for more aggressive LDL-lowering strategies in high-risk patients with atherosclerotic cardiovascular disease and supports the notion that there is no lower limit for LDL-C. Aggressive LDL-C lowering with fully human PCSK9 monoclonal antibodies has been associated by a safety profile superior to that of other classes of LDL-lowering agents. These clinical trials provide evidence that LDL lowering with PCSK9 inhibitors is an effective therapy for lowering cardiovascular events in high-risk patients with LDL-C levels >/=70 mg/dL on maximally tolerated oral therapies, including statins and ezetimibe.

[16] *Di Taranto MD, de Falco R, Guardamagna O et al.* **Lipid profile and genetic status in a familial hypercholesterolemia pediatric population: exploring the LDL/HDL ratio**. Clin Chem Lab Med 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30710474
ABSTRACT
Background Familial hypercholesterolemia (FH) is a genetic disorder caused by mutations in genes involved in low-density lipoprotein (LDL) uptake (LDLR, APOB and PCSK9). Genetic diagnosis is particularly useful in asymptomatic children allowing for the detection of definite FH patients. Furthermore, defining their genetic status may be of considerable importance as the compound heterozygous status is much more severe than the heterozygous one. Our study aims at depicting the genetic background of an Italian pediatric population with FH focusing on the correlation between lipid profile and genetic status. Methods Out of 196 patients with clinically suspected FH (LDL-cholesterol [LDL-C] levels above 3.37 mmol/L, cholesterol level above 6.46 mmol/L in a first-degree relative or the presence of premature cardiovascular acute disease in a first/second-degree relative), we screened 164 index cases for mutations in the LDLR, APOB and PCSK9 genes. Results Patients with mutations (129/164) showed increased levels of LDL-C, 95th percentile-adjusted LDL-C and LDL/high-density lipoprotein (HDL) ratio and decreased levels of HDL-C, adjusted HDL-C. The association of the LDL/HDL ratio with the presence of mutations was assessed independently of age, (body mass index) BMI, parental

hypercholesterolemia, premature coronary artery disease (CAD), triglycerides by multivariate logistic regression (odds ratio [OR]=1.701 [1.103-2.621], p=0.016). The LDL/HDL ratio gradually increased from patients without mutations to patients with missense mutations, null mutations and compound heterozygotes. Conclusions In conclusion, the LDL/HDL ratio proved to be a better parameter than LDL-C for discriminating patients with from patients without mutations across different genetic statuses.

[17] *Kelly KE, Jiroutek MR, Lewis K, Zagar B*. **Assessing Changes in Statin Prescribing Patterns Surrounding the 2013 American College of Cardiology/American Heart Association Lipid Guidelines**. Clinical therapeutics 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30686571
ABSTRACT
PURPOSE: The American College of Cardiology (ACC) and the American Heart Association (AHA) introduced new lipid guidelines in late 2013 that were a vast departure from older guidelines. Concerns were raised regarding the likely increase in the number of adults who would be eligible for lipid-lowering therapy, namely moderate to high intensity statins. We sought to determine whether, in the first year after the ACC/AHA guideline release, more patients were prescribed statins, prescribed moderate- to high-intensity statins, and eligible for statins compared with the previous year. METHODS: This study was a retrospective, cross-sectional, observational analysis of National Ambulatory Medical Care Survey collected by the Centers for Disease Control and Prevention during the years 2013 and 2014. Survey participants who were younger than 40 years or older than 75 years, were pregnant, or had triglyceride levels >/=400 mg/dL were excluded. Descriptive analyses and chi(2) tests of homogeneity (and associated odds ratios [ORs] and CIs) were constructed and reported. FINDINGS: Compared with 2013, a higher percentage of patients in 2014 were prescribed a statin and were eligible to receive a statin. In fact, patients in 2014 were significantly more likely to be prescribed a statin (OR = 1.22; 95% CI, 1.00-1.48) and to be eligible for a statin (OR = 9.26, 95% CI 7.54-11.37) compared with 2013. Although a higher percentage of patients in 2014 were prescribed a higher-intensity statin, the difference was not statistically significant (OR = 1.17; 95% CI, 0.90-1.52). IMPLICATIONS: In the first year after the ACC/AHA guideline introduction, more patients in the United States were prescribed a statin. However, it is unclear whether the new guidelines were strictly adhered to regarding intensity of statin therapy.

[18] *Amor AJ, Perea V*. **Dyslipidemia in nonalcoholic fatty liver disease**. Current opinion in endocrinology, diabetes, and obesity 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30694825
ABSTRACT
PURPOSE OF REVIEW: To summarize recent findings regarding the characterization of lipoprotein disturbances in nonalcoholic fatty liver disease (NAFLD) and their relationship with cardiovascular disease (CVD) and make recommendations for the management of this situation. RECENT FINDINGS: Advanced lipoprotein profile (using NMR spectroscopy) has shown profound lipoprotein derangements which are overlooked with conventional analyses: increased number and size of very low-density lipoproteins particles, increased number of low-density lipoprotein particles (especially small sized), smaller high-density lipoprotein particles, and an increase in

the triglyceride content of all these lipoproteins. Other changes such as impaired functionality of high-density lipoprotein particles have also been observed. Beyond low-density lipoprotein-related parameters, the importance of triglyceride-rich lipoproteins in the pathogenesis of atherosclerosis has recently gained interest. Several studies suggest that these lipoproteins may have an independent role in CVD in NAFLD populations. Although outcome studies with lipid-lowering drugs in NAFLD are lacking, treatment with both statins, and especially, triglyceride-lowering drugs could be promising for these populations at high residual cardiovascular risk. SUMMARY: In addition to being the main determinant of dyslipidemia, disturbances in triglyceride-rich lipoproteins are thought to be the key factor of increased CVD risk in NAFLD. Treatments specifically aimed at modifying these derangements warrant further study in this high-risk population.

[19] *Scognamiglio M, Costa D, Sorriento A, Napoli C*. **Current therapy and nutraceuticals for the treatment of patients with dyslipidemias**. Current pharmaceutical design 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30706799
ABSTRACT
Coronary heart disease (CHD) remain the leading cause of disability and death in industrialized Countries. Among many conditions that contribute to the etiology and progression of CHD, the presence of high LDL-C levels represent the major risk factor. Therefore, the reduction of LDL-C levels play a key role in the management of patients with high or very high cardiovascular risk. Although statins represent the gold standard therapy for the reduction of cholesterol levels, do not allow to achieve target levels of LDL-C in all patients. Indeed, a significant number of patients result statin-intolerants, especially when the dosage increase. The availability of new lipid-lowering drugs such as ezetimibe and PCSK9 inhibitors may represent an important alternative or complement to the conventional lipid-lowering therapies. However, long-term studies are still needed to define efficacy and safety of use of these latter new drugs. Some nutraceuticals may became an adequate and effective support in the management of some patients. To date, several nutraceuticals with different mechanism of actions that provide a good tolerability are available as lipid-lowering agents. In particular, the most investigated are red yeast rice, phytosterols, berberine, beta-glucans and soy. The aim of this review was to report recent data on the efficacy and safety of principle hypocholesterolemic drugs available and to evaluate the possible role of some nutraceuticals as support therapy in the management of patients with dyslipidemias.

[20] *Stoyanova D, Stratmann B, Schwandt A et al.* **Heart failure among people with Type 2 diabetes mellitus: real-world data of 289 954 people from a diabetes database**. Diabetic medicine : a journal of the British Diabetic Association 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30701607
ABSTRACT
AIM: Comparing people with Type 2 diabetes mellitus with and without heart failure in terms of metabolic control, therapeutic regimen and comorbidities. METHODS: The Prospective Diabetes Registry (DPV) is a longitudinal documentation system for demographics, medical care and outcome in people with diabetes mellitus. It consists of follow-up data from people with diabetes mellitus who have agreed to be recorded in the registry. Clinical data are submitted by

general practitioners, specialists and clinics throughout Germany and Austria. Some 289 954 people with Type 2 diabetes mellitus (years 2000 to 2015) were analysed using demographic statistics and adjustment for confounders based on linear and logistic regression analysis. RESULTS: People with Type 2 diabetes mellitus (ICD code: E11) and heart failure (ICD code: I50) (N = 14 723) were older, more often women and presented with longer diabetes duration compared with those without heart failure. After adjustment for age, gender and diabetes duration, people with heart failure showed lower HbA1c , higher BMI and more intense insulin therapy. Analysis revealed that people with heart failure were more often treated with insulin, and more frequently received anti-hypertensives and lipid-lowering medication. They presented with lower systolic and diastolic BP. People with heart failure more frequently showed a history of comorbidities. CONCLUSION: Heart failure is common in diabetes mellitus, but the prevalence in the DPV is lower frequent than expected. The reason for improved metabolic control in heart failure may be intensified therapy with insulin, lipid-lowering medication and anti-hypertensives in this cohort.

[21] *Hwang YC, Jun JE, Jeong IK et al.* **Comparison of the Efficacy of Rosuvastatin Monotherapy 20 mg with Rosuvastatin 5 mg and Ezetimibe 10 mg Combination Therapy on Lipid Parameters in Patients with Type 2 Diabetes Mellitus**. Diabetes Metab J 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30688048

ABSTRACT

BACKGROUND: The apolipoprotein B/A1 (apoB/A1) ratio is a stronger predictor of future cardiovascular disease than is the level of conventional lipids. Statin and ezetimibe combination therapy have shown additional cardioprotective effects over statin monotherapy. METHODS: This was a single-center, randomized, open-label, active-controlled study in Korea. A total of 36 patients with type 2 diabetes mellitus were randomized to either rosuvastatin monotherapy (20 mg/day, n=20) or rosuvastatin/ezetimibe (5 mg/10 mg/day, n=16) combination therapy for 6 weeks. RESULTS: After the 6-week treatment, low density lipoprotein cholesterol (LDL-C) and apoB reduction were comparable between the two groups (-94.3+/-15.4 and -62.0+/-20.9 mg/dL in the rosuvastatin group, -89.9+/-22.7 and -66.8+/-21.6 mg/dL in the rosuvastatin/ezetimibe group, P=0.54 and P=0.86, respectively). In addition, change in apoB/A1 ratio (-0.44+/-0.16 in the rosuvastatin group and -0.47+/-0.25 in the rosuvastatin/ezetimibe group, P=0.58) did not differ between the two groups. On the other hand, triglyceride and free fatty acid (FFA) reductions were greater in the rosuvastatin/ezetimibe group than in the rosuvastatin group (-10.5 mg/dL [interquartile range (IQR), -37.5 to 29.5] and 0.0 muEq/L [IQR, -136.8 to 146.0] in the rosuvastatin group, -49.5 mg/dL [IQR, -108.5 to -27.5] and -170.5 muEq/L [IQR, -353.0 to 0.8] in the rosuvastatin/ezetimibe group, P=0.010 and P=0.049, respectively). Both treatments were generally well tolerated, and there were no differences in muscle or liver enzyme elevation. CONCLUSION: A 6-week combination therapy of low-dose rosuvastatin and ezetimibe showed LDL-C, apoB, and apoB/A1 ratio reduction comparable to that of high-dose rosuvastatin monotherapy in patients with type 2 diabetes mellitus. Triglyceride and FFA reductions were greater with the combination therapy than with rosuvastatin monotherapy.

