Literature update week 05 (2018)

[1] *Rink JS, Sun W, Misener S et al.* **Nitric Oxide-Delivering High-Density Lipoprotein-like Nanoparticles as a Biomimetic Nanotherapy for Vascular Diseases**. ACS applied materials & interfaces 2018.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29385802

ABSTRACT

Disorders of blood vessels cause a range of severe health problems. As a powerful vasodilator and cellular second messenger, nitric oxide (NO) is known to have beneficial vascular functions. However, NO typically has a short half-life and is not specifically targeted. On the other hand, high-density lipoproteins (HDLs) are targeted natural nanoparticles (NPs) that transport cholesterol in the systemic circulation and whose protective effects in vascular homeostasis overlap with those of NO. Evolving the AuNP-templated HDL-like nanoparticles (HDL NPs), a platform of bioinspired HDL, we set up a targeted biomimetic nanotherapy for vascular disease that combines the functions of NO and HDL. A synthetic S-nitrosylated (SNO) phospholipid (1,2-dipalmitoyl-sn-glycero-3-phosphonitrosothioethanol) was synthesized and assembled with S-containing phospholipids and the principal protein of HDL, apolipoprotein A-I, to construct NO-delivering HDL-like particles (SNO HDL NPs). SNO HDL NPs self-assemble under mild conditions similar to natural processes, avoiding the complex postassembly modification needed for most synthetic NO-release nanoparticles. In vitro data demonstrate that the SNO HDL NPs merge the functional properties of NO and HDL into a targeted nanocarrier. Also, SNO HDL NPs were demonstrated to reduce ischemia/reperfusion injury in vivo in a mouse kidney transplant model and atherosclerotic plaque burden in a mouse model of atherosclerosis. Thus, the synthesis of SNO HDL NPs provides not only a bioinspired nanotherapy for vascular disease but also a foundation to construct diversified multifunctional platforms based on HDL NPs in the future.

[2] *Viecelli AK, Irish AB, Polkinghorne KR et al.* **Omega-3 Polyunsaturated Fatty Acid Supplementation to Prevent Arteriovenous Fistula and Graft Failure: A Systematic Review and Meta-analysis of Randomized Controlled Trials**. American journal of kidney diseases : the official journal of the National Kidney Foundation 2018.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29395485

ABSTRACT

BACKGROUND: Arteriovenous access failure frequently occurs in people on hemodialysis and is associated with morbidity, mortality and large healthcare expenditures. Omega-3 polyunsaturated fatty acids (omega-3 PUFA) may improve access outcomes via pleiotropic effects on access maturation and function, but may cause bleeding complications. STUDY DESIGN: Systematic review with meta-analysis. SETTING & POPULATION: Adults requiring hemodialysis via arteriovenous fistula or graft. SELECTION CRITERIA: Trials evaluating omega-3 PUFA for arteriovenous access outcomes identified by searches in CENTRAL, MEDLINE, and Embase to 24 January 2017. INTERVENTION: Omega-3 PUFA. OUTCOMES: Primary patency loss, dialysis suitability failure, access abandonment, interventions to maintain patency or assist maturation, bleeding, gastrointestinal side-effects, all-cause and cardiovascular mortality, hospitalization, and treatment adherence. Treatment effects were summarized as relative risks (RR) and 95% confidence intervals (CI). Evidence was assessed using GRADE. RESULTS: Five eligible trials (833 participants) with a median follow-up of 12 months compared peri-operative omega-3 PUFA supplementation with placebo. One trial (n=567) evaluated treatment for fistulae and four (n=266) for grafts. Omega-3 PUFA supplementation prevented primary patency loss with moderate certainty (761 participants, RR 0.81, CI 0.68-0.98). Low quality evidence suggested, that omega-3 PUFA may have had little or no effect on dialysis suitability failure (536 participants, RR 0.95, CI 0.73-1.23), access

abandonment (732 participants, RR 0.78, CI 0.59-1.03), need for interventions (732 participants, RR 0.82, CI 0.64-1.04), or all-cause mortality (799 participants, RR 0.99, CI 0.51-1.92). Bleeding risk (793 participants, RR 1.40, CI 0.78-2.49) or gastrointestinal side-effects (816 participants, RR 1.22, CI 0.64-2.34) from treatment were uncertain. There was no evidence of different treatment effects for grafts and fistulae. LIMITATIONS: Small number and methodological limitations of included trials. CONCLUSIONS: Omega-3 PUFA supplementation probably protects against primary loss of arteriovenous access patency, but may have little or no effect on dialysis suitability failure, access interventions or access abandonment. Potential treatment harms are uncertain.

[3] *Li WS, Chen ZZ, Zheng YJ et al.* **The efficacy of parenteral fish oil in critical illness patients with sepsis: a prospective, non-randomized, observational study**. Asia Pacific journal of clinical nutrition 2018; 27:306-312.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29384315

ABSTRACT

BACKGROUND AND OBJECTIVES: To investigate the clinical outcomes in septic patients receiving parenteral fish oil. METHODS AND STUDY DESIGN: A prospective, non-randomized, observational clinical study was carried out in 112 patients with sepsis from March, 2013 to May, 2015 in the surgical intensive care unit (SICU) of a tertiaryreferral hospital. The patients were put into one of two groups; either the control or the study group. Patients received the standard treatment of sepsis based on guidelines in the control group. In the study group, patients received parenteral nutrition (PN) containing fish oil. The Acute Physiology and Chronic Health Evaluation II (APACHE II) scores, the length of ICU and hospital stay, duration of mechanical ventilation, mortality, and readmission into the ICU were recorded. Tumor necrosis factor (TNF)-alpha and procalcitonin (PCT) levels were also evaluated. RESULTS: The study group showed a significant reduction for all-cause mortality (20.0% vs 10.0% in study and control groups, p=0.034) and APACHE II score on day 5 (p=0.015), day 7 (p=0.036) and day out of SICU (p=0.045) compared with the control group. The study group tended to show a shortened length of stay in the ICU compared to the control group. However, TNF-alpha and PCT level, 28 d mortality, the length of hospital stay and the duration of mechanical ventilation did not show statistical differences between the two groups. There were no drug-related adverse effects shown during the study. CONCLUSIONS: PN with fish oil is probably safe and may improve clinical outcome in critical ill patients with sepsis.

[4] *Stock JK*. **The challenge of peripheral arterial disease: How do we improve outcome?** Atherosclerosis 2018.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29395100

ABSTRACT

[5] *Dimmitt SB, Stampfer HG, Warren JB*. **The pharmacodynamic and clinical trial evidence for statin dose**. British journal of clinical pharmacology 2018.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29393975

ABSTRACT

Statin doses around estimated effective dose 50 (ED50) can reduce myocardial infarction by over 25% and mortality by around 10%. Being a competitive enzyme inhibitor, statin efficacy plateaus at doses that are multiples above the ED50, whilst on- and off-target adverse events increase in number and severity with increasing dose. For example, myopathy has been shown to increase by up to 29-fold and liver dysfunction by up to 9-fold as statin dose is increased. Doses of up to 40-fold ED50 have been promoted, but above 5-fold ED50, for example 10 mg of atorvastatin, there is no randomised controlled clinical trial evidence that coronary mortality is lowered, or that survival is increased.

[6] *Huang S, Frangogiannis NG*. **Anti-inflammatory therapies in myocardial infarction: failures, hopes, and challenges**. Br J Pharmacol 2018.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29394499

ABSTRACT

In the infarcted heart, damage-associated molecular patterns released by necrotic cells trigger both myocardial and systemic inflammatory responses. Induction of chemokines and cytokines and upregulation of endothelial adhesion molecules mediate leukocyte recruitment in the infarcted myocardium. Inflammatory cells clear the infarct from dead cells and matrix debris and activate reparative myofibroblasts and vascular cells, but may also contribute to adverse fibrotic remodeling of viable segments, accentuate cardiomyocyte apoptosis and exert arrhythmogenic actions. Excessive, prolonged and dysregulated inflammation has been implicated in the pathogenesis of complications and may be involved in the development of heart failure following infarction. Studies in animal models of myocardial infarction (MI) have suggested the effectiveness of pharmacologic interventions targeting the inflammatory response. This manuscript provides a brief overview of the cell biology of the post-infarction inflammatory response and discusses the use of pharmacologic interventions targeting inflammation following infarction. Therapy with broad anti-inflammatory and immunomodulatory agents may abrogate important reparative pathways, thus exerting detrimental actions in patients with MI. Extensive experimental evidence suggests that targeting specific inflammatory signals, such as the complement cascade, chemokines, cytokines, proteases, selectins and leukocyte integrins, may hold promise; however, clinical translation has proved challenging. Targeting Interleukin-1 may benefit patients with exaggerated post-MI inflammatory responses following infarction, not only by attenuating adverse remodeling, but also by stabilizing the atherosclerotic plaque, and by inhibiting arrhythmia generation. Identification of the therapeutic window for specific interventions, and pathophysiological stratification of MI patients using inflammatory biomarkers and imaging strategies are critical for optimal therapeutic design.

[7] *Allahverdian S, Chaabane C, Boukais K et al.* **Smooth Muscle Cell Fate and Plasticity in Atherosclerosis**. Cardiovascular research 2018.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29385543

ABSTRACT

Current knowledge suggests that intimal smooth muscle cells (SMCs) in native atherosclerotic plaque derive mainly from the medial arterial layer. During this process, SMCs undergo complex structural and functional changes giving rise to a broad spectrum of phenotypes. Classically, intimal SMCs are described as dedifferentiated/synthetic SMCs, a phenotype characterized by reduced expression of contractile proteins. Intimal SMCs are considered to have a beneficial role by contributing to the fibrous

cap and thereby stabilizing atherosclerotic plaque. However, intimal SMCs can lose their properties to such an extent that they become hard to identify, contribute significantly to the foam cell population, and acquire inflammatory-like cell features. This review highlights mechanisms of SMC plasticity in different stages of native atherosclerotic plaque formation, their potential for monoclonal or oligoclonal expansion, as well as recent findings demonstrating the underestimated deleterious role of SMCs in this disease.

[8] *Mehta S, Jackson R, Wells S et al.* **Cardiovascular medication changes over 5 years in a national data linkage study: implications for risk prediction models**. Clinical epidemiology 2018; 10:133-141.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29391835

ABSTRACT

Background: Despite widespread use of cardiovascular disease (CVD) preventive medications in cohorts used to develop CVD risk prediction models, only some incorporate baseline CVD pharmacotherapy and none account for treatment changes during study follow-up. Therefore, current risk prediction scores may underestimate the true CVD event risk. We examined changes in CVD pharmacotherapy over 5 years in preparation for developing new 5-year risk prediction models. Methods: Anonymized individual-level linkage of eight national administrative health datasets enabled identification of all New Zealanders aged 30-74 years, without prior hospitalization for CVD or heart failure, who utilized publicly funded health services during 2006. We determined proportions of participants dispensed blood pressure lowering, lipid lowering, and antiplatelet/anticoagulant pharmacotherapy at baseline in 2006, and the proportion of person years of follow-up (2007-2011) where dispensing occurred. Results: The study population comprised of 1,766,584 individuals, representing85% of all New Zealanders aged 30-74 years without prior CVD or heart failure in 2006, with mean follow-up of 4.9 years (standard deviation 0.6 years; 8,589,931 total person years). CVD medications were dispensed to 21% of people at baseline, with most single or combination pharmacotherapies continuing for >/=80% of follow-up. Complete discontinuation of baseline treatment accounted for 2% of follow-up time while CVD pharmacotherapy that commenced after baseline accounted for 7% of total follow-up time. Conclusion: In a national primary prevention cohort of 30-74 year olds, one in five received baseline CVD primary preventive pharmacotherapy and medication changes over the subsequent 5 years were modest. Baseline medication use is an important consideration when estimating CVD risk from modern cohorts. It is currently unclear how to incorporate available methods to account for treatment changes during follow-up into risk prediction scores, but this study demonstrates that baseline therapy captures most of the effect of treatment in 5-year risk models. However, the impact of treatment changes on the more common 10-year risk models requires further investigation.

