Literature update week 01 (2018)

[1] *Hippe DS, Phan BAP, Sun J et al.* **Lp(a) (Lipoprotein(a)) Levels Predict Progression of Carotid Atherosclerosis in Subjects With Atherosclerotic Cardiovascular Disease on Intensive Lipid Therapy: An Analysis of the AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides: Impact on Global Health Outcomes) Carotid Magnetic Resonance Imaging Substudy**. Arteriosclerosis, thrombosis, and vascular biology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29301785
ABSTRACT
OBJECTIVE: To assess whether Lp(a) (lipoprotein(a)) levels and other lipid levels were predictive of progression of atherosclerosis burden as assessed by carotid magnetic resonance imaging in subjects who have been treated with LDL-C (low-density lipoprotein cholesterol)-lowering therapy and participated in the AIM-HIGH trial (Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides: Impact on Global Health Outcomes). APPROACH AND RESULTS: AIM-HIGH was a randomized, double-blind study of subjects with established vascular disease, elevated triglycerides, and low HDL-C (high-density lipoprotein cholesterol). One hundred fifty-two AIM-HIGH subjects underwent both baseline and 2-year follow-up carotid artery magnetic resonance imaging. Plaque burden was measured by the percent wall volume (%WV) of the carotid artery. Associations between annualized change in %WV with baseline and on-study (1 year) lipid variables were evaluated using multivariate linear regression. P values were adjusted for multiple comparisons. Average %WV at baseline was 41.6+/-6.8% and annualized change in %WV over 2 years ranged from -3.2% to 3.7% per year (mean: 0.2+/-1.1% per year; P=0.032). Increases in %WV were significantly associated with higher baseline Lp(a) (beta=0.34 per 1-SD increase of Lp(a); 95% CI, 0.15-0.52; P<0.001) after adjusting for clinical risk factors and other lipid levels. On-study Lp(a) had a similar positive association with %WV progression (beta=0.33; 95% CI, 0.15-0.52; P<0.001). CONCLUSIONS: Despite intensive lipid therapy, aimed at aggressively lowering LDL-C to <70 mg/dL, carotid atherosclerosis continued to progress as assessed by carotid magnetic resonance imaging and that elevated Lp(a) levels were independent predictors of increases in atherosclerosis burden.

[2] *Leng X, Kinnun JJ, Cavazos AT et al.* **All n-3 PUFA are not the same: MD simulations reveal differences in membrane organization for EPA, DHA and DPA**. Biochimica et biophysica acta 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29305832
ABSTRACT
Eicosapentaenoic (EPA, 20:5), docosahexaenoic (DHA, 22:6) and docosapentaenoic (DPA, 22:5) acids are omega-3 polyunsaturated fatty acids (n-3 PUFA) obtained from dietary consumption of fish oils that potentially alleviate the symptoms of a range of chronic diseases. We focus here on the plasma membrane as a site of action and investigate how they affect molecular organization when taken up into a phospholipid. All atom MD simulations were performed to compare 1-stearoyl-2-eicosapentaenoylphosphatylcholine (EPA-PC, 18:0-20:5PC), 1-stearoyl-2-docosahexaenoylphosphatylcholine (DHA-PC, 18:0-22:6PC), 1-stearoyl-2-docosapentaenoylphosphatylcholine (DPA-PC, 18:0-22:5PC) and, as a monounsaturated control, 1-stearoyl-2-oleoylphosphatidylcholine (OA-PC, 18:0-18:1PC) bilayers. They were run in the absence and presence of 20mol% cholesterol. Multiple double bonds confer high disorder

on all three n-3 PUFA. The different number of double bonds and chain length for each n-3 PUFA moderates the reduction in membrane order exerted (compared to OA-PC, S CD = 0.152). EPA-PC (S CD = 0.131) is most disordered, while DPA-PC (S CD = 0.140) is least disordered. DHA-PC (S CD = 0.139) is, within uncertainty, the same as DPA-PC. Following the addition of cholesterol, order in EPA-PC (S CD = 0.169), DHA-PC (S CD = 0.178) and DPA-PC (S CD = 0.182) is increased less than in OA-PC (S CD = 0.214). The high disorder of n-3 PUFA is responsible, preventing the n-3 PUFA-containing phospholipids from packing as close to the rigid sterol as the monounsaturated control. Our findings establish that EPA, DHA and DPA are not equivalent in their interactions within membranes, which possibly contributes to differences in clinical efficacy.