Literature update week 05 (2019)

[22] *Taylor PJ, Thompson CH, Luscombe-Marsh ND et al.* **Efficacy of Real-Time Continuous Glucose Monitoring to Improve Effects of a Prescriptive Lifestyle Intervention in Type 2 Diabetes: A Pilot Study**. Diabetes Ther 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30706365
ABSTRACT
INTRODUCTION: Optimising patient adherence to prescribed lifestyle interventions to achieve improved blood glucose control remains a challenge. Combined use of real-time continuous glucose monitoring systems (RT-CGM) may promote improved glycaemic control. This pilot study examines the effects of a prescriptive lifestyle modification programme when combined with RT-CGM on blood glucose control and cardiovascular disease risk markers. METHODS: Twenty adults (10 men, 10 women) with obesity and type-2 diabetes (T2D) (age 60.55 +/- 8.38 years, BMI 34.22 +/- 4.67 kg/m(2)) were randomised to a prescriptive low-carbohydrate diet and lifestyle plan whilst continuously wearing either an RT-CGM or an 'offline-blinded' monitor (control) for 12 weeks. Outcomes were glycaemic control (HbA1c, fasting glucose, glycaemic variability [GV]), diabetes medication (MeS), weight, blood pressure and lipids assessed pre- and post-intervention. RESULTS: Both groups experienced reductions in body weight (RT-CGM - 7.4 +/- 4.5 kg vs. control - 5.5 +/- 4.0 kg), HbA1c (- 0.67 +/- 0.82% vs. - 0.68 +/- 0.74%), fasting blood glucose (- 1.2 +/- 1.9 mmol/L vs. - 1.0 +/- 2.2 mmol/L), LDL-C (- 0.07 +/- 0.34 mmol/L vs. - 0.26 +/- 0.42 mmol/L) and triglycerides (- 0.32 +/- 0.46 mmol/L vs. - 0.36 +/- 0.53 mmol/L); with no differential effect between groups (P >/= 0.10). At week 12, GV indices were consistently lower by at least sixfold in RT-CGM compared to control (CONGA-1 - 0.27 +/- 0.36 mmol/L vs. 0.06 +/- 0.19 mmol/L; CONGA-2 - 0.36 +/- 0.54 mmol/L vs. 0.05 +/- 2.88 mmol/L; CONGA-4 - 0.44 +/- 0.67 mmol/L vs. - 0.02 +/- 0.42 mmol/L; CONGA-8 - 0.36 +/- 0.61 vs. 0.02 +/- 0.52 mmol/L; MAGE - 0.69 +/- 1.14 vs. - 0.09 +/- 0.08 mmol/L, although there was insufficient power to achieve statistical significance (P >/= 0.11). Overall, there was an approximately 40% greater reduction in blood glucose-lowering medication (MeS) in RT-CGM (- 0.30 +/- 0.59) compared to control (0.02 +/- 0.23). CONCLUSION: This study provides preliminary evidence that RT-CGM may be an effective strategy to optimise glucose control whilst following a low-carbohydrate lifestyle programme that targets improved glycaemic control, with minimal professional support. TRIAL REGISTRATION: Australian New Zealand Clinical Trials Registry identifier, ANZTR: 372898. FUNDING: Grant funding was received for the delivery of the clinical trial only, by the Diabetes Australia Research Trust (DART).

[23] *Prochaska JH, Trobs SO, Wild PS*. **PCSK9: A link between air pollution and cardiovascular disease?** European journal of preventive cardiology 2019:2047487319827726.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30696261
ABSTRACT

[24] *Ferraz-Amaro I, Hernandez-Hernandez MV, Tejera-Segura B et al.* **Effect of IL-6 Receptor Blockade on Proprotein Convertase Subtilisin/Kexin Type-9 and Cholesterol Efflux Capacity in Rheumatoid Arthritis Patients**. Hormone and metabolic research = Hormon- und Stoffwechselforschung = Hormones et metabolisme 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30695794
ABSTRACT

The aim of the work was to examine whether abnormalities in the lipid profile that tocilizumab (TCZ), an anti-IL-6 receptor Ab, exerts in rheumatoid arthritis (RA) patients is related to changes in either proprotein convertase subtilisin/kexin-9 (PCSK9) serum concentrations or in serum cholesterol efflux capacity (CEC). TOCRIVAR is a one-year prospective clinical trial that analyzes the influence of TCZ on cardiovascular risk factors. Twenty-seven RA patients receiving TCZ (8 mg/kg IV/q4w) were assessed at baseline and weeks 12, 24, and 52. Disease activity indexes, adiposity composition, physical activity, serum CEC, PCSK9, and lipoproteins serum concentrations were assessed at every visit. Basal high-sensitivity C-reactive protein (hs-CRP) and disease activity were markedly reduced throughout one-year TCZ treatment. While initially total cholesterol and LDL cholesterol increased their plasma concentration, decreasing to basal afterwards, lipoprotein(a) was significantly lower than basal in all visits of the study. CEC increased after 24 week of treatment proportionally to hs-CRP reduction, and remained significantly higher after week 52 [median % change 32 (3-141), p=0.021]. Interestingly, variations in LDL cholesterol basal concentration along the one year of TCZ treatment correlated directly with changes of PCSK9 serum concentration (r=0.37, p=0.003). Basal abdominal adiposity, BMI, and physical activity remained stable during the study. Long-term TCZ-treated RA patients show an increment in CEC inversely proportional to hs-CRP reduction and changes in LDL cholesterol that might be explained, at least in part, by variations in PCSK9 plasma concentration. Overall, TCZ treatment produces a favorable qualitative net effect in terms of atherogenic implication in RA patients.

[25] *Yu XB, Zhang HN, Dai Y et al.* **Simvastatin prevents and ameliorates depressive behaviors via neuroinflammatory regulation in mice**. Journal of affective disorders 2019; 245:939-949.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30699879

ABSTRACT

BACKGROUND: Statins play a beneficial role in the treatment of coronary artery disease and are widely prescribed to prevent hypercholesterolemia. Previous studies have demonstrated that statins also have anti-inflammatory and immunomodulatory properties, and these are being explored for potential benefits in depression. However, the role of statins in the treatment of depression has not been well examined. METHODS: We investigated the effects of simvastatin on depressive behaviors and neuroinflammation in lipopolysaccharide (LPS) and chronic mild stress (CMS) induced depression model in mice. Sucrose preference test (SPT), forced swimming test (FST), novelty-suppressed feeding test (NSFT) were used to detect the depressive behaviors. The microglial activation was detected by immunohistochemistry analysis and the pro-inflammatory cytokines expressions including IL-1beta, TNF-alpha and IL-6 were examined by Western blot analysis. RESULTS: Our data indicated that oral administration of simvastatin at 20mg/kg significantly prevented and ameliorated depressive behaviors reflected by better performance in the SPT, FST and NSFT. Moreover, simvastatin markedly prevented and ameliorated LPS and CMS-induced neuroinflammation, as shown by the suppressed activation of microglia in hippocampus and decreased hippocampal pro-inflammatory cytokines expressions including IL-1beta, TNF-alpha, IL-6, which might be mediated via the inhibition of NF-kappaB pathway, as shown by the decreased nuclear NF-kappaB p65 expression. LIMITATIONS: The interpretation of the evidence of a positive treatment effect of simvastatin on the depressive manifestations, multifaceted etiology of depression, and confirmation of this

finding from animal models to humans is needed. CONCLUSION: These results suggest that simvastatin has the potential to be employed as a therapy for depression associated with neuroinflammation.

[26] *Armitage J, Holmes MV, Preiss D*. **Cholesteryl Ester Transfer Protein Inhibition for Preventing Cardiovascular Events: JACC Review Topic of the Week**. Journal of the American College of Cardiology 2019; 73:477-487.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30704580
ABSTRACT
Cholesteryl ester transfer protein (CETP) facilitates exchange of triglycerides and cholesteryl ester between high-density lipoprotein (HDL) and apolipoprotein B100-containing lipoproteins. Evidence from genetic studies that variants in the CETP gene were associated with higher blood HDL cholesterol, lower low-density lipoprotein cholesterol, and lower risk of coronary heart disease suggested that pharmacological inhibition of CETP may be beneficial. To date, 4 CETP inhibitors have entered phase 3 cardiovascular outcome trials. Torcetrapib was withdrawn due to unanticipated off-target effects that increased risk of death, and major trials of dalcetrapib and evacetrapib were terminated early for futility. In the 30,000-patient REVEAL (Randomized Evaluation of the Effects of Anacetrapib through Lipid Modification) trial, anacetrapib doubled HDL cholesterol, reduced non-HDL cholesterol by 17 mg/dl (0.44 mmol/l), and reduced major vascular events by 9% over 4 years, but anaceptrapib was found to accumulate in adipose tissue, and regulatory approval is not being sought. Therefore, despite considerable initial promise, CETP inhibition provides insufficient cardiovascular benefit for routine use.