[9] *Millan J, Pinto X, Brea A et al.* **Fibrates in the secondary prevention of cardiovascular disease (infarction and stroke). Results of a systematic review and meta-analysis of the Cochrane collaboration**. Clinica e investigacion en arteriosclerosis : publicacion oficial de la Sociedad Espanola de Arteriosclerosis 2018; 30:30-35.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29395493

ABSTRACT

Fibrates are a group of drugs that are known mainly for reducing triglycerides, increasing high density lipoproteins (HDL), and reducing the fraction of small, dense LDL particles. The results of a Cochrane

Collaboration study have recently been published on their efficacy and safety in the secondary prevention of severe cardiovascular accidents, including coronary and cerebrovascular disease. The study included randomised clinical trials in which the fibrate was compared with placebo or with no treatment. Clinical trials comparing two different fibrates were excluded. The clinical trials evaluated included a total of 16,112 patients (13 trials). The meta-analysis (including all the trials with fibrates) showed evidence of a protective effect of the fibrates compared with placebo as regards a compound objective of non-fatal stroke, non-fatal myocardial infarction, and death of cardiovascular origin (hazard ration of 0.88, with a 95% confidence interval of 0.83 to 0.94; in 16,064 individuals included in 12 studies). Thus, the results showed, with a moderate level of evidence, that fibrates could be effective in secondary prevention considering a compound objective of non-fatal stroke, non-fatal myocardial infarction, and death of cardiovascular origin.

[10] *Muniz F, Taminski K, Cavagni J et al.* **The effect of statins on periodontal treatment-a systematic review with meta-analyses and meta-regression**. Clinical oral investigations 2018.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29396642

ABSTRACT

OBJECTIVE: This study aimed to systematically review clinical trials about the effect of statins as adjunct to mechanical periodontal therapy, on probing pocket depth, clinical attachment level, and intrabony defects, in comparison to mechanical periodontal therapy alone or in association with placebo. MATERIAL AND METHODS: Three databases were searched for controlled clinical trials that used any locally delivered or systemically statin as a sole adjunctive therapy to mechanical periodontal treatment. Weighted mean differences between baseline and 6 months after periodontal treatment for clinical attachment level (CAL), probing pocket depth (PPD), and intrabony defect (IBD) were calculated. A high heterogeneity was detected. Therefore, a meta-regression adjusted for type of statin and year of publication was performed. RESULTS: Fifteen studies were included in the systematic review, and ten studies were included in the meta-analysis. In the meta-regression, the adjunct use of simvastatin, rosuvastatin, and atorvastatin additionally reduced PPD in comparison to mechanical periodontal therapy and a placebo gel (2.90 +/- 0.35, 3.90 +/- 0.77, 3.06 +/- 0.71 mm, respectively; $p < 0.05$). Regarding the resolution of IBD, simvastatin and rosuvastatin significantly improved in comparison to control group (0.89 +/- 0.35 and 1.93 +/- 0.77 mm, respectively; $p < 0.05$). No statistically significant difference was found between the statins for both PPD and IBD ($p < 0.05$). Regarding CAL gain, simvastatin provided a statistically significant improvement as compared to the control group (2.02 +/- 0.79 mm; $p = 0.043$). CONCLUSIONS: The use of statins, used as sole adjuncts to mechanical periodontal treatment, improved the periodontal parameters. In the quantitative analyses, simvastatin was the only drug that showed additional benefits in all evaluated parameters. CLINICAL RELEVANCE: Statins promote significantly clinical periodontal improvements when administered in association with non-surgical scaling and root planning (SRP), when compared to SRP alone or in association with a placebo.

[11] *Mao J, Doshi U, Wright M et al.* **Prediction of the Pharmacokinetics of Pravastatin as an OATP Substrate Using Plateable Human Hepatocytes With Human Plasma Data and PBPK Modeling**. CPT: pharmacometrics & systems pharmacology 2018.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29388346

ABSTRACT

Plateable human hepatocytes with human plasma were utilized to generate the uptake transporter kinetic data for pravastatin, an organic anion-transporting polypeptide (OATP) transporter substrate. The active hepatic uptake of pravastatin was determined with a Jmax value of 134.4 pmol/min/million cells and Km of 76.77 microM in plateable human hepatocytes with human plasma. The physiologically-based pharmacokinetic (PBPK) model with incorporation of these in vitro kinetic data successfully simulated the i.v. pharmacokinetic profile of pravastatin without applying scaling factor (the mean predicted area under the curve (AUC) is within 1.5-fold of the observed). Furthermore, the PBPK model also adequately described the oral plasma concentration-time profiles of pravastatin at different dose levels. The current investigation demonstrates an approach allowing us to build upon the translation of in vitro OATP uptake transporter data to in vivo, with a hope of utilizing the in vitro data for the prospective human pharmacokinetic (PK) prediction.

[12] *Colussi G, Catena C, Fagotto V et al.* **Atrial fibrillation and its complications in arterial hypertension: the potential preventive role of omega-3 polyunsaturated fatty acids**. Critical reviews in food science and nutrition 2018:0.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29381383

ABSTRACT

Atrial fibrillation (AF) is the most common type of arrhythmia in the general population with a prevalence that reaches one third of patients with arterial hypertension. Several risk factors frequently associated with hypertension predispose the myocardium to AF by inducing atrial inflammation and fibrosis and altering atrial electrical and mechanical characteristics. AF influences the quality of life of hypertensive patients since it increases incidence of stroke and other thromboembolic events, and mortality. Polyunsaturated fatty acids of the omega-3 family (omega-3 PUFA) have been demonstrated to be beneficial in cardiovascular disease prevention by reducing plasma lipids and blood pressure levels and decreasing the risk of sudden death. These fatty acids can act as potent anti-inflammatory and anti-arrhythmic agents. Many studies have investigated a possible preventive effect of omega-3 PUFA on incident AF reporting contradictory results. This article overviews the evidence currently available on this important topic and provides some conclusive remarks on the possibility that these fatty acids could be beneficial in hypertensive patients.

[13] *Giglio RV, Patti AM, Cicero AF et al.* **Polyphenols: Potential Use In The Prevention And Treatment Of Cardiovascular Diseases**. Current pharmaceutical design 2018.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29384050

ABSTRACT

BACKGROUND: Polyphenols are bioactive compounds that can be found mostly in foods like fruits, cereals, vegetables, dry legumes, chocolate and beverages such as coffee, tea and wine. They are extensively used in the prevention and treatment of cardiovascular disease (CVD) providing protection against many chronic illnesses. Their effects on human health depend on the amount consumed and on their bioavailability. Many studies have demonstrated that polyphenols have also good effects on the vascular system by lowering blood pressure, improving endothelial function, increasing antioxidant defences, inhibiting platelet aggregation and low-density lipoprotein oxidation, and reducing inflammatory responses. METHODS: This review is focused on some groups of polyphenols and their effects on several cardiovascular risk factors such as hypertension, oxidative stress, atherogenesis,

endothelial dysfunction, carotid artery intima-media thickness, diabetes and lipid disorders. RESULTS: It is proved that these compounds have many cardio protective functions: they alter hepatic cholesterol absorption, triglyceride biosynthesis and lipoprotein secretion, the processing of lipoproteins in plasma, and inflammation. In some cases, human long-term studies did not show conclusive results because they lacked in appropriate controls and in an undefined polyphenol dosing regimen. CONCLUSION: Rigorous evidence is necessary to demonstrate whether or not polyphenols beneficially impact CVD prevention and treatment.

[14] *Ghadge AA, Khaire AA, Kuvalekar AA*. **Adiponectin: A potential therapeutic target for metabolic syndrome**. Cytokine & growth factor reviews 2018.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29395659

ABSTRACT

Adiponectin is an important adipocytokine secreted chiefly by fat containing adipocytes, and plays a crucial role in glucose and lipid metabolism, inflammation and oxidative stress. Alterations in adiponectin levels have been shown to directly affect lipid and glucose metabolism that further increase the synthesis of lipids, free fatty acids and inflammatory cytokines. Changes in adiponectin levels also contribute to insulin resistance, obesity, cardiovascular diseases and type 2 diabetes. In the present review, we provide a comprehensive evaluation of the role of adiponectin and its molecular mechanisms in metabolic syndrome. Clinical improvement in adiponectin levels have been shown to positively modulate lipid and glucose metabolism, thus further substantiating its role in regulation of lipid and glucose metabolism. Currently adiponectin is being investigated as a potential therapeutic target for metabolic syndrome, although more research is required to understand the underlying mechanisms controlling adiponectin levels, including dietary and lifestyle interventions, that may target adiponectin as a therapeutic intervention in metabolic syndrome.

[15] *Goikuria H, Vandenbroeck K, Alloza I*. **Inflammation in human carotid atheroma plaques**. Cytokine & growth factor reviews 2018.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29396056

ABSTRACT

Inflammation in carotid atherosclerotic plaque is linked to plaque rupture and cerebrovascular accidents. The balance between pro- and anti-inflammatory mediators governs development of the plaque, and may mediate enhancement of lesion broadening or, on the contrary, delay progression. In addition to macrophages and endothelial cells, smooth muscle cells (SMCs), which are the dominant cell subset in advanced plaques, are crucial players in carotid atherosclerosis development given their ability to differentiate into distinct phenotypes in reponse to specific signals received from the environment of the lesion. Carotid atheroma SMCs actively contribute to the inflammation in the lesion because of their acquired capacity to produce inflammatory mediators. We review the successive stages of carotid atheroma plaque formation via fatty streak early-stage toward more advanced rupture-prone lesions and document involvement of cytokines and chemokines and their cellular sources and targets in plaque progression and rupture.

Literature update week 05 (2018)

[16] *Cao YX, Liu HH, Dong QT et al.* **Effect of the PCSK9-monoclonal antibodies on new-onset diabetes mellitus and glucose metabolism: a systematic review and meta-analysis**. Diabetes Obes Metab 2018.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29377473

ABSTRACT

AIMS: To investigate the effect of two clinically applied proprotein convertase subtilisin/kexin type 9 monoclonal antibody (PCSK9-mAb) on glycaemia and new-onset diabetes mellitus (NODM). MATERIALS AND METHODS: PubMed, MEDLINE, Embase, Cochrane databases and ClinicalTrials.gov websites were systematically searched for randomized controlled trials that reported the fasting plasma glucose (FPG), Hemoglobin A1c (HbA1c) or NODM incidence. Risk ratios (RR) for NODM and Mean Difference (MD) for FPG and HbA1c with 95% confidence intervals (CI) were calculated using a fixed-effect model. Heterogeneity was examined using the I(2) statistic and potential publication bias was assessed with funnel plots and Egger's test. RESULTS: A total of 18 studies with 26,123 non-diabetic participants were identified. No significant difference was observed in terms of NODM (RR:1.05, 95%CI:0.95 to 1.16), FPG (MD:0.00 mmol/L,95%CI:-0.02 to 0.02) and HbA1c (MD:0.00%, 95%CI:-0.01 to 0.01) compared with control group. Subgroup (PCSK9-mAb types, participant characteristics, treatment duration, treatment method and differences of control treatment) and sensitivity analyses did not significantly alter the results. Meta-regression analyses showed that risk of NODM was not associated with baseline age, baseline body mass index (BMI), proportion of male, treatment duration or percent LDL-C reduction. CONCLUSIONS: Alirocumab and Evolocumab, two kinds of PCSK9-mAb approved by FDA and EMA, had no significant impact on NODM and glucose homeostasis, despite of PCSK9-mAb types, participant characteristics, treatment duration, treatment method and differences of control treatment. Baseline age, BMI, male rate, treatment duration, and percent change of LDL-C did not influence diabetes risks.

[17] *Awad K, Mikhailidis DP, Katsiki N et al.* **Effect of Ezetimibe Monotherapy on Plasma Lipoprotein(a) Concentrations in Patients with Primary Hypercholesterolemia: A Systematic Review and Meta-Analysis of Randomized Controlled Trials**. Drugs 2018.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29396832

ABSTRACT

BACKGROUND AND AIMS: Ezetimibe reduces plasma low-density lipoprotein cholesterol (LDL-C) levels by up to 20%. However, its effect on plasma lipoprotein(a) [Lp(a)] concentrations in patients with primary hypercholesterolemia has not been defined. OBJECTIVE: Therefore, we performed a systematic review and meta-analysis to assess this effect based on the available randomized controlled trials (RCTs). METHODS: We searched the PubMed and SCOPUS databases from inception until 28 February 2017 to identify RCTs that investigated the effect of ezetimibe monotherapy on plasma Lp(a) concentrations in patients with primary hypercholesterolemia. We pooled mean percentage changes in plasma Lp(a) concentrations as a mean difference (MD) with a 95% confidence interval (CI). RESULTS: Seven RCTs with 2337 patients met the selection criteria and were included in the analysis. Overall pooled analysis suggested that ezetimibe 10 mg significantly reduced plasma Lp(a) concentrations in patients with primary hypercholesterolemia by - 7.06% (95% CI - 11.95 to - 2.18; p = 0.005) compared with placebo. No significant heterogeneity was observed (chi(2) = 5.34; p = 0.5). Excluding one study from the analysis resulted in insignificant differences between the two groups (p = 0.2). Meta-regression did not find a significant association between the mean percentage changes in Lp(a) and other potential moderator variables, which included the mean percentage changes of LDL-C concentrations (p = 0.06) and baseline Lp(a) mean values (p = 0.46). CONCLUSIONS: Ezetimibe monotherapy (10 mg/day) showed

a small (7.06%) but statistically significant reduction in the plasma levels of Lp(a) in patients with primary hypercholesterolemia. According to current literature, this magnitude of reduction seems to have no clinical relevance. However, further studies are warranted to clarify the mechanism mediating this effect of ezetimibe and to investigate its efficacy in combination with other drugs that have shown promise in lowering Lp(a) levels.

[18] *Whayne TF*. **Outcomes, Access, and Cost Issues Involving PCSK9 Inhibitors to Lower LDL-Cholesterol**. Drugs 2018.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29396831

ABSTRACT

The clinical importance and benefit of the proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors appears well established for the high-risk cardiovascular (CV) patient. This applies especially to the statin-intolerant patient or the patient who does not attain an appropriate low-density lipoprotein cholesterol (LDL-C) target. Therefore, the barriers to appropriate clinical use of the PCSK9 inhibitors involve cost and not the documented CV benefit or LDL-C lowering. Multiple roadblocks affect many high-risk CV patients in arranging approval of a PCSK9 inhibitor. Overcoming these roadblocks may require legal pressures, some increased regulation, and facilitation by competitive forces.

[19] *Schooling CM, Huang JV, Zhao JV et al.* **Disconnect Between Genes Associated With Ischemic Heart Disease and Targets of Ischemic Heart Disease Treatments**. EBioMedicine 2018.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29396305

ABSTRACT

BACKGROUND: Development of pharmacological treatments to mitigate ischemic heart disease (IHD) has encompassed disappointing results and expensive failures, which has discouraged investment in new approaches to prevention and control. New treatments are most likely to be successful if they act on genetically validated targets. We assessed whether existing pharmacological treatments for IHD reduction are acting on genetically validated targets and whether all such targets for IHD are currently being exploited. METHODS: Genes associated with IHD were obtained from the loci of single nucleotide polymorphisms reported in either of two recent genome wide association studies supplemented by a gene-based analysis (accounting for linkage disequilibrium) of CARDIoGRAMplusC4D 1000 Genomes, a large IHD case (n=60,801)-control (n=123,504) study. Treatments targeting the products of these IHD genes and genes with products targeted by current IHD treatments were obtained from Kyoto Encyclopedia of Genes and Genomes and Drugbank. Cohen's kappa was used to assess agreement. RESULTS: We identified 173 autosomal genes associated with IHD and 236 autosomal genes with products targeted by current IHD treatments, only 8 genes (PCSK9, EDNRA, PLG, LPL, CXCL12, LRP1, CETP and ADORA2A) overlapped, i.e. were both associated with IHD and had products targeted by current IHD treatments. The Cohen's kappa was 0.03. Interventions related to another 29 IHD genes exist, including dietary factors, environmental exposures and existing treatments for other indications. CONCLUSIONS: Closer alignment of IHD treatments with genetically validated physiological targets may represent a major opportunity for combating a leading cause of global morbidity and mortality through repurposing existing interventions.

Literature update week 05 (2018)

[20] *Biedermann JS, Kruip M, van der Meer FJ et al.* **Rosuvastatin use improves measures of coagulation in patients with venous thrombosis**. European heart journal 2018.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29394348

ABSTRACT

Aims: Observational studies indicate that statins reduce the risk of recurrent venous thrombosis (VT). However, trials have not been performed and the mechanism is unknown. We aimed to determine whether statin therapy improves the coagulation profile in patients with prior VT. Methods and results: Randomized clinical trial (NCT01613794). Patients were randomized to rosuvastatin 20 mg/day for 4 weeks or no intervention. Blood was drawn at baseline and at end of study. The primary outcome was factor (F) VIII:C. In total, five coagulation factors were measured: FVIII:C, von Willebrand factor:Ag, FVII:C, FXI:C, and D-dimer. Among 247 randomized participants, mean age was 58 years, 62% were women and 49% had unprovoked VT. For all tested coagulation factors, mean levels were clearly decreased at end of study in rosuvastatin users, whereas they hardly differed in non-statin users. Results were most consistent for FVIII:C where mean FVIII:C levels were 7.2 IU/dL [95% CI (confidence interval) 2.9-11.5] lower in rosuvastatin users, while among non-users, no change in FVIII:C was observed (mean difference -0.1; 95% CI -3.0 to 2.9). The mean age and sex adjusted difference in FVIII:C change was -6.7 IU/dL (95% CI -12.0 to -1.4) in rosuvastatin users vs. non-users. Subgroup analyses revealed that the decrease in coagulation factors by rosuvastatin was more pronounced in participants with unprovoked VT and in those with cardiovascular risk factors. Conclusion: Rosuvastatin 20 mg/day substantially improved the coagulation profile among patients with prior VT. These results suggest that statin therapy might be beneficial in patients at risk of recurrent VT.

[21] *Chistiakov DA, Melnichenko AA, Grechko AV et al.* **Potential of anti-inflammatory agents for treatment of atherosclerosis**. Experimental and molecular pathology 2018; 104:114-124.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29378168

ABSTRACT

Chronic inflammation is a central pathogenic mechanism of atherosclerosis induction and progression. Vascular inflammation is associated with accelerated onset of late atherosclerosis complications. Atherosclerosis-related inflammation is mediated by a complex cocktail of pro-inflammatory cytokines, chemokines, bioactive lipids, and adhesion molecules, and blocking the key pro-atherogenic inflammatory mechanisms can be beneficial for treatment of atherosclerosis. Therapeutic agents that specifically target some of the atherosclerosis-related inflammatory mechanisms have been evaluated in preclinical and clinical studies. The most promising anti-inflammatory compounds for treatment of atherosclerosis include non-specific anti-inflammatory drugs, phospholipase inhibitors, blockers of major inflammatory cytokines, leukotrienes, adhesion molecules, and pro-inflammatory signaling pathways, such as CCL2-CCR2 axis or p38 MAPK pathway. Ongoing studies attempt evaluating therapeutic utility of these anti-inflammatory drugs for treatment of atherosclerosis. The obtained results are important for our understanding of atherosclerosis-related inflammatory mechanisms and for designing randomized controlled studies assessing the effect of specific anti-inflammatory strategies on cardiovascular outcomes.

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[22] *Gu C, Wu Y, Fan Z, Han W*. **Simvastatin improves intracerebral hemorrhage through NF-kappaB-mediated apoptosis via the MyD88/TRIF signaling pathway**. Experimental and therapeutic medicine 2018; 15:377-382.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29375693

ABSTRACT

The aim was to investigate the neuroprotective effects and potential mechanism mediated by simvastatin in a mouse model of intracerebral hemorrhage. CD-1 mice were subjected to infusion of collagenase type IV into the left striatum in order to induce intracerebral hemorrhage. Western blot analysis, the TUNEL assay and the modified neurological severity score were used in the present study to analyze the efficacy of simvastatin for intracerebral hemorrhage. The results demonstrated that simvastatin treatment improved the cerebral water content and blood-brain barrier disruption in the intracerebral hemorrhage animals. Intracerebral hemorrhage-induced neuronal cell death was downregulated by simvastatin treatment compared with the vehicle-treated model group. In addition, the expression levels of aquaporin-4, matrix metallopeptidase 9 and caspase-3 were downregulated and B-cell lymphoma-2 was upregulated by simvastatin treatment compared with the vehicle-treated model. Simvastatin treatment also significantly reduced the Evans blue leakage into the injured hemispheres and improved motor function. Mechanism analysis further indicated that simvastatin treatment downregulated nuclear factor (NF)-kappaB expression, and upregulated the myeloid differentiation primary response 88 (MyD88) and TIR domain-containing adaptor protein inducing interferon-beta (TRIF) expression levels in neuronal cells in experimental mice. Furthermore, the results revealed that NF-kappaB overexpression abolished the simvastatin-downregulated MyD88 and TRIF expression levels, as well as the apoptosis of neuronal cells. In conclusion, these results indicated that simvastatin was able to attenuate brain edema and reduce cellular apoptosis by suppressing the NF-kappaB-mediated MyD88/TRIF signaling pathway subsequent to the induction of intracerebral hemorrhage in mice.