[27] *Umeda R, Takanari H, Ogata K et al.* **Direct free radical scavenging effects of water-soluble HMG-CoA reductase inhibitors**. Journal of clinical biochemistry and nutrition 2019; 64:20-26.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30705508
ABSTRACT
3-Hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, statins, are widely used for preventing cardiovascular and cerebrovascular diseases by controlling blood cholesterol level. Additionally, previous studies revealed the scavenging effects of statins on free radicals. We assessed direct scavenging activities of two water-soluble statins, fluvastatin and pravastatin, on multiple free radicals using electron spin resonance spectrometry with spin trapping method. We estimated reaction rate constants (k fv for fluvastatin, and k pv for pravastatin). Superoxide anion was scavenged by fluvastatin and pravastatin with k fv and k pv of 4.82 M(-1)s(-1) and 49.0 M(-1)s(-1), respectively. Scavenging effects of fluvastatin and pravastatin on hydroxyl radical were comparable; both k fv and k pv were >10(9) M(-1)s(-1). Fluvastatin also eliminated tert-butyl peroxyl radical with relative k fv of 2.63 to that of CYPMPO, whereas pravastatin did not affect tert-butyl peroxyl radical. Nitric oxide was scavenged by fluvastatin and pravastatin with k fv and k pv of 68.6 M(-1)s(-1) and 701 M(-1)s(-1), respectively. Both fluvastatin and pravastatin had scavenging effects on superoxide anion, hydroxyl radical and nitric oxide radical. On the other hand, tert-butyl peroxyl radical was scavenged only by fluvastatin, suggesting that fluvastatin might have more potential effect than pravastatin to prevent atherosclerosis and ischemia/reperfusion injury via inhibiting oxidation of lipids.

[28] *Simon MC, Moller-Horigome A, Strassburger K et al.* **Correlates of Insulin-Stimulated glucose Disposal in Recent Onset Type 1 and Type 2 Diabetes**. The Journal of clinical endocrinology and metabolism 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30689904
ABSTRACT
Context and Objective: Not only type 2, but also type 1 diabetes can associate with insulin resistance, as assessed from insulin-stimulated whole body glucose disposal (M-value). We hypothesized that different factors affect the M-value at the onset of type 1 and type 2 diabetes. Design and Patients: We examined 132 patients with type 1 or type 2 diabetes matched for sex, age, and body mass index with known diabetes duration of less than 12 months. Multivariable linear regression analyses were applied to test the associations between glycemic control, blood lipids, adiponectin, pro-inflammatory immune mediators and M-value, obtained from from hyperinsulinemic-euglycemic clamps. Results: Despite comparable age, BMI and near-normoglycemic control, mean M-value was lower in type 2 than in type 1 diabetes patients. Patients with type 1 diabetes had lower waist-to-hip ratio and serum triglycerides, but higher serum adiponectin than patients with type 2 diabetes, while circulating pro-inflammatory markers were not different. Even upon adjustments for glucose-lowering treatments, fasting blood glucose correlated negatively with M-value in both groups. But only in type 2 diabetes, gamma-glutamyl transferase - independent of any treatments - correlated negatively, whereas serum adiponectin correlated positively with M-values. Conclusions: Fasting glycemia correlate with insulin-stimulated glucose disposal in both diabetes types, while altered liver and adipose tissue function associate with insulin-stimulated glucose disposal only in type 2 diabetes, underpinning specific differences between these diabetes types.

[29] *Lui DTW, Lee ACH, Yap DYH et al.* **A young Chinese man with nephrotic syndrome due to lipoprotein glomerulopathy**. Journal of clinical lipidology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30685233
ABSTRACT
Lipoprotein glomerulopathy (LPG) is a rare autosomal dominant renal disease with incomplete penetrance, associated with specific protein-modifying mutations in the APOE gene. LPG is associated with poor renal prognosis, in which lipoprotein thrombi are seen in the glomerular capillaries. Dyslipidemia in LPG generally resembles type III hyperlipoproteinemia with elevated serum apolipoprotein E level. Fibrate is the most frequently reported lipid-lowering therapy in LPG as hypertriglyceridemia is common in these individuals. There are few existing case reports on effectiveness of statin monotherapy for LPG. We report a 32-year-old Chinese man who presented with nephrotic syndrome, renal impairment, severe hypercholesterolemia without hypertriglyceridemia, and hypertension. Renal biopsy confirmed lipoprotein glomerulopathy. Genetic testing confirmed APOE Kyoto mutation. Anti-hypertensive therapy, including angiotensin receptor blocker, and statin were initiated. Concomitant with normalization of lipid profile, his proteinuria markedly improved, and his renal function has remained stable up to 3 years, demonstrating sustained benefit with statin monotherapy in LPG.

[30] *AlZahrani NR, Yassin AF*. **Chest pain as a possible side effect of pitavastatin (Livalo)**. Journal of family & community medicine 2019; 26:61-63.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30697107

ABSTRACT

Coronary heart disease is a serious complication of dyslipidemia. Pitavastatin is a more commonly prescribed medication for the treatment of dyslipidemia. Here, we report the case of a 37-year-old female, a known patient with well-controlled bronchial asthma. She was recently found to be dyslipidemic and started on pitavastatin calcium 4 mg once a day (OD). On the 10(th) day of treatment, she began to have crushing chest pain and was admitted to the hospital. All investigations for coronary heart disease came out negative. Her symptoms improved dramatically when pitavastatin was stopped. Pitavastatin is reported to cause myalgia and muscle spasm, especially at higher doses. There is evidence in literature that this medication might cause chest pain in old obese ladies if taken at high doses. We report this case as a possibility of chest pain even in younger females.

[31] *Lee JK, Hung CS, Huang CC et al.* **Use of the CHA2DS2-VASc Score for Risk Stratification of Hospital Admissions Among Patients With Cardiovascular Diseases Receiving a Fourth-Generation Synchronous Telehealth Program: Retrospective Cohort Study**. Journal of medical Internet research 2019; 21:e12790.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30702437

ABSTRACT

BACKGROUND: Telehealth programs are generally diverse in approaching patients, from traditional telephone calling and texting message and to the latest fourth-generation synchronous program. The predefined outcomes are also different, including hypertension control, lipid lowering, cardiovascular outcomes, and mortality. In previous studies, the telehealth program showed both positive and negative results, providing mixed and confusing clinical outcomes. A comprehensive and integrated approach is needed to determine which patients benefit from the program in order to improve clinical outcomes. OBJECTIVE: The CHA2DS2-VASc (congestive heart failure, hypertension, age >75 years [doubled], type 2 diabetes mellitus, previous stroke, transient ischemic attack or thromboembolism [doubled], vascular disease, age of 65-75 years, and sex) score has been widely used for the prediction of stroke in patients with atrial fibrillation. This study investigated the CHA2DS2-VASc score to stratify patients with cardiovascular diseases receiving a fourth-generation synchronous telehealth program. METHODS: This was a retrospective cohort study. We recruited patients with cardiovascular disease who received the fourth-generation synchronous telehealth program at the National Taiwan University Hospital between October 2012 and June 2015. We enrolled 431 patients who had joined a telehealth program and compared them to 1549 control patients. Risk of cardiovascular hospitalization was estimated with Kaplan-Meier curves. The CHA2DS2-VASc score was used as the composite parameter to stratify the severity of patients' conditions. The association between baseline characteristics and clinical outcomes was assessed via the Cox proportional hazard model. RESULTS: The mean follow-up duration was 886.1 (SD 531.0) days in patients receiving the fourth-generation synchronous telehealth program and 707.1 (SD 431.4) days in the control group (P<.001). The telehealth group had more comorbidities at baseline than the control group. Higher CHA2DS2-VASc scores (>/=4) were associated with a lower estimated rate of remaining free from cardiovascular hospitalization (46.5% vs 54.8%, log-rank P=.003). Patients with CHA2DS2-VASc scores >/=4

receiving the telehealth program were less likely to be admitted for cardiovascular disease than patients not receiving the program. (61.5% vs 41.8%, log-rank P=.01). The telehealth program remained a significant prognostic factor after multivariable Cox analysis in patients with CHA2DS2-VASc scores >/=4 (hazard ratio=0.36 [CI 0.22-0.62], P<.001). CONCLUSIONS: A higher CHA2DS2-VASc score was associated with a higher risk of cardiovascular admissions. Patients accepting the fourth-generation telehealth program with CHA2DS2-VASc scores >/=4 benefit most by remaining free from cardiovascular hospitalization.

[32] *Ference BA, Kastelein JJP, Ray KK et al.* **Association of Triglyceride-Lowering LPL Variants and LDL-C-Lowering LDLR Variants With Risk of Coronary Heart Disease**. Jama 2019; 321:364-373.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30694319
ABSTRACT
Importance: Triglycerides and cholesterol are both carried in plasma by apolipoprotein B (ApoB)-containing lipoprotein particles. It is unknown whether lowering plasma triglyceride levels reduces the risk of cardiovascular events to the same extent as lowering low-density lipoprotein cholesterol (LDL-C) levels. Objective: To compare the association of triglyceride-lowering variants in the lipoprotein lipase (LPL) gene and LDL-C-lowering variants in the LDL receptor gene (LDLR) with the risk of cardiovascular disease per unit change in ApoB. Design, Setting, and Participants: Mendelian randomization analyses evaluating the associations of genetic scores composed of triglyceride-lowering variants in the LPL gene and LDL-C-lowering variants in the LDLR gene, respectively, with the risk of cardiovascular events among participants enrolled in 63 cohort or case-control studies conducted in North America or Europe between 1948 and 2017. Exposures: Differences in plasma triglyceride, LDL-C, and ApoB levels associated with the LPL and LDLR genetic scores. Main Outcomes and Measures: Odds ratio (OR) for coronary heart disease (CHD)-defined as coronary death, myocardial infarction, or coronary revascularization-per 10-mg/dL lower concentration of ApoB-containing lipoproteins. Results: A total of 654783 participants, including 91129 cases of CHD, were included (mean age, 62.7 years; 51.4% women). For each 10-mg/dL lower level of ApoB-containing lipoproteins, the LPL score was associated with 69.9-mg/dL (95% CI, 68.1-71.6; P = 7.1 x 10-1363) lower triglyceride levels and 0.7-mg/dL (95% CI, 0.03-1.4; P = .04) higher LDL-C levels; while the LDLR score was associated with 14.2-mg/dL (95% CI, 13.6-14.8; P = 1.4 x 10-465) lower LDL-C and 1.9-mg/dL (95% CI, 0.1-3.9; P = .04) lower triglyceride levels. Despite these differences in associated lipid levels, the LPL and LDLR scores were associated with similar lower risk of CHD per 10-mg/dL lower level of ApoB-containing lipoproteins (OR, 0.771 [95% CI, 0.741-0.802], P = 3.9 x 10-38 and OR, 0.773 [95% CI, 0.747-0.801], P = 1.1 x 10-46, respectively). In multivariable mendelian randomization analyses, the associations between triglyceride and LDL-C levels with the risk of CHD became null after adjusting for differences in ApoB (triglycerides: OR, 1.014 [95% CI, 0.965-1.065], P = .19; LDL-C: OR, 1.010 [95% CI, 0.967-1.055], P = .19; ApoB: OR, 0.761 [95% CI, 0.723-0.798], P = 7.51 x 10-20). Conclusions and Relevance: Triglyceride-lowering LPL variants and LDL-C-lowering LDLR variants were associated with similar lower risk of CHD per unit difference in ApoB. Therefore, the clinical benefit of lowering triglyceride and LDL-C levels may be proportional to the absolute change in ApoB.