[23] *Venkatakrishnan K, Chiu HF, Cheng JC et al.* **Comparative studies on the hypolipidemic, antioxidant and hepatoprotective activities of catechin-enriched green and oolong tea in a double-blind clinical trial**. Food & function 2018.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29384173

ABSTRACT

This study aimed to compare the beneficial effect of catechin-enriched green tea and oolong tea on mildly hypercholesterolemic subjects. Sixty mildly hypercholesterolemic subjects (180-220 mg dL(-1)) were enrolled and divided into three groups as catechin-enriched green tea (CEGT), catechin-enriched oolong tea (CEOT) or placebo. The subjects were instructed to drink 2 x 300 mL of CEGT (780.6 mg of catechin), CEOT (640.4 mg of catechin) or placebo beverage for 12 weeks. Drinking CEGT and CEOT significantly decreased ($p < 0.05$) the body weight, fat, and BMI, lipid peroxidation as well as lipid profile (TC, LDL-c, HDL-c, and TG). Also, intervention with CEGT and CEOT significantly improved ($p < 0.05$) the oxidative indices (TEAC and GSH) and antioxidant enzymes (SOD, CAT, GPx, and GR). Moreover, ultrasound examination endorsed the hepatoprotective activity of CEGT and CEOT by reverting mild fatty liver to the normal hepatic condition because of antioxidant and hypolipidemic activities. To summarize, both CEGT and CEOT showed similar antioxidant and hepatoprotective activities. However, CEOT displayed superior lipid-lowering activity compared to CEGT or placebo, and hence it could be used to amend the wellness condition of mildly hypercholesterolemic subjects.

Literature update week 05 (2018)

[24] *He W, Liu Y, Tian X*. **Rosuvastatin Improves Neurite Outgrowth of Cortical Neurons against Oxygen-Glucose Deprivation via Notch1-mediated Mitochondrial Biogenesis and Functional Improvement**. Frontiers in cellular neuroscience 2018; 12:6.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29387001

ABSTRACT

Neurogenesis, especially neurite outgrowth is an essential element of neuroplasticity after cerebral ischemic injury. Mitochondria may supply ATP to power fundamental developmental processes including neuroplasticity. Although rosuvastatin (RSV) displays a potential protective effect against cerebral ischemia, it remains unknown whether it modulates mitochondrial biogenesis and function during neurite outgrowth. Here, the oxygen-glucose deprivation (OGD) model was used to induce ischemic injury. We demonstrate that RSV treatment significantly increases neurite outgrowth in cortical neurons after OGD-induced damage. Moreover, we show that RSV reduces the generation of reactive oxygen species (ROS), protects mitochondrial function, and elevates the ATP levels in cortical neurons injured by OGD. In addition, we found that, under these conditions, RSV treatment increases the mitochondrial DNA (mtDNA) content and the mRNA levels of mitochondrial transcription factor A (TFAM) and nuclear respiratory factor 1 (NRF-1). Furthermore, blocking Notch1, which is expressed in primary cortical neurons, reverses the RSV-dependent induction of mitochondrial biogenesis and function under OGD conditions. Collectively, these results suggest that RSV could restore neurite outgrowth in cortical neurons damaged by OGD in vitro, by preserving mitochondrial function and improving mitochondrial biogenesis, possibly through the Notch1 pathway.

[25] *Qiao L, Zhang X, Liu M et al.* **Corrigendum: Ginsenoside Rb1 Enhances Atherosclerotic Plaque Stability by Improving Autophagy and Lipid Metabolism in Macrophage Foam Cells**. Frontiers in pharmacology 2017; 8:964.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29377020

ABSTRACT

[This corrects the article on p. 727 in vol. 8, PMID: 29114222.].

[26] *Li H, Wang C, Sun J et al.* **Pravastatin Decreases Infarct Size Induced by Coronary Artery Ischemia/Reperfusion with Elevated eNOS Expression in Rats**. Int Heart J 2018; 59:154-160.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29375110

ABSTRACT

Our previous study showed that pravastatin prevents ischemia and reperfusion-induced lethal ventricular fibrillation in rats. This study explored whether pravastatin decreases myocardial infarct size and this effect is associated with endothelial nitric oxide synthase (eNOS) expression in myocardium. Rats were treated with ischemia (30 minutes) and reperfusion (60 minutes) after chronic oral administration of pravastatin, fluvastatin, or vehicle once daily for 22 days. Electrocardiograms and blood pressure were continuously recorded, myocardial infarct size was measured by TTC-staining, and eNOS expression was measured by western blot. The results showed that pravastatin and fluvastatin significantly reduced myocardial infarct size. No statistical differences were found in the areas at risk

among all groups. However, a significant reduction in infarct size was observed in three pravastatin groups and one fluvastatin group compared to control. Both pravastatin and fluvastatin significantly increased eNOS protein expression in ischemic and non-ischemic tissues compared to control. Our results suggest that pravastatin decreases cardiovascular mortality beyond its cholesterol-lowering effect. Pravastatin is more potent than fluvastatin in reducing infarct size. These effects may be associated with elevation of eNOS expression.

[27] *Taechalertpaisarn J, Zhao B, Liang X, Burgess K*. **Small Molecule Inhibitors Of The PCSK9*LDLR Interaction**. Journal of the American Chemical Society 2018.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29378408

ABSTRACT

The protein-protein interaction between proprotein convertase subtilisin/kexin type 9 (PCSK9) and low-density lipoprotein receptor (LDLR) is a relatively new, and extremely important, validated therapeutic target for treatment and prevention of heart disease. Experts in the area agree that the first small molecules to disrupt PCSK9*LDLR would represent a milestone in this field, yet no credible leads have been reported. This paper describes how side-chain orientations in preferred conformations of carefully designed chemotypes were compared with LDLR side-chains at the PCSK9*LDLR interface to find molecules that would mimic interface regions of LDLR. This approach is an example of the procedure called EKO (Exploring Key Orientations). The guiding hypothesis on which EKO is based is that good matches indicate the chemotypes bearing the same side-chains as the protein at the sites of overlay have the potential to disrupt the parent protein-protein interaction (PPI). In the event, the EKO procedure and one round of combinatorial fragment-based virtual docking, led to the discovery of seven compounds that bound PCSK9 (SPR and ELISA) and had a favorable outcome in a cellular assay (hepatocyte uptake of fluorescently labeled LDL particles) and increased the expression LDLR on hepatocytes in culture. Three promising hit compounds in this series had dissociation constants for PCSK9 binding in the 20 - 40 microM range, and one of these was modified with a photoaffinity label and shown to form a covalent conjugate with PCSK9 on photolysis.

[28] *Stoka K, Maedeker J, Bennett L et al.* **Effects of Increased Arterial Stiffness on Atherosclerotic Plaque Amounts**. Journal of biomechanical engineering 2018.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29392300

ABSTRACT

Increased arterial stiffness is associated with atherosclerosis in humans, but there have been limited animal studies investigating the relationship between these factors. We bred elastin wildtype (Eln+/+) and heterozygous (Eln+/-) mice to apolipoprotein E wildtype (Apoe+/+) and knockout (Apoe-/-) mice and fed them normal (ND) or Western diet (WD) for 12 weeks. Eln+/- mice have increased arterial stiffness. Apoe-/- mice develop atherosclerosis on ND that is accelerated by WD. It has been reported that Apoe-/- mice have increased arterial stiffness and that the increased stiffness may play a role in atherosclerotic plaque progression. We found that Eln+/+Apoe-/- arterial stiffness is similar to Eln+/+Apoe+/+ mice at physiologic pressures, suggesting that changes in stiffness do not play a role in atherosclerotic plaque progression in Apoe-/- mice. We found that Eln+/-Apoe-/- mice have increased structural arterial stiffness compared to Eln+/+Apoe-/- mice, but they only have increased amounts of ascending aortic plaque on ND, not WD. The results suggest a change in atherosclerosis progression but

not end stage disease in Eln+/-Apoe-/- mice due to increased arterial stiffness. Possible contributing factors include increased blood pressure and changes in circulating levels of interleukin-6 (IL6) and transforming growth factor beta 1 that are also associated with Eln+/- genotype.

[29] *Sperlongano S, Gragnano F, Natale F et al.* **Lomitapide in homozygous familial hypercholesterolemia: cardiology perspective from a single-center experience**. Journal of cardiovascular medicine (Hagerstown, Md.) 2018; 19:83-90.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29389816

ABSTRACT

AIMS: Homozygous familial hypercholesterolemia (HoFH) is a genetic dyslipidemia characterized by elevated levels of low-density lipoprotein cholesterol (LDL-C) and accelerated atherosclerosis. Frequently, traditional lipid-lowering therapy is ineffective in these patients, and lipoprotein apheresis is required. Lomitapide has been recently approved for HoFH. We reported our experience in HoFH patients treated with lomitapide, evaluating its efficacy and safety profile. METHODS: Probands suspected for familial hypercholesterolemia were extrapolated from the registry of patients admitted to our cardiology department. Dutch Lipid Clinic Network (DLCN) criteria were adopted to diagnose familial hypercholesterolemia clinically. Individuals receiving a definite or probable diagnosis of familial hypercholesterolemia underwent family cascade screening and genetic test. Patients with a genetic diagnosis of HoFH were treated with lomitapide and monitored with serial follow-up visits. RESULTS: Within 1 year of screening, from a population of 3250 patients admitted to our cardiology department, seven probands were selected with a DLCN score greater than 5. A total of two patients resulted genetically homozygotes for familial hypercholesterolemia and started lomitapide. A marked reduction in LDL-C occurred in both patients on lomitapide (78% reduction in patient 1 and 86% in patient 2 already on lipoprotein apheresis, compared with baseline LDL-C), allowing the apheresis treatment to be stopped in the second case. Lomitapide was well tolerated, and both patients experienced only mild gastrointestinal events. CONCLUSION: Lomitapide is an effective and well tolerated cholesterol-lowering drug approved for the treatment of HoFH patients. It would be useful to administer it early in these patients to reduce LDL-C and avoid the development of fatal cardiovascular complications.

[30] *Chu F, Wang M, Ma H, Zhu J*. **Simvastatin Modulates Interaction Between Vascular Smooth Muscle Cell / Macrophage and TNF-alpha-activated Endothelial Cell**. Journal of cardiovascular pharmacology 2018.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29389739

ABSTRACT

Cellular interactions between Endothelial Cell (EC) and Vascular Smooth Muscle Cell (VSMC) /macrophages appear to be greatly changed under inflammatory conditions. Simvastatin could regulate inflammatory transcription factors in EC and VSMC and also could inhibit leukocyte-endothelium interaction, whether it could modulate VSMC/macrophage functions which induced by TNF-alpha-activated EC remained unclear. The purpose of this study was to investigate the effects of simvastatin on VSMC/macrophage functions which induced by TNF-alpha-activated EC in co-culture system in vitro. The results showed that under non-contacting conditions, simvastatin could reduce the proliferation, apoptosis and TNF-alpha, IL-6 and VEGF secretion both in VSMC and macrophage which induced by TNF-alpha-activated EC. And a hypothesis that regulating interactions and the soluble factors between EC

and VSMC/macrophages might be a potential mechanism of simvastatin anti-atherosclerosis could be draw.