[33] *Yun UJ, Lee JH, Shim J et al.* **Anti-cancer effect of doxorubicin is mediated by downregulation of HMG-Co A reductase via inhibition of EGFR/Src pathway**. Lab Invest 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30700846
ABSTRACT
Doxorubicin is a widely used DNA damage-inducing anti-cancer drug. However, its use is limited by its dose-dependent side effects, such as cardiac toxicity. Cholesterol-lowering statin drugs increase the efficacy of some anti-cancer drugs. Cholesterol is important for cell growth and a critical component of lipid rafts, which are plasma membrane microdomains important for cell signaling. 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase (HMG-CR) is a critical enzyme in cholesterol synthesis. Here, we show that doxorubicin downregulated HMG-CR protein levels and thus reduced levels of cholesterol and lipid rafts. Cholesterol addition attenuated doxorubicin-induced cell death, and cholesterol depletion enhanced it. Reduction of HMG-CR activity by simvastatin, a statin that acts as an HMG-CR inhibitor, or by siRNA-mediated HMG-CR knockdown enhanced doxorubicin cytotoxicity. Doxorubicin-induced HMG-CR downregulation was associated with inactivation of the EGFR-Src pathway. Furthermore, a high-cholesterol-diet attenuated the anti-cancer activity of doxorubicin in a tumor xenograft mouse model. In a multivulva model of Caenorhabditis elegans expressing an active-EGFR mutant, doxorubicin decreased hyperplasia more efficiently in the absence than in the presence of cholesterol. These data indicate that EGFR/Src/HMG-CR is a new pathway mediating doxorubicin-induced cell death and that cholesterol control could be combined with doxorubicin treatment to enhance efficacy and thus reduce side effects.

[34] *Mayer K, Sommer N, Hache K et al.* **Resolvin E1 Improves Mitochondrial Function in Human Alveolar Epithelial Cells during Severe Inflammation**. Lipids 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30697748
ABSTRACT
Severe inflammatory disorders such as sepsis are a major cause of morbidity and mortality worldwide. Mitochondrial dysfunction is regarded as a key feature involved in inflammation pathogenesis. In the present study, we investigated the impact of the omega-3 fatty acid-derived lipid mediator Resolvin E1 (RvE1) on mitochondrial function in experimental pulmonary inflammation. RvE1 was found to exert anti-inflammatory properties in human alveolar epithelial cells during severe inflammation. RvE1 is capable of restoring inflammation-induced mitochondrial dysfunction and the impaired imbalance of mitochondrial fission and fusion. Experimental inhibition of mitochondrial fission with Mdivi-1 in our model is associated with a significantly reduced inflammatory response and improved mitochondrial function. These findings suggest a novel functional mechanism for the beneficial effects of RvE1 in experimental pulmonary inflammatory reactions.

[35] *Thota RN, Acharya SH, Garg ML*. **Curcumin and/or omega-3 polyunsaturated fatty acids supplementation reduces insulin resistance and blood lipids in individuals with high risk of type 2 diabetes: a randomised controlled trial**. Lipids in health and disease 2019; 18:31.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30684965
ABSTRACT

BACKGROUND: Lowering insulin resistance and dyslipidaemia may not only enhance glycaemic control but also preserve the beta-cell function, reducing the overall risk of developing type 2 diabetes (T2D). The current study was aimed to evaluate the effects of curcumin and/or long-chain omega-3 polyunsaturated fatty acids (LCn-3PUFA) supplementation on glycaemic control and blood lipid levels in individuals at high risk of developing T2D. METHODS: This was a 2 x 2 factorial, randomised, double-blinded, placebo-controlled study. Participants were allocated to either double placebo (PL) or curcumin plus placebo matching for LCn-3PUFA (CC), or LCn-3PUFA plus placebo matching for curcumin (FO), or curcumin plus LCn-3PUFA (CC-FO) for twelve weeks. Primary outcome of the trial was glycaemic indices (HbA1C, fasting glucose and insulin). Insulin resistance and sensitivity is measured using homeostatic model assessment model. RESULTS: A total of sixty-four participants (PL, n = 16; CC, n = 15; FO, n = 17, CC-FO, n = 16) were included in the final analysis. Post-intervention, HbA1c and fasting glucose remained unchanged across all the groups. Insulin sensitivity was significantly improved in the CC supplemented group (32.7 +/- 10.3%) compared to PL (P = 0.009). FO and CC-FO tended to improve insulin sensitivity by 14.6 +/- 8.5% and 8.8 +/- 7.7% respectively, but the difference did not reach significance. Triglyceride levels were further increased in the PL (26.9 +/- 7.4%), however, CC and CC-FO supplementation reduced the triglycerides, FO resulted in the greatest reduction in triglycerides (- 16.4 +/- 4.5%, P < 0.001). CONCLUSION: Reduction in insulin resistance and triglycerides by curcumin and LCn-3PUFA appears to be attractive strategies for lowering the risk of developing T2D. However, this study failed to demonstrate complimentary benefits of curcumin and LCn-3PUFA on glycaemic control. TRAIL REGISTRATION: ACTRN12615000559516 .

[36] *Yan X, Li Y, Dong Y et al.* **Blood pressure and low-density lipoprotein cholesterol control status in Chinese hypertensive dyslipidemia patients during lipid-lowering therapy**. Lipids in health and disease 2019; 18:32.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30696435
ABSTRACT
: The present study comprised 17,096 Chinese hypertensive dyslipidemia patients who received lipid-lowering treatment for > 3 months in order to investigate blood pressure (BP) as well as low-density lipoprotein cholesterol (LDL-C) goal attainment rates in Chinese hypertensive dyslipidemia patients on antidyslipidemia drugs. The factors that interfered with BP, or BP and LDL-C goal attainment rates and antihypertensive treatment patterns, were analyzed. In total, 89.9% of the 17,096 hypertensive dyslipidemia patients received antihypertensive medications mainly consisting of a calcium channel blocker (CCB) (48.7%), an angiotensin receptor antagonist (ARB) (25.4%) and an angiotensin-converting enzyme inhibitor (ACEI) (15.1%). In cardiology departments, usage rates of beta-blockers (19.2%) were unusually high compared to other departments (4.0-8.3%), whereas thiazide diuretics were prescribed at the lowest rate (0.3% vs 1.2-3.6%). The overall goal attainment rates for combined BP and LDL-C as well as BP or LDL-C targets were 22.9, 31.9 and 60.1%, respectively. The lowest BP, LDL-C and BP combined with LDL-C goal attainment rates were achieved in endocrine departments (19.9, 48.9 and 12.4%, respectively). Combination therapies showed no benefit particularly for BP goal achievement. A multivariate logistic regression analysis showed that age < 65 years, alcohol consumption, diabetes, coronary heart disease (CHD), cerebrovascular disease (CVD), chronic

kidney disease (CKD), body mass index (BMI) >/= 28 kg/m(2) and not achieving total cholesterol goals were independent predictors for achieving BP, LDL-C or combined BP and LDL-C goals. In summary, the BP and LDL-C goal achievement rates in Chinese dyslipidemia outpatients with hypertension were low, especially in endocrine departments. Combination therapies were not associated with improvement of the goal achievement rates. TRIAL REGISTRATION: Clinical trial registration number NCT01732952.

[37] *Wei H, Yang M, Yu K et al.* **Atorvastatin Protects Against Cerebral Aneurysmal Degenerative Pathology by Promoting Endothelial Progenitor Cells (EPC) Mobilization and Attenuating Vascular Deterioration in a Rat Model**. Medical science monitor : international medical journal of experimental and clinical research 2019; 25:928-936.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30710072
ABSTRACT
BACKGROUND Endothelial injury is the early pathological change of cerebral aneurysm (CA) formation. In addition to its lipid-lowering activity, atorvastatin (ATR) also reportedly promotes vascular repair via mobilizing endothelial progenitor cells (EPC). Here, we investigated the influence of ATR on vascular worsening after CA induction in rats. MATERIAL AND METHODS Adult male Sprague-Dawley rats were randomly assigned to 3 groups: a control (CTR) group, a CA group, and a CA+ATR treatment group. Circulating EPC level and hematological and lipid profiles were measured 3 months after CA induction. Verhoeff-Van Gieson staining and transmission electron microscopy were performed to assess pathological changes in the artery wall. RT-PCR was also performed to evaluate the expression of inflammation-related genes in the aneurysmal wall. RESULTS ATR significantly restored the impaired level of circulating EPC without changing hematological and lipid profiles 3 months after CA induction. ATR markedly inhibited endothelial injury, media thinning, and CA enlargement, accompanied by reduced vascular inflammation. CONCLUSIONS Our preliminary results demonstrate that the mobilization of EPC and improvement of endothelial function by ATR contribute to the prevention of cerebral aneurysm. Further studies are warranted to investigate the detailed mechanism.

[38] *Yang S, Gu YY, Jing F et al.* **The Effect of Statins on Levels of Dehydroepiandrosterone (DHEA) in Women with Polycystic Ovary Syndrome: A Systematic Review and Meta-Analysis**. Medical science monitor : international medical journal of experimental and clinical research 2019; 25:590-597.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30698163
ABSTRACT
BACKGROUND Currently, statins are used to treat polycystic ovary syndrome (PCOS). This systematic review and meta-analysis aimed to investigate the effect of statins on serum or plasma levels of dehydroepiandrosterone (DHEA) in women with PCOS. MATERIAL AND METHODS Databases that were searched included PubMed, Embase, and the Cochrane Library from their inception to August of 2018. Published randomized controlled trials (RCTs) were identified that evaluated the impact of statins on plasma DHEA levels in women with PCOS. The Cochrane risk of bias tool was used to assess the quality of the included RCTs. A random-effects model was used to analyze the pooled results.