[31] *Lee J, Kil J, Kim DW, Kang SD*. **Usefulness of Plaque Magnetic Resonance Imaging in Identifying High-Risk Carotid Plaques Irrespective of the Degree of Stenosis**. Journal of cerebrovascular and endovascular neurosurgery 2017; 19:291-300.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29387630

ABSTRACT

Objective: Measurement of the degree of stenosis is not enough to decide on the treatment strategy for patients with carotid stenosis. Plaque morphology examination is needed for such a decision-making. Thus, we evaluated the usefulness of plaque magnetic resonance imaging (MRI) to decide on the modality of treatment for patients with carotid atherosclerotic plaques. Materials and Methods: Fifteen patients presenting with carotid stenosis between 2014 and 2016 were included. They underwent angiography for measurement of the degree of stenosis. Carotid plaques were visualized using MRI. Results: There were six (40%) stable and nine (60%) unstable plaques. Seven symptomatic patients (77.7%) had unstable lesions and two symptomatic patients (33.3%) had stable lesions (p = 0.096). There were six (40%) intraplaque hemorrhage (IPH) cases. There were six symptomatic patients (100%) in the IPH group and three symptomatic patients (33.3%) in the non-IPH group (p = 0.013). The mean stenosis degree was 58.9% in the IPH group and 70.4% in the non-IPH group (p = 0.094). Symptoms occurred irrespective of the degree of the stenosis in the IPH groups. In the IPH group, the recurrent ischemic cerebrovascular event rate was 33.3%. Particularly, the recurrent ischemic cerebrovascular event rate was 66.7% in the IPH group with mild stenosis treated with medications. Conclusion: IPH in plaque MRI is significantly associated with ischemic symptoms and has a high risk for subsequent ischemic cerebrovascular events irrespective of the degree of stenosis. Plaque MRI is a useful tool in predicting symptomatic risks for carotid stenosis irrespective of the degree of such stenosis.

[32] *Hartgers ML, Defesche JC, Langslet G et al.* **Alirocumab efficacy in patients with double heterozygous, compound heterozygous, or homozygous familial hypercholesterolemia**. Journal of clinical lipidology 2017.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29396260

ABSTRACT

BACKGROUND: Mutations in the genes for the low-density lipoprotein receptor (LDLR), apolipoprotein B, and proprotein convertase subtilisin/kexin type 9 have been reported to cause heterozygous and homozygous familial hypercholesterolemia (FH). OBJECTIVE: The objective is to examine the influence of double heterozygous, compound heterozygous, or homozygous mutations underlying FH on the efficacy of alirocumab. METHODS: Patients from 6 alirocumab trials with elevated low-density lipoprotein cholesterol (LDL-C) and FH diagnosis were sequenced for mutations in the LDLR, apolipoprotein B, proprotein convertase subtilisin/kexin type 9, LDLR adaptor protein 1 (LDLRAP1), and signal-transducing adaptor protein 1 genes. The efficacy of alirocumab was examined in patients who had double heterozygous, compound heterozygous, or homozygous mutations. RESULTS: Of 1191 patients sequenced, 20 patients were double heterozygotes (n = 7), compound heterozygotes (n = 10), or homozygotes (n = 3). Mean baseline LDL-C levels were similar between patients treated with alirocumab (n = 11; 198 mg/dL) vs placebo (n = 9; 189 mg/dL). All patients treated with alirocumab 75/150 or 150

mg every 2 weeks had an LDL-C reduction of >/=15% at either week 12 or 24. At week 12, 1 patient had an increase of 7.1% in LDL-C, whereas in others, LDL-C was reduced by 21.7% to 63.9% (corresponding to 39-114 mg/dL absolute reduction from baseline). At week 24, LDL-C was reduced in all patients by 8.8% to 65.1% (10-165 mg/dL absolute reduction from baseline). Alirocumab was generally well tolerated in the 6 trials. CONCLUSION: Clinically meaningful LDL-C-lowering activity was observed in patients receiving alirocumab who were double heterozygous, compound heterozygous, or homozygous for genes that are causative for FH.

[33] *Khokhar B, Simoni-Wastila L, Slejko JF et al.* **Mortality and Associated Morbidities Following Traumatic Brain Injury in Older Medicare Statin Users**. The Journal of head trauma rehabilitation 2018.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29385012

ABSTRACT

OBJECTIVE: To assess the relationship between posttraumatic brain injury statin use and (1) mortality and (2) the incidence of associated morbidities, including stroke, depression, and Alzheimer's disease and related dementias following injury. SETTING AND PARTICIPANTS: Nested cohort of all Medicare beneficiaries 65 years of age and older who survived a traumatic brain injury (TBI) hospitalization during 2006 through 2010. The final sample comprised 100 515 beneficiaries. DESIGN: Retrospective cohort study of older Medicare beneficiaries. Relative risks (RR) and 95% confidence interval (CI) were obtained using discrete time analysis and generalized estimating equations. MEASURES: The exposure of interest included monthly atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, and simvastatin use. Outcomes of interest included mortality, stroke, depression, and Alzheimer's disease and related dementias. RESULTS: Statin use of any kind was associated with decreased mortality following TBI hospitalization discharge. Any statin use was also associated with a decrease in any stroke (RR, 0.86; 95% confidence intervals (CI), 0.81-0.91), depression (RR, 0.85; 95% CI, 0.79-0.90), and Alzheimer's disease and related dementias (RR, 0.77; 95% CI, 0.73-0.81). CONCLUSION: These findings provide valuable information for clinicians treating older adults with TBI as clinicians can consider, when appropriate, atorvastatin and simvastatin to older adults with TBI in order to decrease mortality and associated morbidities.

[34] *Alcivar-Franco D, Purvis S, Penn MS, Klemes A*. **Knowledge of an inflammatory biomarker of cardiovascular risk leads to biomarker-based decreased risk in pre-diabetic and diabetic patients**. J Int Med Res 2018:300060517749111.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29383972

ABSTRACT

Objective Diabetes is a risk equivalent for cardiovascular events. The increase in vascular inflammation with diabetes is believed to be responsible for increased risk of ischemic events in diabetic patients. Our goal was to assess whether knowledge of vascular inflammation alters cardiovascular risk over time, and how knowledge of vascular inflammation changes risk in non-diabetic, pre-diabetic and diabetic patients. Methods We retrospectively studied >100,000 primary-care patients per annum for 5 years (baseline in 2011 through 2015) with tests including lipoprotein profile, hemoglobin A1C and the vascular-specific inflammation risk marker myeloperoxidase. Results were obtained during the patient's MD Value In Prevention (MDVIP) annual wellness program physical. Results We show that rates of patients with elevated myeloperoxidase levels were reduced from 14.4%, 15.2% and 21.3% to 4.0%,

4.0% and 6.7% in non-diabetic, pre-diabetic and diabetic patients, respectively, over the 5-year period. Decreases in vascular inflammation were achieved without decreases in the prevalence of pre-diabetes (hemoglobin A1C 5.7%-6.4%) or diabetes (hemoglobin A1C >6.4%) and were observed in patients below or above guideline low-density lipoprotein targets. Conclusions These data demonstrate that physicians informed of elevated markers of vascular inflammation can lower vascular inflammation correlating with biomarker-based decreased risk of cardiovascular events.

[35] *Wang H, Chen J, Zhao L*. **N-3 polyunsaturated fatty acids for prevention of postoperative atrial fibrillation: updated meta-analysis and systematic review**. Journal of interventional cardiac electrophysiology : an international journal of arrhythmias and pacing 2018.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29380237

ABSTRACT

BACKGROUND OR PURPOSE: N-3 polyunsaturated fatty acids (PUFA) have been postulated to have an anti-arrhythmic effect on postoperative atrial fibrillation (POAF), with conflicting results among studies. This study on pooled data evaluated the effect of PUFA on POAF among patients undergoing cardiac surgery. METHODS: The Pubmed, EMBASE, and CENTRAL databases were searched without restriction on language for randomized controlled trials on the effect of PUFA on POAF that were published before August 31, 2017. The incidence of POAF was extracted as primary endpoint. Pooled data were assessed by using a random-effects model. RESULTS: Out of 269 articles identified, 14 studies with 3570 patients were eligible and included in the meta-analysis. PUFA reduced incidence of POAF (RR 0.84 [95% CI 0.73-0.98], P = 0.03). The funnel plot and fail-safe number suggested insignificant publication bias. In sensitivity and subgroup analyses, (1) PUFA was effective in preventing POAF for eicosapentaenoic acid (EPA)/DHA < 1 (0.51 [0.36-0.73], P = 0.0003) but not EPA/DHA > 1 or unknown; (2) the efficacy in reducing POAF was apparent when placebo was usual care (0.59 [0.44-0.80], P = 0.0005), but not when placebo was non-fish oils; and (3) PUFA reduced POAF after CABG (0.68 [0.47-0.97], P = 0.03), but not other cardiac surgery. CONCLUSIONS: PUFA appears to reduce the incidence of POAF. However, the said protective effect may be influenced by EPA/DHA ratio, with < 1 appearing preferable. PUFA efficacy on POAF prevention appeared insignificant when compared with non-fish oils and only apparent in the setting of CABG alone. Further studies are needed to confirm the effect of PUFA on POAF and to assess the proper use of PUFA against POAF.

[36] *Guo K, Hu L, Xi D et al.* **PSRC1 overexpression attenuates atherosclerosis progression in apoE(-/-) mice by modulating cholesterol transportation and inflammation**. Journal of molecular and cellular cardiology 2018; 116:69-80.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29378206

ABSTRACT

AIMS: Human genome-wide association studies (GWAS) have found that proline/serine-rich coiled-coil 1 (PSRC1) encodes a protein that is associated with serum lipid levels and coronary artery disease. In addition, our previous study showed that the cholesterol efflux capacity is decreased in macrophages following a treatment silencing Psrc1, indicating that PSRC1 has anti-atherosclerotic effects. However, the role of PSRC1 in the development of atherosclerosis is unknown. This study aims to explore the effect of PSRC1 on atherosclerosis and its underlying mechanisms. METHOD AND RESULTS: A recombinant adenovirus expressing Psrc1 (Ad-PSRC1) was constructed and transfected in RAW264.7

cells as well as injected intravenously into apoE(-/-) mice. The in vitro study showed that PSRC1 overexpression reduced the cellular cholesterol content, increased the cholesterol efflux capacity and inhibited foam cell formation by upregulating the expression of peroxisome proliferator-activated receptor gamma (PPAR-gamma) and liver X receptor alpha (LXR-alpha), which are key cholesterol transportation-related proteins. Infecting apoE(-/-) mice with Ad-PSRC1 inhibited the development of atherosclerotic lesions and enhanced atherosclerotic plaque stability. Consistent with these results, PSRC1 overexpression in apoE(-/-) mice decreased the plasma levels of TC, TG, LDL-C, TNF-alpha, IL-1beta and IL-6, increased the plasma HDL-C levels and improved HDL function. Similarly, the PPAR-gamma and LXR-alpha expression levels were upregulated in the liver and in peritoneal macrophages of PSRC1-overexpressing apoE(-/-) mice. Finally, the liver and peritoneal macrophages of apoE(-/-) mice displayed elevated expression of beta-catenin, which is a direct downstream gene of PSRC1 and an upstream gene of PPAR-gamma and LXR-alpha, but decreased activity of nuclear transcription factor (NF-kappaB), which acts as a key gene in the regulation of inflammation. CONCLUSIONS: PSRC1 protects against the development of atherosclerosis and enhances the stability of plaques by modulating cholesterol transportation and inflammation in macrophages and the liver of apoE(-/-) mice.

[37] *Katz ML, Guo Z, Laffel LM*. **Management of Hypertension and High Low-Density Lipoprotein in Pediatric Type 1 Diabetes**. J Pediatr 2018.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29395184

ABSTRACT

OBJECTIVE: To evaluate hypertension and hyperlipidemia management patterns in youth with type 1 diabetes and to assess perceived effectiveness of management strategies and barriers to management. STUDY DESIGN: An electronic survey, including clinical scenarios, fielded to pediatric providers (members of the American Diabetes Association Diabetes in Youth Interest Group, Pediatric Endocrine Society, or T1D Exchange). RESULTS: Respondents (N = 207, 86% MDs, 68% female) were practicing clinicians for youth with type 1 diabetes. As an initial recommendation, the overwhelming majority of respondents (83%-99%) endorsed lifestyle and nonmedical recommendations (eg, improve glycemic control) for hypertension and hyperlipidemia. Yet, few (6%-17%) reported these recommendations as effective. Many respondents (57%) reported referring to another specialist for hypertension, whereas few (8%) reported referring to another specialist for hyperlipidemia management. Approximately one-fifth (21%) of respondents never initiate antihypertensive medications, whereas only 8% never initiate lipid-lowering medication. Among prescribers, the majority of respondents only started antihypertensive or lipid-lowering medications after persistent elevations and in the setting of either ineffective lifestyle or nonmedical interventions or additional cardiovascular risk factors. More than two-thirds of respondents endorsed medications as often effective for hypertension and hyperlipidemia (68% and 69%, respectively). CONCLUSIONS: Pediatric diabetes providers commonly defer prescribing antihypertensive and lipid-lowering medications until nonmedication interventions have been ineffective. Most providers describe medications, but not lifestyle interventions, as often effective. Efforts to align clinical practice with clinical guidelines are needed.

[38] *Zhang J, Wang H, Yang S, Wang X*. **Comparison of lipid profiles and inflammation in pre- and post-menopausal women with cerebral infarction and the role of atorvastatin in such populations**. Lipids in health and disease 2018; 17:20.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29391065

ABSTRACT

BACKGROUND: The risks of atherosclerotic cardiovascular and cerebrovascular diseases in women rapidly increase with age in post-menopausal women. We aimed to investigate the lipid profiles in peri-menopausal women with cerebral infarction and to explore the effects of atorvastatin intervention. METHODS: We collected women aged 40-60 with cerebral infarction between January 2013 and December 2016. Atorvastatin was applied for 6 months in all included patients. Blood lipid profiles, serum pro-inflammation cytokines, intracranial plaque and NIH stroke scale (NIHSS) scores were evaluated before and after atorvastatin treatment. RESULTS: Totally 210 patients were included. Before atorvastatin treatment, post-menopausal patients had significantly higher levels of triglyceride, cholesterol, low-density lipoprotein and a reduced level of high-density lipoprotein than those in pre-menopausal patients. Blood levels of pro-inflammatory cytokines including interleukin (IL)-1, IL-6 and tumor necrosis factor-alpha were higher in post-menopausal patients, who had larger intracranial plaques than pre-menopausal patients. Consistently, post-menopausal patients had higher NIHSS scores than pre-menopausal ones. Atorvastatin reduced NIHSS scores and improved dyslipidemia in patients and eliminated the differences of these parameters between pre- and post-menopausal patients. CONCLUSIONS: Post-menopausal patients were severer than pre-menopausal patients in terms of dyslipidemia, systemic inflammation and NIHSS scores. Atorvastatin may be beneficial for women with cerebral infarction.

[39] *Marginean CO, Melit LE, Dobreanu M, Marginean MO*. **Type V hypertriglyceridemia in children, a therapeutic challenge in pediatrics: A case report and a review of the literature**. Medicine (Baltimore) 2017; 96:e8864.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29390422

ABSTRACT

RATIONALE: Hypertriglyceridemia is defined as a level of triglycerides above 150 mg/dL. The complex causes and classification of hypertriglyceridemia lead to difficulties in the diagnosis and management of this condition. PATIENT CONCERNS: We present the case of a 15 years and 6 months old female teenager, admitted in our clinic for the following complaints: severe abdominal pain predominantly in the lateral left quadrant, nausea, vomiting, and the lack of stools for 2 days. The clinical exam showed: impaired general status, painful abdomen at superficial and deep palpation in the left and upper abdominal quadrants, the absence of stools for 2 days. DIAGNOSES: The laboratory parameters revealed leukocytosis with neutrophilia, thrombocytopenia, high level of serum amylase and triglycerides, and increased inflammatory biomarkers. The imagistic investigations showed ascites and paralytic ileus. INTERVENTIONS: The management was burdened by the side-effects of hypolipidemic drugs impairing the liver function and leading to rhabdomyolysis, but eventually the patient's outcome was good. OUTCOMES: Type V hyperlipoproteinemia is a rare condition accounting for approximately 5% of the cases. The risk for acute pancreatitis is well-known to be associated with hypertriglyceridemia, even though in rare cases. LESSONS: The prognosis of hypertriglyceridemia is pediatrics is burdened not only by the long-term risk factors associated to the diseases itself, but also by the negative effects of long-term hypolipidemic treatment.

[40] *Zhang Y, Liu S, Yue W et al.* **Association of apolipoprotein E genotype with outcome in hospitalized ischemic stroke patients**. Medicine (Baltimore) 2017; 96:e8964.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29390290

ABSTRACT

The aim of this study was to study the ability of the genotype to predict impairment and disability in hospitalized ischemic stroke (IS) patients after hospital discharge and 6 months after the onset of stroke symptoms.A total of 786 patients with a first IS were enrolled. Apolipoprotein E (ApoE) polymorphism was examined using polymerase chain reaction. Stroke subtype was classified using the Oxfordshire Community Stroke Project classification scheme and the Trial of Org 10172 in Acute Stroke Treatment criteria. Impairment as assessed using the National Institutes of Health Stroke Scale (NIHSS), and disability as measured using the modified Rankin Scale (mRS), were compared against the ApoE genotype.There was no significant association between the type of ApoE allele present and the stroke subtype. On multivariate regression analysis, the apolipoprotein EE4 allele genotype did not predict poor outcome at discharge and or at 6 months after stroke onset. A higher NIHSS score on admission, older age, and higher fasting glucose levels did predict poor outcome at hospital discharge. Higher glucose levels and higher NIHSS scores on admission were independent risk factors predicting poor neurologic status at 6 months after stroke onset.The presence of the apolipoprotein EE4 and apolipoprotein EE2 genotypes, although related to cholesterol and triglyceride levels, do not affect recovery during rehabilitation. A higher NIHSS score on admission and a higher fasting glucose level predict poor neurologic status, both at hospital discharge and 6 months after onset.

[41] *Zhao C, Zhu P, Shen Q, Jin L*. **Prospective association of a genetic risk score with major adverse cardiovascular events in patients with coronary artery disease**. Medicine (Baltimore) 2017; 96:e9473.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29390587

ABSTRACT

Many susceptibility loci associated with coronary artery disease (CAD) have been identified using genome-wide association studies (GWAS). This study aimed to examine whether a composite of single nucleotide polymorphisms (SNPs) derived from GWAS could identify the risk of major adverse cardiovascular events (MACEs) in patients with established CAD. There were 1059 patients with CAD were included in the analysis. Of the participants, 686 were on statin treatment at the start of follow-up. A weighted genetic risk score (wGRS) was calculated as the sum of risk alleles multiplied by the hazard ratio for a particular SNP. In single variant analyses, rs579459, rs4420638, and rs2107595 were associated with an increased risk of MACE. A wGRS was further constructed to evaluate the cumulative effect of the 3 SNPs on the prognosis of CAD. The risk of MACE among patients with high and intermediate wGRS was 1.968- and 1.838-fold, respectively, higher than those with low wGRS. This effect was more evident in patients using lipid-lowering medication and with hypertension. Furthermore, the interaction analysis revealed that lipid-lowering medication and hypertension interacted with the genetic effect off wGRS on the risk of MACE in patients using lipid-lowering medication or with hypertension (Pinteraction < .001). We further analyzed the follow-up change in low-density lipoprotein cholesterol (LDL-C) level at 6 months after CAD disclosure and evaluated whether that was due to wGRS or statin use. The lowest reduction in LDL-C was observed in patients with high GRS who received statin treatment. Furthermore, LDL-C reduction of patients with intermediate wGRS was less than those with low wGRS in patients treated with statin. Taken together, a wGRS comprised of SNPs significantly predicts MACE in CAD patients receiving statin treatment and hypertension.

Literature update week 05 (2018)

[42] *Mbikay M, Mayne J, Sirois F et al.* **Mice Fed a High-Cholesterol Diet Supplemented with Quercetin-3-Glucoside Show Attenuated Hyperlipidemia and Hyperinsulinemia Associated with Differential Regulation of PCSK9 and LDLR in their Liver and Pancreas**. Molecular nutrition & food research 2018.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29396908

ABSTRACT

SCOPE: Hepatic LDL receptor (LDLR) and proprotein convertase subtilisin/kexin type 9 (PCSK9) regulate the clearance of plasma LDL-cholesterol (LDL-C): LDLR promotes it, and PCSK9 opposes it. These proteins also expressed in pancreatic beta cells. Using cultured hepatocytes, we previously showed that the plant flavonoid quercetin-3-glucoside (Q3G) inhibited PCSK9 secretion, stimulated LDLR expression, and enhanced LDL-C uptake. Here, we examined whether Q3G supplementation could reverse the hyperlipidemia and hyperinsulinemia of mice fed a high-cholesterol diet, and how it affected hepatic and pancreatic LDLR and PCSK9 expression. METHODS AND RESULTS: For 12 weeks, mice were fed a low- (0%) or high- (1%) cholesterol diet (LCD or HCD), supplemented or not with Q3G at 0.05% or 0.1% (w/w). Tissue LDLR and PCSK9 was analyzed by immunoblotting; plasma PCSK9 and insulin, by ELISA; plasma cholesterol and glucose, by colorimetry. In LCD-fed mice, Q3G had no effect. In HCD-fed mice, it attenuated the increase in plasma cholesterol and insulin, accentuated the decrease in plasma PCSK9, and increased hepatic and pancreatic LDLR and PCSK9. In cultured pancreatic beta cells, however, it stimulated PCSK9 secretion. CONCLUSION: In mice, dietary Q3G could counter HCD-induced hyperlipidemia and hyperinsulinemia, in part by oppositely modulating hepatic and pancreatic PCSK9 secretion.