RESULTS Meta-analysis was performed on data from ten published studies that included 735 patients and showed that statin treatment could significantly reduce plasma DHEA levels when compared with controls (SMD, -0.43; 95% CI, -0.81-0.06; p=0.02; I(2)=82%). Statins were significantly more effective than placebo in reducing the levels of DHEAs. Subgroup analysis based on statin type showed that atorvastatin significantly reduced DHEA levels (SMD, -0.63; 95% CI, -1.20 - -0.05; p=0.03; I(2)=38%) but simvastatin did not significantly reduce DHEA levels (SMD: -0.14; 95% CI, -0.49-0.28; p=0.43; I(2)=77%). Subgroup analysis based on duration of treatment showed no significant difference between 12 weeks of statin treatment (SMD, -0.61; 95% CI, -1.23-0.02; p=0.06; I(2)=85%) and 24 weeks (SMD, -0.34; 95% CI -0.95-0.28; p=0.29; I(2)=83%). CONCLUSIONS Meta-analysis showed that statins significantly reduced the levels of DHEA when compared with placebo in patients with PCOS.

[39] *Christensen JJ, Bakke SS, Ulven SM et al.* **Serum Omega 6 Fatty Acids and Immunology-Related Gene Expression in Peripheral Blood Mononuclear Cells: A Cross-Sectional Analysis in Healthy Children**. Molecular nutrition & food research 2019:e1800990.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30702198
ABSTRACT
SCOPE: Some studies suggest that a high dietary intake of omega 6 fatty acids is pro-inflammatory. However, whether omega 6 fatty acids actually cause pathogenic inflammation in humans is debated. Therefore, we investigated the associations between expression of immunology-related genes in peripheral blood mononuclear cells (PBMCs) and serum total omega 6 PUFA status. METHODS AND RESULTS: We measured serum fatty acid profile and expression of 460 immunology-related genes in PBMCs from 58 healthy children (6-13 years), and examined the expression differences between children with high or low total omega 6 PUFA status (upper versus lower tertile). Taken together, both univariate analyses and integrated omics analyses support that while high omega 6 PUFA level associated with higher expressing of genes related to innate immune responses, it also associated with lower expression of several genes related to adaptive immune responses. CONCLUSION: Omega 6 PUFA status associated both positively and negatively with expression of specific immunology-related genes in PBMCs in healthy children. Our results may suggest a nuanced role for omega 6 fatty acids in the interphase of lipids and inflammation, which warrants further examination in gene-environment studies and randomized controlled trials.

[40] *Andrews GP, Li S, Almajaan A et al.* **Fixed Dose Combination Formulations: Multi-Layered Platforms Designed for the Management of Cardiovascular Disease**. Molecular pharmaceutics 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30702301
ABSTRACT
Hyperlipidaemia is considered as one of the main risk factors associated with cardiovascular diseases (CVDs). Among different lipid-lowering agents used to manage hyperlipidaemia, statins are highly prescribed for management of hyperlipidaemia with simvastatin being one of the most common. Simvastatin is susceptible to extensive metabolism by CYP450 3A4 and 3A5

which are expressed both in the liver and the gastrointestinal tract. Nevertheless, the localization of these enzymes is site dependent with lower concentration at the distal/proximal regions of the small intestine/colon. In addition to statins, medications such as antihypertensive and anti-coagulants are introduced as adjuvants, for the treatment of cardiovascular disease. The aim of this study was to design a bi-layer delivery system capable of delivering bi-phasic release of Simvastatin and Aspirin, within a fixed dose combination. A delayed release platform based on a combination of anionic polymers prepared using hot melt extrusion was developed to delay the release of simvastatin. An optimized formulation was tested for dissolution performance clearly demonstrated an ability to delay the release of Simvastatin. In addition, an immediate release layer based on Kollidon VA64 was successfully developed to deliver Aspirin. Both formulations were then manufactured as a bi-layer drug delivery system (tablets and co-extrudates) and the release performance examined. Based on the obtained results, these formulations may be used as a platform for the delivery wide range of medications in a bi-phasic manner.

[41] *Chang HY, Wu JR, Gao WY et al.* **The Cholesterol-Modulating Effect of Methanol Extract of Pigeon Pea (Cajanus cajan (L.) Millsp.) Leaves on Regulating LDLR and PCSK9 Expression in HepG2 Cells**. Molecules (Basel, Switzerland) 2019; 24.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30704067
ABSTRACT
Pigeon pea (Cajanus cajan (L.) Millsp.) is a legume crop consumed as an indigenous vegetable in the human diet and a traditional medicinal plant with therapeutic properties. The current study highlights the cholesterol-modulating effect and underlying mechanisms of the methanol extract of Cajanus cajan L. leaves (MECC) in HepG2 cells. We found that MECC increased the LDLR expression, the cell-surface LDLR levels and the LDL uptake activity in HepG2 cells. We further demonstrated that MECC suppressed the proprotein convertase subtilisin/kexin type 9 (PCSK9) mRNA and protein expression, but not affected the expression of other cholesterol or lipid metabolism-related genes including inducible degrader of LDLR (IDOL), HMG-CoA reductase (HMGCR), fatty acid synthase (FASN), acetyl-CoA carboxylase (ACC1), and liver X receptor-alpha (LXR-alpha) in HepG2 cells. Furthermore, we demonstrated that MECC down-regulated the PCSK9 gene expression through reducing the amount of nuclear hepatocyte nuclear factor-1alpha (HNF-1alpha), a major transcriptional regulator for activation of PCSK9 promoter, but not that of nuclear sterol-responsive element binding protein-2 (SREBP-2) in HepG2 cells. Finally, we identified the cajaninstilbene acid, a main bioactive stilbene component in MECC, which significantly modulated the LDLR and PCSK9 expression in HepG2 cells. Our current data suggest that the cajaninstilbene acid may contribute to the hypocholesterolemic activity of Cajanus cajan L. leaves. Our findings support that the extract of Cajanus cajan L. leaves may serve as a cholesterol-lowering agent.

[42] *Perucha E, Melchiotti R, Bibby JA et al.* **The cholesterol biosynthesis pathway regulates IL-10 expression in human Th1 cells**. Nature communications 2019; 10:498.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30700717
ABSTRACT

The mechanisms controlling CD4(+) T cell switching from an effector to an anti-inflammatory (IL-10(+)) phenotype play an important role in the persistence of chronic inflammatory diseases. Here, we identify the cholesterol biosynthesis pathway as a key regulator of this process. Pathway analysis of cultured cytokine-producing human T cells reveals a significant association between IL-10 and cholesterol metabolism gene expression. Inhibition of the cholesterol biosynthesis pathway with atorvastatin or 25-hydroxycholesterol during switching from IFNgamma(+) to IL-10(+) shows a specific block in immune resolution, defined as a significant decrease in IL-10 expression. Mechanistically, the master transcriptional regulator of IL10 in T cells, c-Maf, is significantly decreased by physiological levels of 25-hydroxycholesterol. Strikingly, progression to rheumatoid arthritis is associated with altered expression of cholesterol biosynthesis genes in synovial biopsies of predisposed individuals. Our data reveal a link between sterol metabolism and the regulation of the anti-inflammatory response in human CD4(+) T cells.

[43] *Yin C, Ackermann S, Ma Z et al.* **ApoE attenuates unresolvable inflammation by complex formation with activated C1q**. Nat Med 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30692699
ABSTRACT
Apolipoprotein-E (ApoE) has been implicated in Alzheimer's disease, atherosclerosis, and other unresolvable inflammatory conditions but a common mechanism of action remains elusive. We found in ApoE-deficient mice that oxidized lipids activated the classical complement cascade (CCC), resulting in leukocyte infiltration of the choroid plexus (ChP). All human ApoE isoforms attenuated CCC activity via high-affinity binding to the activated CCC-initiating C1q protein (KD~140-580 pM) in vitro, and C1q-ApoE complexes emerged as markers for ongoing complement activity of diseased ChPs, Abeta plaques, and atherosclerosis in vivo. C1q-ApoE complexes in human ChPs, Abeta plaques, and arteries correlated with cognitive decline and atherosclerosis, respectively. Treatment with small interfering RNA (siRNA) against C5, which is formed by all complement pathways, attenuated murine ChP inflammation, Abeta-associated microglia accumulation, and atherosclerosis. Thus, ApoE is a direct checkpoint inhibitor of unresolvable inflammation, and reducing C5 attenuates disease burden.

[44] *Jazayeri-Tehrani SA, Rezayat SM, Mansouri S et al.* **Nano-curcumin improves glucose indices, lipids, inflammation, and Nesfatin in overweight and obese patients with non-alcoholic fatty liver disease (NAFLD): a double-blind randomized placebo-controlled clinical trial**. Nutrition & metabolism 2019; 16:8.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30705687
ABSTRACT
Background: Since lifestyle changes are main therapies for non-alcoholic fatty liver disease (NAFLD), changing dietary components (nutritional or bioactive) may play a parallel important role. Few studies have assessed the effects of curcumin on NAFLD (mainly antioxidant and anti-inflammatory effects). We aimed to determine the effects of nano-curcumin (NC) on overweight/obese NAFLD patients by assessing glucose, lipids, inflammation, insulin resistance, and liver function indices, especially through nesfatin. Methods: This double-blind, randomized, placebo-controlled clinical trial was conducted in the Oil Company Central Hospital, Tehran. 84

overweight/obese patients with NAFLD diagnosed using ultrasonography were recruited according to the eligibility criteria (age 25-50 yrs., body mass index [BMI] 25-35 kg/m(2)). The patients were randomly divided into two equal NC (n = 42) and placebo (n = 42) groups. Interventions were two 40 mg capsules/day after meals for 3 months. Lifestyle changes were advised. A general questionnaire, a 24-h food recall (at the beginning, middle and end), and the short-form international physical activity questionnaire (at the beginning and end) were completed. Also, blood pressure, fatty liver degree, anthropometrics, fasting blood sugar (FBS) and insulin (FBI), glycated hemoglobin (HbA1c), homeostasis model assessment-insulin resistance (HOMA-IR), quantitative insulin sensitivity check index (QUICKI), total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-c), high-density lipoprotein cholesterol (HDL-c), tumor necrosis factor-alpha (TNF-alpha), high sensitive c-reactive protein (hs-CRP), interleukin-6 (IL-6), liver transaminases, and nesfatin were determined at the beginning and end. Results: NC compared with placebo significantly increased HDL, QUICKI, and nesfatin and decreased fatty liver degree, liver transaminases, waist circumference (WC), FBS, FBI, HbA1c, TG, TC, LDL, HOMA-IR, TNF-alpha, hs-CRP, and IL-6 ($P < 0.05$). The mean changes in weight, BMI, body composition (BC), and blood pressure were not significant ($P > 0.05$). After adjustment for confounders, the changes were similar to the unadjusted model. Conclusion: NC supplementation in overweight/obese NAFLD patients improved glucose indices, lipids, inflammation, WC, nesfatin, liver transaminases, and fatty liver degree. Accordingly, the proposed mechanism for ameliorating NAFLD with NC was approved by the increased serum nesfatin and likely consequent improvements in inflammation, lipids, and glucose profile. Further trials of nano-curcumin's effects are suggested. Trial registration: Iranian Registry of Clinical Trials, IRCT2016071915536N3. Registered 2016-08-02.