[43] *Jiang C, Zhao Y, Yang Y et al.* **Evaluation of the Combined Effect of Recombinant High-Density Lipoprotein Carrier and the Encapsulated Lovastatin in RAW264.7 Macrophage Cells Based on the Median-Effect Principle**. Molecular pharmaceutics 2018.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29382194

ABSTRACT

Recombinant high-density lipoprotein (rHDL) displays a similar anti-atherosclerotic effect with native HDL and could also be served as a carrier of cardiovascular drug for atherosclerotic plaque targeting. In our previous studies, rHDL has shown a more potent anti-atherosclerotic efficacy as compared to the other conventional nanoparticles with a payload of lovastatin (LS). Therefore, we hypothesized that a synergistic anti-atherosclerotic effect of the rHDL carrier and the encapsulated LS might exist. In this study, the dose-effect relationships and the combined effect of the rHDL and LS were quantitatively evaluated in RAW 264.7 macrophage cells using the median-effect analysis, in which the rHDL carrier was regarded as a drug combined. Median-effect analysis suggested that rHDL and LS exerted a desirable synergistic inhibition on the oxLDL internalization at a ratio of 6:1 (Dm,LS:Dm,rHDL) in RAW 264.7 macrophage cells. About 50% of the reduction on the intracellular lipid contents was found when RAW264.7 cells were treated with LS-loaded rHDLs at their respective median-effect dose (Dm) concentrations and a synergistic effect on the mediating cholesterol efflux was also observed, which verified the accuracy of the results obtained from the median-effect analysis. The mechanism underlying the synergistic effect of the rHDL carrier and the drug might be attributed to their potent inhibitory effects on SR-A expression. In conclusion, the median-effect analysis was proven to be a feasible method to quantitatively evaluate the synergistic effect of the biofunctional carrier and the drug encapsulated.

Literature update week 05 (2018)

[44] *Jamilian M, Samimi M, Mirhosseini N et al.* **A Randomized Double-Blinded, Placebo-Controlled Trial Investigating the Effect of Fish Oil Supplementation on Gene Expression Related to Insulin Action, Blood Lipids, and Inflammation in Gestational Diabetes Mellitus-Fish Oil Supplementation and Gestational Diabetes**. Nutrients 2018; 10.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29385062

ABSTRACT

Gestational diabetes mellitus (GDM) is a common complication of pregnancy, and it is mostly associated with postpartum diabetes, insulin resistance, and dyslipidemia. Fish oil (omega-3) supplementation has been shown to reduce the risk of different chronic diseases such as cardiovascular disease, type 2 diabetes, and cancers, though the evidence of its impact on gestational diabetes is scarce. Our goal in this study was to determine the effect of fish oil administration on gene expression related to insulin action, blood lipids, and inflammation in women with GDM. Participants with GDM (n = 40), aged 18-40 years, were randomized to take either 1000 mg fish oil capsules, containing 180 mg eicosapentaenoic acid and 120 mg docosahexaenoic acid (n = 20), or placebo (n = 20) twice a day for 6 weeks. Gene expression related to insulin, lipids, and inflammation was quantified in peripheral blood mononuclear cells (PBMCs) of GDM women using Reverse Transcription Polymerase Chain Reaction (RT-PCR) method. Results of RT-PCR indicated that omega-3 supplementation upregulated gene expression of peroxisome proliferator-activated receptor gamma (PPAR-gamma) ($P = 0.04$) in PBMCs of patients with GDM, compared with the placebo. In addition, gene expression of the low-density lipoprotein receptor (LDLR) ($P < 0.001$), interleukin-1 (IL-1) ($P = 0.007$), and tumor necrosis factor alpha (TNF-alpha) ($P = 0.01$) was downregulated in PBMCs of women with GDM, following omega-3 supplementation. No significant effect of omega-3 supplementation was indicated on gene expression of IL-8 in PBMCs of patients with GDM. Overall, fish oil supplementation for 6 weeks in women with GDM significantly improved gene expression of PPAR-gamma, IL-1, and TNF-alpha, but not gene expression of IL-8.

[45] *Jonsson BH*. **Nicotinic Acid Long-Term Effectiveness in a Patient with Bipolar Type II Disorder: A Case of Vitamin Dependency**. Nutrients 2018; 10.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29382049

ABSTRACT

Nicotinic acid (NA), often called niacin, a form of vitamin B(3), is a water-soluble nutrient found in animal and vegetarian foods. Vitamin B(3) for healthy people is considered to be needed in doses of less than 20 mg daily. In higher doses, NA has been described to be beneficial in some patients with psychiatric disorders. This report describes a male patient with bipolar type II disorder who for many years had been treated with lithium and other medications applied in affective disorders. These pharmacological drugs had beneficial effects but were at times insufficient. When the patient was prescribed NA, he experienced a comparatively strong effect. Slowly it was discovered that the patient could lower and cease all medications except NA. For over 11 years he has been stable and calm with NA and currently takes 1 g three times daily. When not taking NA, he consistently became anxious and depressed within 2-3 days. The resumption of NA resulted in a normal state usually within 1 day. This finding has been described as a vitamin dependency. The paper discusses possible mechanisms for the effect of NA in this patient. Further studies are needed to investigate the prevalence of vitamin B(3) dependency and the biochemical explanations for this phenomenon.

Literature update week 05 (2018)

[46] *Xu J, Xia Z, Rong S et al.* **Yirui Capsules Alleviate Atherosclerosis by Improving the Lipid Profile and Reducing Inflammation in Apolipoprotein E-Deficient Mice**. Nutrients 2018; 10.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29382111

ABSTRACT

Atherosclerosis (AS) is the main cause of cardiovascular diseases. This study investigated Yirui (YR) capsules, whose ingredients are available in health food stores, against AS and the underlying mechanisms. Male apolipoprotein E-deficient mice fed a high-fat diet for 10 weeks developed severe aortic lesions, but YR significantly decreased the plaque area in the total aorta and aortic root. YR affected the serum lipid profile by significantly reducing total cholesterol, low-density lipoprotein cholesterol (LDL-C), triglyceride (TG), and oxidative modification of LDL-C (Ox-LDL) levels. In addition, multi-cytokine analysis revealed that higher serum levels of interleukin-1 alpha (IL-1alpha), interleukin-1 beta (IL-1beta), interleukin-3 (IL-3), interleukin-6 (IL-6), interleukin-27 (IL-27), tumor necrosis factor alpha, interferon gamma, and regulated on activation, normal T cell expressed and secreted (RANTES), which were induced by a high-fat diet, declined with YR treatment. These results suggest that YR reduces the atherosclerotic plaque burden, thereby alleviating AS by modulating the lipid profile and inhibiting inflammation.

[47] *Lieb W, Enserro DM, Larson MG, Vasan RS*. **Residual cardiovascular risk in individuals on lipid-lowering treatment: quantifying absolute and relative risk in the community**. Open heart 2018; 5:e000722.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29387429

ABSTRACT

Objective: The residual cardiovascular disease (CVD) risk in individuals on long-term lipid-lowering treatment (LLT) in the general population is not well described. Methods: We estimated absolute CVD risks by age and sex for different categories of low-density lipoprotein cholesterol (LDL-C) levels, stratified by LLT status, and assessed subclinical carotid atherosclerosis in 3012 Framingham Study participants (mean age, 58.4 years; 55% women) free of CVD. Individuals were categorised into five groups: (1) LDL-C <100 mg/dL without LLT; (2) LDL-C >/=100 mg/dL to <130 mg/dL without LLT; (3) LDL-C <130 mg/dL on LLT; (4) LDL-C >/=130 mg/dL without LLT; and (5) LDL-C >/=130 mg/dL on LLT. Results: Individuals in groups 3-5 had significantly more carotid atherosclerosis compared with group 1. During follow-up (median, 13.7 years), 548 CVD events occurred. Individuals on LLT (groups 3 and 5) had substantial residual CVD risk (26.7 (95% CI 19.5 to 34.0) and 24.1 (95% CI 16.2 to 31.9) per 1000 person-years, respectively), representing approximately three times the risk for untreated individuals with LDL <100 mg/dL (group 1: 9.0 (95% CI 6.8 to 11.3) per 1000 person-years). Absolute CVD risks rose with age and were slightly greater in men than in women. After adjustment for traditional risk factors, groups 3-5 displayed increased hazards for CVD (HR=1.47, 1.42 and 1.54, respectively) compared with group 1. Further adjustment for carotid atherosclerosis modestly attenuated these results. Conclusions: There is substantial residual CVD risk in individuals on LLT, compared with participants with optimal LDL-C (<100 mg/dL), even when LDL-C levels <130 mg/dL are reached.

[48] *Di Rocco M, Pisciotta L, Madeo A et al.* **Long term substrate reduction therapy with ezetimibe alone or associated with statins in three adult patients with lysosomal acid lipase deficiency**. Orphanet journal of rare diseases 2018; 13:24.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29374495

ABSTRACT

BACKGROUND: Lysosomal acid lipase deficiency is an autosomal recessive metabolic disease with a wide range of severity from Wolman Disease to Cholesterol Ester Storage Disease. Recently enzyme replacement therapy with sebelipase alpha has been approved by drug agencies for treatment of this lysosomal disease. Ezetimibe is an azetidine derivative which blocks Niemann Pick C1-Like 1 Protein; as its consequence, plasmatic concentration of low density lipoproteins and other apoB-containing lipoproteins, that are the substrate of lysosomal acid lipase, are decreased. Furthermore, ezetimibe acts by blocking inflammasome activation which is the cause of liver fibrosis in steatohepatitis and in lysosomal storage diseases. RESULTS: Two patients with Cholesterol Ester Storage Disease were treated with ezetimibe for 9 years and a third patients for 10 years. Treatment was supplemented with low dose of atorvastatin in the first two patients during the last 6 years. All patients showed a significant reduction of alanine aminotransferase, cholesterol and triglyceride. Furthermore, no progression of liver fibrosis was demonstrated. CONCLUSION: In this observational case series, ezetimibe is effective, safe, and sustainable treatment for lysosomal acid lipase deficiency. Further studies are warranted to demonstrate that ezetimibe is an alternative therapy to enzyme replacement therapy.

[49] *Muhlbacher AC, Sadler A, Dippel FW, Juhnke C*. **Treatment Preferences in Germany Differ Among Apheresis Patients with Severe Hypercholesterolemia**. PharmacoEconomics 2018.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29388056

ABSTRACT

BACKGROUND: Severe hypercholesterolemia is a major risk factor of death in patients with coronary heart disease. New adjunctive drug therapies (proprotein convertase subtilisin/kexin type 9 [PCSK9] inhibitors) have gained approval in Europe and the USA. OBJECTIVE: In this empirical study, we documented preferences regarding adjuvant drug therapy in apheresis-treated patients with severe familial hypercholesterolemia. METHODS: We conducted a systematic literature search to identify patient-relevant outcomes in patients with severe hypercholesterolemia currently undergoing apheresis. Data were used to generate a semi-structured qualitative interview that enabled seven patient-relevant characteristics with three levels each to be identified. For the discrete choice experiment, an experimental design (7 x 3) was generated using NGene Software that consisted of 96 choices divided into eight blocks. The survey was conducted between November 2015 and April 2016 using computer-assisted personal interviews. RESULTS: The survey was completed by 348 patients (64.9% male). The random parameter logit estimation showed predominance for the attribute 'reduction of LDL-C (low-density lipoprotein cholesterol) level'. 'Risk of myopathy' and 'frequency of apheresis' dominated next. Within the random parameter logit estimation, all coefficients were significant (P </= 0.01). The latent class analysis identified three patient groups. The first group (126 patients) found 'reduction of LDL-C level in blood' to be most important. This group focused solely on this treatment outcome independently of apheresis frequency or additional injections. The second group (106 patients) focused on three attributes: 'frequency of apheresis', 'risk of myopathy', and 'reduction of LDL-C level in blood'. Respondents clearly considered a high frequency of apheresis to have a negative impact. The third group (116 patients) demonstrated the highest preference for apheresis. These patients have adjusted to apheresis for > 10 years. CONCLUSION: Regarding patient preference, clinical efficacy seems to dominate. Hence, 'reduction of LDC-C in blood' was ranked highest above patient-relevant modes of administration and adverse effects. In the patient groups identified, reduction

of apheresis was important for only a subsegment (30%) of patients. Another 30% wanted effective LDL-C reduction by whatever means necessary. Most strikingly, another 30% preferred higher frequencies of apheresis.

[50] *Copeland LA, Swendsen CS, Sears DM et al.* **Association between triglyceride levels and cardiovascular disease in patients with acute pancreatitis**. PloS one 2018; 13:e0179998.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29381696

ABSTRACT

Conventional wisdom supports prescribing "fibrates before statins", that is, prioritizing treatment of hypertriglyceridemia (hTG) to prevent pancreatitis ahead of low-density lipoprotein cholesterol to prevent coronary heart disease. The relationship between hTG and acute pancreatitis, however, may not support this approach to clinical management. This study analyzed administrative data from the Veterans Health Administration for evidence of (1) temporal association between assessed triglycerides level and days to acute pancreatitis admission; (2) association between hTG and outcomes in the year after hospitalization for acute pancreatitis; (3) relative rates of prescription of fibrates vs statins in patients with acute pancreatitis; (4) association of prescription of fibrates alone versus fibrates with statins or statins alone with rates of adverse outcomes after hospitalization for acute pancreatitis. Only modest association was found between above-normal or extremely high triglycerides and time until acute pancreatitis. CHD/MI/stroke occurred in 23% in the year following AP, supporting cardiovascular risk management. Fibrates were prescribed less often than statins, defying conventional wisdom, but the high rates of cardiovascular events in the year following AP support a clinical focus on reducing cardiovascular risk factors.

[51] *Elbitar S, Susan-Resiga D, Ghaleb Y et al.* **New Sequencing technologies help revealing unexpected mutations in Autosomal Dominant Hypercholesterolemia**. Scientific reports 2018; 8:1943.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29386597

ABSTRACT

Autosomal dominant hypercholesterolemia (ADH) is characterized by elevated LDL-C levels leading to coronary heart disease. Four genes are implicated in ADH: LDLR, APOB, PCSK9 and APOE. Our aim was to identify new mutations in known genes, or in new genes implicated in ADH. Thirteen French families with ADH were recruited and studied by exome sequencing after exclusion, in their probands, of mutations in the LDLR, PCSK9 and APOE genes and fragments of exons 26 and 29 of APOB gene. We identified in one family a p.Arg50Gln mutation in the APOB gene, which occurs in a region not usually associated with ADH. Segregation and in-silico analysis suggested that this mutation is disease causing in the family. We identified in another family with the p.Ala3396Thr mutation of APOB, one patient with a severe phenotype carrying also a mutation in PCSK9: p.Arg96Cys. This is the first compound heterozygote reported with a mutation in APOB and PCSK9. Functional studies proved that the p.Arg96Cys mutation leads to increased LDL receptor degradation. This work shows that Next-Generation Sequencing (exome, genome or targeted sequencing) are powerful tools to find new mutations and identify compound heterozygotes, which will lead to better diagnosis and treatment of ADH.

Literature update week 05 (2018)

[52] *Ricci C, Ruscica M, Camera M et al.* **PCSK9 induces a pro-inflammatory response in macrophages**. Scientific reports 2018; 8:2267.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29396513

ABSTRACT

Intraplaque release of inflammatory cytokines from macrophages is implicated in atherogenesis by inducing the proliferation and migration of media smooth muscle cells (SMCs). PCSK9 is present and released by SMCs within the atherosclerotic plaque but its function is still unknown. In the present study, we tested the hypothesis that PCSK9 could elicit a pro-inflammatory effect on macrophages. THP-1-derived macrophages and human primary macrophages were exposed to different concentrations (0.250 / 2.5 microg/ml) of human recombinant PCSK9 (hPCSK9). After 24 h incubation with 2.5 microg/ml PCSK9, a significant induction of IL-1beta, IL-6, TNF-alpha, CXCL2, and MCP1 mRNA, were observed in both cell types. Co-culture of THP-1 macrophages with HepG2 overexpressing hPCSK9 also showed the induction of TNF-alpha (2.4 +/- 0.5 fold) and IL-1beta (8.6 +/- 1.8 fold) mRNA in macrophages. The effect of hPCSK9 on TNF-alpha mRNA in murine LDLR(-/-) bone marrow macrophages (BMM) was significantly impaired as compared to wild-type BMM (4.3 +/- 1.6 fold vs 31.1 +/- 6.1 fold for LDLR(-/-) and LDLR(+/+), respectively). Finally, a positive correlation between PCSK9 and TNF-alpha plasma levels of healthy adult subjects (males 533, females 537) was observed (B = 8.73, 95%CI 7.54 / 9.93, $p < 0.001$). Taken together, the present study provides evidence of a pro-inflammatory action of PCSK9 on macrophages, mainly dependent by the LDLR.

[53] *Pratchayasakul W, Thongnak LO, Chattipakorn K et al.* **Atorvastatin and insulin equally mitigate brain pathology in diabetic rats**. Toxicology and applied pharmacology 2018; 342:79-85.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29391240

ABSTRACT

Although insulin and atorvastatin have been shown to exert glycemic control and could improve brain function, the effects of atorvastatin or insulin as well as the combination of atorvastatin plus insulin on brain pathology in diabetes mellitus type 1 (T1DM) are unclear. Therefore, this study investigated the effect of atorvastatin, insulin or combined drugs on brain pathology in streptozotocin-induced diabetic rats. Thirty-six male rats were divided into two groups, a control group (n=12) and a diabetic or experimental group (n=24). Diabetic rats were further divided into four groups (n=6/group) and the groups received either a vehicle (normal saline), atorvastatin (10mg/kg/day), insulin (4U/day) or a combination of the drugs for 4weeks. The control group rats were divided into two groups (n=6/group) to receive either just the vehicle or atorvastatin for 4weeks. We found that streptozotocin-induced diabetic rats developed hyperglycemia, showing evidence of increased brain oxidative stress, impaired brain mitochondrial function, increased brain apoptosis, increased tau protein expression, increased phosphorylation of tau protein expression and amyloid beta levels, and decreased dendritic spine density. Although atorvastatin and insulin therapies led to an equal reduction in plasma glucose level in these diabetic rats, the combined drug therapy showed the greatest efficacy in decreasing plasma glucose level. Interestingly, atorvastatin, insulin and the combined drugs equally mitigated brain pathology. Our findings indicate that the combined drug therapy showed the greatest efficacy in improving metabolic parameters. However, atorvastatin, insulin and the combined drug therapy shared a similar efficacy in preventing brain damage in T1DM rats.

Literature update week 05 (2018)

[54] *Serhiyenko VA*. **[Effects of omega-3 polyunsaturated fatty acids on the state of insulin resistance, the content of some pro- and antiinflammatory factors in patients with type 2 diabetes mellitus and cardiovascular autonomic neuropathy]**. Voprosy pitaniia 2015; 84:76-82.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29378101

ABSTRACT

We have investigated the influence of the long-chain omega-3 polyunsaturated fatty acids (omega-3 PUFA) administration on the insulin resistance parameters, levels of high sensitivity C-reactive protein (hsCRP), some pro- and anti-inflammatory cytokines in patients with type 2 diabetes mellitus (T2 DM) and cardiovascular autonomic neuropathy (CAN). The study involved 12 patients with T2 DM without verified cardiovascular diseases (CVD), 36 patients with T2 DM and functional stage of CAN, of median age 50-59 years, disease duration 1-6 years and HbA1c levels - 7.1+/-0.6%. 15 healthy subjects were control group. Screening for CAN, that included five standard cardiovascular tests, was performed. The levels of blood glucose, HbA1c, immunoreactive insulin (IRI), hsCRP, tumor necrosis factor alpha (TNFalpha), interleukin (IL)-6, IL-8 and IL-10 were measured. The index of insulin resistance (HOMA-IR) and TNFalpha/IL-10 ratio were calculated. Patients with T2 DM and CAN were divided into 2 groups: patients of the 1st group (group of comparison, n=15) received standard glucose-lowering therapy; patients of the 2nd group (n=21) received one capsule/day of the omega-3 PUFA (approximately 90% ethyl ester of PUFA (1000 mg), in particular eicosapentaenoic - 460 mg, docosahexaenoic acid - 380 mg and 4 mg alpha-tocopherol acetate) in addition to the standard therapy. The duration of the study was 3 months. Obtained results showed, that development of CAN in patients with T2 DM is accompanied by increase of the IRI (26.6+/-1.73 mcIU/ml, $p<0.001$ - compared to the control; $p1<0.001$ - compared to T2 DM patients without CVD); hsCRP (2.77+/-0.24 mg/l, $p<0.001$, $p1<0,001$); TNFalpha (5.75+/-0.24 pg/ml, $p<0.001$, $p1<0.001$); IL-6 (5.88+/-0.38 pg/ml, $p<0.001$, $p1<0.001$); IL-8 (6.65+/-0.3 pg/ml, $p<0.001$, $p1>0.05$); IL-10 (15.86+/-1.4 pg/ml, $p<0.05$, $p1>0.05$) levels; TNFalpha/IL-10 (44.2+/-3.57%, $p<0.01$, $p1<0.05$) and HOMA-IR. After 3 months of treatment no statistically significant changes ($p>0.05$) of investigated parameters, in particular levels of IRI (-6.8+/-2.0%); hsCRP (-7.2+/-1.63%); TNFalpha (-6.1+/-1.0%); IL-6 (-5.8+/-1.77%); IL-8 (-3.9+/-1.57%); IL-10 (-3.7+/-2.34%); TNFalpha/IL-10 (-0.5+/-2.3%) in patients from the group of comparison were found. The administration of omega-3 PUFA to patients with T2 DM and CAN promoted to the statistically significant decrease in hsCRP (-14.8+/-2.91%, $p<0.05$), TNFalpha (-14.1+/-2.15%, $p<0.01$), IL-6 (-13.5+/-2.7%, $p<0.05$), IL-8 (-9.8+/-2.13%, $p<0.05$), TNFalpha/IL-10 ratio (-34.6+/-1.93%, $p<0.05$); a slighty decrease in the content of the IRI (-10.3+/-1.1%, $p>0.05$), IL-10 (+7.9 +/-6.42%, $p>0.05$), HOMA-IR was observed. Obtained results could witness, that prescription of omega-3 PUFA leads to decrease of the proinflammatory immune response activity and allows to consider omega-3 PUFA as a promising medicine in treatment and/or prevention of CAN in patients with DM 2.