[45] *Johnson M, McElhenney WH, Egnin M*. **Influence of Green Leafy Vegetables in Diets with an Elevated omega-6:omega-3 Fatty Acid Ratio on Rat Blood Pressure, Plasma Lipids, Antioxidant Status and Markers of Inflammation**. Nutrients 2019; 11.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30709032

ABSTRACT

The typical Western dietary pattern has an elevated omega-6:omega-3 fatty acid ratio (FAR), which may exacerbate the risk of chronic disease. Conversely, the consumption of diets containing green leafy vegetables (GLVs) have been demonstrated to attenuate disease risk. This study investigated the effects of collard greens (CG), purslane (PL) and orange flesh sweetpotato greens (SPG) on measures of disease risk in rats fed diets with a 25:1 omega-6:omega-3 FAR. Male spontaneously hypertensive rats (SHRs) were randomly assigned to four dietary groups (n = 10/group) with a 25:1 omega-6:omega-3 FAR. Experimental diets contained 4% (dried weight) CG, PL or SPG. Dietary intake, body weight, blood pressure, plasma adiponectin, high sensitivity C-reactive protein (hsCRP), oxygen radical absorbance capacity and lipid profile were determined using standardized procedures. Following a 6-week consumption period, systolic blood pressure, plasma adiponectin, total and low-density lipoprotein (LDL) cholesterol decreased following the consumption of diets containing GLVs. While hsCRP increased in SHRs fed diets containing CG and PL, plasma antioxidant capacity was significantly reduced ($p < 0.05$) with the consumption of diets containing the GLVs. These findings suggest

that CG, PL and SPG have the potential to decrease risks for cardiovascular disease (CVD) associated with the consumption of diets with an elevated omega-6:omega-3 FAR.

[46] *Langlois PL, D'Aragon F, Hardy G, Manzanares W*. **Omega-3 polyunsaturated fatty acids in critically ill patients with acute respiratory distress syndrome: A systematic review and meta-analysis**. Nutrition 2018; 61:84-92.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30703574
ABSTRACT
OBJECTIVE: Acute respiratory distress syndrome (ARDS) is characterized by an acute inflammatory response in the lung parenchyma leading to severe hypoxemia. Because of its anti-inflammatory and immunomodulatory properties, omega-3 polyunsaturated fatty acids (omega-3 PUFA) have been administered to ARDS patients, mostly by the enteral route, as immune-enhancing diets with eicosapentaenoic acid, gamma-linolenic acid, and antioxidants. However, clinical benefits of omega-3 PUFAs in ARDS patients remain unclear because clinical trials have found conflicting results. Considering the most recent randomized controlled trials (RCTs) and recent change in administration strategies, the aim of this updated systematic review and meta-analysis was to evaluate clinical benefits of omega-3 PUFA administration on gas exchange and clinical outcomes in ARDS patients. METHODS: We searched for RCTs conducted in intensive care unit (ICU) patients with ARDS comparing the administration of omega-3 PUFAs to placebo. The outcomes assessed were PaO2-to-FiO2 ratio evaluated early (3-4 d) and later (7-8 d), mortality, ICU and hospital length of stay (LOS), length of mechanical ventilation (MV), and infectious complications. Two independent reviewers assessed eligibility, risk of bias, and abstracted data. Data were pooled using a random effect model to estimate the relative risk or weighted mean difference (WMD). RESULTS: Twelve RCTs (n=1280 patients) met our inclusion criteria. Omega-3 PUFAs administration was associated with a significant improvement in early PaO2-to-FiO2 ratio (WMD=49.33; 95% confidence interval [CI] 20.88-77.78; P=0.0007; I(2)=69%), which persisted at days 7 to 8 (WMD=27.87; 95% CI 0.75-54.99; P=0.04; I(2)=57%). There was a trend in those receiving omega-3 PUFA toward reduced ICU LOS (P = 0.08) and duration of MV (P = 0.06), whereas mortality, hospital LOS, and infectious complications remained unchanged. Continuous enteral infusion was associated with reduced mortality (P = 0.02), whereas analysis restricted to enteral administration either with or without bolus found improved early PaO2 and FiO2 (P=0.001) and MV duration (P = 0.03). Trials at higher risk of bias had a significant reduction in mortality (P=0.04), and improvement in late PaO2-to-FiO2 ratio (P = 0.003). CONCLUSIONS: In critically ill patients with ARDS, omega-3 PUFAs in enteral immunomodulatory diets may be associated with an improvement in early and late PaO2-to-FiO2 ratio, and statistical trends exist for an improved ICU LOS and MV duration. Considering these results, administering omega-3 PUFAs appears a reasonable strategy in ARDS.

[47] *Elamin AFM, Grafton-Clarke C, Wen Chen K et al.* **Potential use of PCSK9 inhibitors as a secondary preventative measure for cardiovascular disease following acute coronary syndrome: a UK real-world study**. Postgraduate medical journal 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30709868
ABSTRACT

BACKGROUND: Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are a major development in the prevention of cardiovascular disease (CVD) and is one of the most significant discoveries since the development of statin therapy. Administration of two human monoclonal antibodies to PCSK9 (alirocumab and evolocumab) can significantly reduce low-density lipoprotein cholesterol (LDL-c) concentrations, thus improving lipid management. Accordingly, guidelines on the specific indications for alirocumab and evolocumab usage have been released. This multicentre study aimed to estimate the proportion of patients treated for an acute myocardial infarction (MI) who could be considered for PCSK9 inhibitors under the current National Institute for Health and Care Excellence (NICE) lipid targets criteria. METHODS: The records of 596 patients in two large hospitals in Liverpool, UK were analysed. Information was collected on lipid profiles during and after admission, lipid-lowering therapy and previous CVD. RESULTS: At least 2.2% of patients were eligible for PCSK9 inhibitors post-MI under the current NICE guidance. Additionally, 29% of patients failed to achieve LDL-c concentrations <2.0 mmol/L despite maximum statin therapy and failed to meet eligibility for PCSK9 inhibitors as per the NICE criteria. This cohort represents a group of patients 'in limbo', in which statin therapy alone is not sufficient to reduce LDL-c. CONCLUSIONS: PCSK9 inhibitors are expensive and so their use must be highly selective. At present, in a real-world setting with ezetimibe underprescribing, ~2% of patients are eligible and a further 30% are deprived of benefit and improved outcomes by lack of optimisation and/or potential use of PCSK9 inhibitors.

[48] *Wang Y, Zhang HW, Guo YL et al.* **Free fatty acids as a marker for predicting periprocedural myocardial injury after coronary intervention**. Postgraduate medical journal 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30700582
ABSTRACT
BACKGROUND: Previous studies have revealed that plasma levels of free fatty acids (FFAs) are related to cardiovascular risk. However, whether FFAs could predict periprocedural myocardial injury (PMI) following percutaneous coronary intervention (PCI) in patients with stable coronary artery disease (CAD) remains unclear. PURPOSE: This study aimed to investigate the relationship of FFAs to PMI in untreated patients with CAD who underwent PCI. METHODS: A total of 374 consecutive patients with CAD without lipid-lowering treatment on admission and with normal preprocedural cardiac troponin I (cTnI) levels who underwent PCI were prospectively enrolled. The baseline characteristics were collected and PMI was evaluated by cTnI analysis within 24 hours. The relation of preprocedural FFA levels to peak cTnI values after PCI was examined. RESULTS: Preprocedural FFAs were positively correlated with peak cTnI values after PCI in both simple regression model (beta=0.119, p=0.021) and multiple regression model (beta=0.198, p=0.001). Patients with higher FFA levels had higher postprocedural cTnI levels compared with those with normal FFA levels (0.27+/-0.68 ng/mL vs 0.66+/-0.31 ng/mL, p=0.014). In the multivariable model, preprocedural FFA levels were associated with an increased risk of postprocedural cTnI elevation above 1x upper limit of normal (ULN, OR: 1.185, 95% CI 0.997 to 1.223, p=0.019) up to 10x ULN (OR: 1.132, 95% CI 1.005 to 1.192, p=0.003) . CONCLUSIONS: The present study first suggested that elevated FFA levels were associated with an increased risk of PMI in untreated patients with CAD. Further study with large sample size may be needed to confirm our findings.

[49] *Sahebekhtiari N, Saraswat M, Joenvaara S et al.* **Plasma Proteomics Analysis Reveals Dysregulation of Complement Proteins and Inflammation in Acquired Obesity - A Study on Rare Bmi-Discordant Monozygotic Twin Pairs**. Proteomics. Clinical applications 2019:e1800173.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30688043
ABSTRACT
PURPOSE: The purpose of this study was to elucidate the effect of excess body weight and liver fat on the plasma proteome without interference from genetic variation. EXPERIMENTAL DESIGN: The effect of excess body weight was assessed in young, healthy monozygotic twins from pairs discordant for body mass index (intrapair difference (Delta) in BMI > 3 kg/m2, n = 26) with untargeted LC-MS proteomics quantification. The effect of liver fat was interrogated via subgroup analysis of the BMI-discordant twin cohort: liver fat discordant pairs (Deltaliver fat > 2%, n = 12) and liver fat concordant pairs (Deltaliver fat < 2%, n = 14), measured by magnetic resonance spectroscopy. RESULTS: 75 proteins were differentially expressed within the BMI-discordant pairs, with significant enrichment for complement and inflammatory response pathways in the heavier co-twins. The complement dysregulation was found in obesity in both the liver fat subgroups. The complement and inflammatory proteins were significantly associated with adiposity measures, insulin resistance and impaired lipids. CONCLUSIONS AND CLINICAL RELEVANCE: The early pathophysiological mechanisms in obesity are incompletely understood. We showed that aberrant complement regulation in plasma is present in very early stages of clinically healthy obese persons, independently of liver fat and in the absence of genetic variation that typically confounds human studies.

[50] *Morch RH, Dieset I, Faerden A et al.* **Inflammatory markers are altered in severe mental disorders independent of comorbid cardiometabolic disease risk factors - inflammatory markers and immune activation in severe mental disorders**. Psychological medicine 2019:1-9.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30688187
ABSTRACT
BACKGROUND: Inflammation and immune activation have been implicated in the pathogenesis of severe mental disorders and cardiovascular disease (CVD). Despite high level of comorbidity, many studies of the immune system in severe mental disorders have not systematically taken cardiometabolic risk factors into account. METHODS: We investigated if inflammatory markers were increased in schizophrenia (SCZ) and affective (AFF) disorders independently of comorbid CVD risk factors. Cardiometabolic risk factors (blood lipids, body mass index and glucose) and CVD-related inflammatory markers CXCL16, soluble interleukin-2 receptor (sIL-2R), soluble CD14 (sCD14), macrophage inhibitory factor and activated leukocyte cell adhesion molecule (ALCAM) were measured in n = 992 patients (SCZ, AFF), and n = 647 healthy controls. We analyzed the inflammatory markers before and after controlling for comorbid cardiometabolic risk factors, and tested for association with psychotropic medication and symptom levels. RESULTS: CXCL16 (p = 0.03) and sIL-2R (p = 7.8 x 10-5) were higher, while sCD14 (p = 0.05) were lower in patients compared to controls after controlling for confounders, with significant differences in SCZ for CXCL16 (p = 0.04) and sIL-2R (p = 1.1 x 10-5). After adjustment for

cardiometabolic risk factors higher levels of sIL-2R (p = 0.001) and lower sCD14 (p = 0.002) remained, also in SCZ (sIL-2R, p = 3.0 x 10-4 and sCD14, p = 0.01). The adjustment revealed lower ALCAM levels (p = 0.03) in patients. We found no significant associations with psychotropic medication or symptom levels. CONCLUSION: The results indicate that inflammation, in particular enhanced T cell activation and impaired monocyte activation, are associated with severe mental disorders independent of comorbid cardiometabolic risk factors. This suggests a role of novel pathophysiological mechanisms in severe mental disorders, particularly SCZ.

[51] *Kimura H*. **[Renal Dyslipidemia]**. Rinsho Byori 2016; 64:527-532.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30695362
ABSTRACT
Renal diseases have been recognized as a major cause of secondary dyslipidemia since the late 1950's. Two main pathological conditions of renal diseases, impaired renal function and severe proteinuria (nephrotic syndrome), are individually or conjointly associated with altered lipid metabolism depending on the primary diseases. An impaired renal function causes reductions in lipoprotein and hepatic TG lipase activity, the VLDL recep- tor abundance, and ApoC-II to apoC-III ratio, as well as in ApoA-I and LCAT activities. These alterations result in reduced VLDL clearance and the disturbance of HDL synthesis and maturation, leading to uremic dyslipidemia: increased levels of TG, IDL-C, and small-dense LDL-C and decreased levels of HDL-C. Lipid disorders in nephrotic syndrome (NS) are characterized by increased levels of LDL-C and/or TG. NS-induced hypoalbuminemia enhances the synthesis of cholesterol, cholesterol ester, and ApoB, leading to the increased production of LDL and VLDL. Recently, two intriguing molecules were newly identified as inhibitors of lipoprotein clearance. Pro-protein Convertase Subtilisin/Kexin type 9 (PCSK9) is upregulated in NS, and decreases LDL clearance via prompting degradation of the LDL receptor, while angiopoietin-like 4 (Angptl4) is also induced in NS and restricts VLDL clearance via inhibiting lipoprotein lipase. NS impairs HDL maturation from HDL3 to HDL2 due to a reduction of LCAT, with HDL-C levels preserved. Finally, considering that diabetic nephropathy is representative of progressive renal disease and that gluco- corticoids are an anchor drug for the treatment of NS, diabetes- or drug-associated dyslipidemia is occasional- ly superimposed on the original renal dyslipidemia. [Review].

[52] *Gaisenok OV, Kurnosov PA, Leonov AS, Zateeyshikov DA*. **Screening of familial hypercholesterolemia among patients in age under 40 years old exposed by duplex scanning of carotid arteries, by the local registry data**. Terapevticheskii arkhiv 2018; 90:37-41.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30701733
ABSTRACT
AIM: To identify patients with probable FH among Duplex-2013 registry patients under the age of 40 years, to analyze their lipid spectrum and duplex carotid artery data, to evaluate the changes of their lipid spectrum parameters. MATERIALS AND METHODS: The Duplex-2013 registry database was used for this study (n=2550). Patients under the age of 40 years were selected for follow-up analysis (n=192). RESULTS: 20 of them were selected on the basis of Simon Broome criteria as patients with possible FH. The FH group (n=20) and the control group (n=172) had significant differences in age (35.1 +/- 4.01 vs. 32.62 +/- 5.29, p=0.044), male

gender (18 of 20 (90%) vs 92 of 172 (53%), p=0.003), TC (7.64 +/- 0.63 vs 5.34 +/- 0.91, p=0.0001) and LDL-C cholesterol (5.45 +/- 0.62 vs 3.28 +/- 0.78, p=0.00001). When comparing the groups by the combined criterion of atherosclerosis (IMT > 1.0 mm and / or atherosclerotic plaque in the carotid artery >20%), it was noted that signs of carotid atherosclerosis were more often recorded in the FH group compared with the control group (40% vs 26%). Repeated laboratory studies of TC and LDL-C in the FH group after 2.5 years showed their significant dynamics (7.64 +/- 0.63 vs 6.03 +/- 1.04, p=0.007, 5.45 +/- 0.63 vs 3.84 +/- 1.24, p=0.035). CONCLUSION: The frequency of detection of FH in the cohort study was 1:10 (11% of all patients). Thus, patients referred for duplex scanning of carotid arteries can be a potential target for screening for FH.

[53] *Lankin VZ, Tikhaze AK, Viigimaa M, Chazova Icapital Ie C*. **PCSK9 Inhibitor causes a decrease in the level of oxidatively modified low-density lipoproteins in patients with coronary artery diseases**. Terapevticheskii arkhiv 2018; 90:27-30.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30701731
ABSTRACT
AIM: We study the dynamics of oxidatively modified low-density lipoprotein (ox-LDL) content in blood plasma, as well as changes in the activity of key antioxidant enzymes such as Se-containing glutathione peroxidase (GSH-Px) Cu,Zn-superoxide dismutase (SOD) and catalase in erythrocytes of patients with coronary artery disease during treatment with PCSK9 inhibitor (ewolocumab). MATERIALS AND METHODS: The study included 9 men (59 +/- 10 years) with coronary artery disease with atherosclerotic lesion at least one main coronary artery according to coronary angiography. Patients took standard therapy before taking the study, everyone took the maximum tolerated dose of statins. Since the target cholesterol levels of low-density lipoprotein cholesterol (LDL-C) were not achieved during the statin therapy, patients were prescribed lipid-lowering therapy with the inclusion of the inhibitor PCSK9-emocoucumab from Amgen 420 mg once a month. The content of lipid metabolism indices was determined by standard biochemical methods. The level of ox-LDL in the blood plasma was determined by the immunochemical method. The activity of antioxidant enzymes was determined in blood erythrocytes using biochemical techniques. RESULTS: Cholesterol-lowering drug of the new type - inhibitor protein convertase subtilisin/kexin type 9 (PCSK9) evolocumab (Amgen) not only effectively lowers the level of cholesterol in low density lipoprotein (LDL), but also significantly reduces the content of oxdatively modified LDL in blood plasma. Unlike statins, the inhibitor of PCSK9 does not cause a decrease in the activity of antioxidant enzymes of the blood. CONCLUSION: PCSK9 inhibitor has no effect on the parameters of oxidative stress.

[54] *Elnaem MH, Mohamed MHN, Huri HZ, Shah ASM*. **Effectiveness and prescription pattern of lipid-lowering therapy and its associated factors among patients with type 2 diabetes mellitus in Malaysian primary care settings**. Therapeutics and clinical risk management 2019; 15:137-145.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30705590
ABSTRACT
Background: Cardiovascular diseases (CVDs) are the main complication leading to morbidity and mortality among patients with type 2 diabetes mellitus (T2DM). There is a large amount of

evidence to support the use of lipid-lowering therapy (LLT) for the prevention of CVD. This study aimed to assess the effectiveness and prescription quality of LLT among T2DM patients and to identify its associated factors. Methods: A multicenter cross-sectional study included 816 T2DM patients from four different primary care centers in Pahang, Malaysia. We involved LLT-eligible T2DM patients as per the national clinical practice guidelines (CPG). The assessment of therapy effectiveness focused on the attainment of target lipid measures stated in the CPG. Evaluation of the prescription quality was classified into appropriate, potentially inappropriate, and inappropriate, based on the compliance with guidelines and existence of potential safety concerns. Binomial logistic regression was employed to identify the predictors of LLT effectiveness and prescription quality. Results: The overall percentage of T2DM patients receiving statin therapy was 87.6% (715/816). Statin therapy was appropriately prescribed in 71.5% of the cases. About 17.5% of the LLT prescriptions have at least one significant drug interaction with co-prescribed medications. The achievement of the primary target of low-density lipoprotein cholesterol (LDL-C) levels was observed in only 37% of T2DM patients. The LLT indication and appropriateness of prescription were significantly associated with the attainment of LDL-C treatment goals. Primary prevention, Malay race, and hypertension were identified as predictors for appropriate prescribing of LLT among T2DM subjects. Conclusion: There is a need to enhance the quality of LLT prescribing in the primary care setting to cover all eligible high-risk patients and ensure patient safety. Strategies to improve the achievement of LDL-C goals among patients with T2DM, such as investigating the potential role of the combination therapy and high-intensity statin therapy, are required.

[55] *Denzinger V, Busygina K, Jamasbi J et al.* **Optimizing Platelet GPVI Inhibition versus Haemostatic Impairment by the Btk Inhibitors Ibrutinib, Acalabrutinib, ONO/GS-4059, BGB-3111 and Evobrutinib**. Thrombosis and haemostasis 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30685871
ABSTRACT
Ibrutinib and acalabrutinib are approved for B cell malignancies and novel Bruton's tyrosine kinase (Btk) inhibitors undergo clinical testing also in B cell-driven autoimmune disorders. Btk in platelets mediates platelet activation via glycoprotein (GP) VI, which is crucial for atherosclerotic plaque-induced platelet thrombus formation. This can be selectively inhibited by Btk inhibitors. Since patients on second-generation Btk inhibitors apparently show less bleeding than patients on ibrutinib, we compared the effects of ibrutinib and four novel irreversible Btk inhibitors on GPVI-dependent platelet aggregation in blood and in vitro bleeding time. Low concentrations of collagen which induced the same low degree of GPVI-mediated platelet aggregation as atherosclerotic plaque material were applied. IC50 values for collagen (0.2-0.5 microg/mL)-induced platelet aggregation after 15-minute pre-incubation were: ibrutinib 0.12 microM, BGB-3111 0.51 microM, acalabrutinib 1.21 microM, ONO/GS-4059 1.20 microM and evobrutinib 5.84 microM. Peak venous plasma concentrations of ibrutinib (0.5 microM), acalabrutinib (2 microM) and ONO/GS-4059 (2 microM) measured after anti-proliferative dosage inhibited collagen-induced platelet aggregation, but did not increase PFA-200 closure time on collagen/epinephrine. Closure times were moderately increased by 2- to 2.5-fold higher concentrations of these inhibitors, but not by BGB-3111 (1 microM) and evobrutinib (10 microM). Prolonging platelet drug exposure to 60 minutes lowered IC50 values

of any Btk inhibitor for GPVI-mediated aggregation by several fold, and 5- to 10-fold below anti-proliferative therapeutic drug plasma levels. In conclusion, low blood concentrations of ibrutinib and the novel Btk inhibitors suffice for GPVI selective platelet inhibition relevant for atherothrombosis but do not impair primary haemostasis.

[56] *Wildes TJ, Grippin A, Fasanya H et al.* **Effect of atorvastatin on humoral immune response to 23-valent pneumococcal polysaccharide vaccination in healthy volunteers: The StatVax randomized clinical trial**. Vaccine 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30686636
ABSTRACT
BACKGROUND: The immunomodulatory effects of statins on vaccine response remain uncertain. Therefore, the objective of this study was to determine if atorvastatin enhances pneumococcal-specific antibody titer following 23-valent pneumococcal polysaccharide vaccination. METHODS: Double-blind, placebo-controlled, single-center randomized clinical trial entitled StatVax. Subjects were enrolled between June and July 2014 and followed up through September 2014. 33 healthy volunteers signed informed consent after volunteer sampling. 11 participants were excluded; 22 healthy volunteers without prior pneumococcal vaccination were enrolled and completed the study. Participants were randomized to receive a 28-day course of 40mg atorvastatin (n=12) or matching lactose placebo (n=10). On day 7 of treatment, Pneumovax 23 was administered intramuscularly. The primary outcome was fold change in total pneumococcal-specific antibody titer determined by a ratio of post-vaccination titer over baseline titer. Secondary outcomes included serotype-specific pneumococcal antibody titer, seroconversion, complete blood counts (CBC), erythrocyte sedimentation rate (ESR), and serum cytokine analysis. RESULTS: Of the 22 randomized patients (mean age, 23.86; SD, 4.121; 11 women [50%]), 22 completed the trial. Total anti-pneumococcal antibody titer in the atorvastatin group went from a baseline mean of 32.58 (SD, 15.96) to 147.7 (SD, 71.52) mug/mL at 21days post-vaccination while titer in the placebo group went from a mean of 30.81 (SD, 13.04) to 104.4 (SD, 45) mug/mL. When comparing fold change between treatment groups, there was a significant increase in fold change of total anti-pneumococcal antibody titer in the atorvastatin group compared to the placebo group (2-way ANOVA, p=.0177). CONCLUSIONS: Atorvastatin enhances antigen-specific primary humoral immune response to a T cell-independent pneumonia vaccination. Pending confirmation by larger cohort studies of target populations, peri-vaccination conventional doses of statins can become a novel adjuvant for poorly-immunogenic polysaccharide-based vaccines. TRIAL REGISTRATION: clinicaltrials.gov Identifier: NCT02097589.

[57] *Blaha V*. **Lipoprotein(a) - the cardiovascular risk factor: significance and therapeutic possibilities**. Vnitr Lek 2019; 64:1160-1168.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30704252
ABSTRACT
About 20 % of the population has raised Lp(a) concentrations and evidence suggests that high levels of Lp(a) are an independent cardiovascular risk factor. Both the European Society of Cardiology and the European Atherosclerosis Society recommend measuring Lp(a) values in intermediate to high-risk patients for risk stratification, as well as in patients already under

statin treatment and with recurrent clinical events as a residual risk factor that calls for lipid-lowering therapy intensification. Strategies used to lower Lp(a) concentrations have either been partially disappointing in the past or lack cardiovascular outcome data. Therefore, Lp(a) has often been considered as a nonmodifiable cardiovascular risk factor. New and consistent data retrieved from the PCSK9 inhibitor trials now suggest that Lp(a) can be decreased effectively by roughly 30 %, while emerging data from apo(a) antisense therapy trials suggest that selective and potent Lp(a) reduction is a feasible treatment approach in the future. The impact of such decreases on the occurrence of cardiovascular outcomes, independent from LDL-C, could, if established, herald Lp(a) in the treatment of atherosclerosis. Key words: alirocumab - atherosclerosis - cardiovascular disease - evolocumab - hypercholesterolaemia - lipoprotein(a) - lipoprotein apheresis.

[58] *Ceska R*. **Comments on the most important and recent studies involving PCSK9i**. Vnitr Lek 2019; 64:1137-1141.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30704247
ABSTRACT
The paper provides a brief overview of the key studies focused on PCSK9 inhibitors. It mainly examines positive results of the FOURIER studies on evolocumab, the SPIRE study on boccocizumab and the ODYSSEY Outcomes study on alirocumab. All these studies have not only shown a significant decrease in LDL-cholesterol levels, but also the reduction of cardiovascular events just correlating with these levels. The treatment leading to a dramatic drop in LDL-cholesterol levels was safe and well tolerated by patients. All the studies provided with comments demonstrate a positive impact of biological treatment of hypercholesterolemia on cardiovascular disease and confirm validity of the hypothesis saying “the lower the better”, at least for LDL-cholesterol. In conclusion, Professor Braunwalds hypothesis is mentioned saying that this treatment might eventually lead to as much as eradication of atherothrombotic cardiovascular diseases. Key words: alirocumab - bococizumab - evolocumab - FOURIER - cardiovascular disease - LDL-cholesterol - ODYSSEY Outcomes - SPIRE.

[59] *Ceska R, Taborsky M, Vrablik M*. **Consensus statement of professional associations on prescribing of PCSK9-inhibitors**. Vnitr Lek 2019; 64:1131-1136.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30704246
ABSTRACT
A new class of drugs known as PCSK9 inhibitors (PCSK9i) provide biological treatment for hypercholesterolemia. These drugs are administered using a subcutaneous injection once in two or four weeks. PCSK9i are not a replacement of the existing hypolipidemics, they just expand the therapeutic spectrum for the critically ill and those who cannot use the standard therapy and do not reach satisfactory target values. There are essentially two indications: (1) hypercholesterolemie and mixed dyslipidemia and (2) secondary prevention of cardiovascular diseases (CVD). Statin intolerance is not the only indication for treatment. However as its presence sometimes plays an essential role as to choosing the treatment, it will be also discussed in the paragraph on reimbursement conditions. Reimbursement conditions (very simplified): the treatment will be provided at selected centres. A list of the centres is included in an annexe to this article. You will find it also on www.interna-cz.eu, on www.kardio-cz.cz and

www.athero.cz. The indicative concentration of LDL-cholesterol (LDL-C) from which on PCSK9i can be prescribed as covered from the public health insurance, is the following: (1) familial hypercholesterolemia 4.0 mmol/l, (2) for secondary prevention CVD 3.0 mmol/l - Please note: the presented LDL-C level is one reached under maximum (tolerated) high intensity hypolipidemic therapy. High intensity hypolipidemic therapy is defined as atorvastatin 40-80 mg or rosuvastatin 20-40 mg + ezetimibe. In the case of demonstrated intolerance of both the mentioned statins the patient has to be treated with a maximum tolerated dose of statins, in combination with another hypolipidemic drug (ezetimibe). Statin intolerance is defined as intolerance of at least two successive statins, which results in their discontinuation. Statin intolerance alone is not the indication for PCSK9i treatment! The payment criteria must always be complied with. A medical officer can of course be asked to approve such treatment in exceptional cases. Key words: alirocumab - PCSK9 inhibitors centers - center therapy - evolocumab - familial hypercholesterolemia - proprotein konvertase subtilisin kexin 9 inhibitors (PCSK9i) - secondary prevention - statins intolerance.

[60] *Karasek D*. **Combined lipid-lowering therapy**. Vnitr Lek 2019; 64:1177-1184.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30704254
ABSTRACT
Dyslipidemia belongs to the main risk factors for atherosclerosis. To achieve current blood lipid targets, it is often necessary to use intensive hypolipidemic therapy including a combination of individual hypolipidemic drugs. In terms of cardiovascular risk reduction, it is important that the patient is treated with the highest tolerated dose of statin. In the next step, we decide to co-administer ezetimibe and/or fibrate, and for high-risk patients an additional treatment with proprotein convertase subtilisin kexin 9 inhibitors should be considered. The manuscript provides an overview of the individual combinations effectiveness to influence lipid spectrum and the incidence of cardiovascular diseases. Key words: cardiovascular disease - dyslipidemia - ezetimibe - fibrates - PCSK9 inhibitors - statins.

[61] *Vohnout B, Lisicanova J, Havranova A*. **PCSK9 inhibitors and diabetes mellitus**. Vnitr Lek 2019; 64:1186-1189.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30704255
ABSTRACT
Proproteinconvertase subtilisin kexin 9 (PCSK9) is a key regulator of low-density lipoprotein receptor (LDLR) expression. Anti-PCSK9 monoclonal antibody (MAb) therapy reduces LDL-cholesterol (LDL-C) by ~60 % and reduces also the risk of major adverse cardiovascular events. Mendelian randomisation studies showed that patients carrying loss-of-function PCSK9 genetic variants display lower LDL-C and have an increased risk of developing type 2 diabetes (T2DM). Randomized controlled trials with anti-PCSK9 MAbs however showed no effect on the risk. A possible explanation of the discrepancy is that the deficiency of locally but not circulating PCSK9 is responsible for increased LDLR expression in pancreatic islets, which results in cholesterol accumulation and B-cell dysfunction. Thus PCSK9 lowering therapy with MAb targeting mainly circulating PCSK9 might have a limited impact on LDLR expression in pancreatic cells and on the risk of T2DM. Long-term clinical trials are however needed to confirm it. Key words: diabetes mellitus - LDL receptor - PCSK9.