[3] *Moxon JV, Moran CS, Golledge J*. **Comment on 'Pharmacological inhibition of protein tyrosine phosphatase 1B protects against atherosclerotic plaque formation in the LDLR(-/-) mouse model of atherosclerosis'**. Clinical science (London, England : 1979) 2018; 132:37-38.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29295951
ABSTRACT

[4] *Saxon DR, Rasouli N, Eckel RH*. **Pharmacological Prevention of Cardiovascular Outcomes in Diabetes Mellitus: Established and Emerging Agents**. Drugs 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29305768
ABSTRACT
Cardiovascular disease is a major cause of morbidity and mortality in patients with type 2 diabetes. For this reason, there is a great deal of interest in determining how therapies commonly used to treat patients with diabetes impact cardiovascular outcomes. Results from recently completed cardiovascular outcomes trials of diabetes agents from several medication classes are leading to a sea change in how we think about diabetes treatment. The primary focus of this paper is to review recently completed and ongoing diabetes medication cardiovascular outcomes trials. We also review cardiovascular outcome evidence for other classes of medications commonly used in patients with diabetes (i.e., aspirin, anti-hypertensive agents, lipid-lowering agents, and weight loss medications).

[5] *Zheng-Lin B, Ortiz A*. **Lipid Management in Chronic Kidney Disease: Systematic Review of PCSK9 Targeting**. Drugs 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29299849
ABSTRACT
Cardiovascular disease is the leading cause of death in patients with chronic kidney disease (CKD) and CKD is considered a coronary artery disease risk equivalent. So far, statins have been the mainstay of primary and secondary prevention of cardiovascular disease in the general population. However, their benefit on outcomes is limited and controversial in CKD patients and new therapeutic approaches to reduce cardiovascular risk are needed. Monoclonal antibodies targeting proprotein convertase subtilisin/kexin 9 (PCSK9) reduce low-density lipoprotein cholesterol (LDL-C) and lipoprotein(a) in high-risk populations and cardiovascular events in secondary prevention. We now review the limitations of the current approach to lipid management in CKD and information on CKD patients from clinical trials of anti-PCSK9

monoclonal antibodies alirocumab and evolocumab. In CKD sub-group analysis, ODYSSEY COMBO I and ODYSSEY COMBO II studies demonstrated significant superiority of alirocumab on LDL-cholesterol lowering in comparison to placebo and ezetimibe, respectively, when added to statins, and case reports have shown efficacy in nephrotic syndrome. A detailed analysis of CKD subgroups in general population trials of anti-PCSK9 strategies addressing events is needed, given the limited efficacy of statins in CKD both in terms of lipid lowering and events, the high rate of statin non-compliance in these patients, and the high lipoprotein(a) levels. This information should guide the design of trials addressing the safety profile and efficacy on cardiovascular outcomes of PCSK9-targeted therapies in CKD patients.

[6] *Katsiki N, Kolovou G, Perez-Martinez P, Mikhailidis DP*. **Dyslipidaemia in the elderly: to treat or not to treat?** Expert Rev Clin Pharmacol 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29303009
ABSTRACT
INTRODUCTION: The elderly population (i.e. aged >/= 65 years) is increasing worldwide. Ageing is associated with a higher incidence and prevalence of cardiovascular disease (CVD). Areas covered: The prevalence of CVD risk factors including type 2 diabetes mellitus, hypertension and dyslipidaemia also increases with advancing age, contributing to the higher absolute CVD risk observed in the elderly. The present narrative review comments on the associations of dyslipidaemia with CVD as well as the effects of lifestyle measures and lipid-lowering drugs on lipids and CVD risk with a special focus on the elderly population. Individual treatment goals and therapeutic options according to current guidelines are also reviewed. Finally, we discuss special characteristics of the elderly that may influence the efficacy and safety of drug therapy and should be considered before selection of hypolipidaemic pharmacotherapy. Expert Commentary: There may be a greater CVD benefit in older patients following drug therapy compared with younger ones. Treatment goals and therapeutic options should be individualized according to current guidelines. Specific characteristics that may influence the efficacy and safety of drug therapy in the elderly should be considered in relation to dyslipidaemia treatment.

[7] *Bukhari IA, Almotrefi AA, Mohamed OY et al.* **Protective effect of fenofibrate against ischemia-reperfusion induced cardiac arrhythmias in isolated rat hearts**. Fundamental & clinical pharmacology 2017.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29290096
ABSTRACT
Fenofibrate is a peroxisome proliferator-activated receptor (PPAR)-alpha activator that lowers triglycerides and influences cytochrome P-450 (CYP-450) epoxygenase dependent arachidonic acid (AA) metabolism. CYP-450 epoxygenase metabolizes AA to epoxyeicosatrienoic acids (EETs). EETs have coronary dilating, cardiac and renal protective properties. Fibrates possess similar properties due to their CYP-450 epoxygenase inducing properties that leads to increase in endogenous EETs production. In the current investigations fenofibrate (100 mg/kg, orally) for two weeks decreased ischemia/reperfusion (I/R)-induced premature ventricular contractions (PVCs), ventricular tachycardia (VT) and ventricular fibrillation (VF) in the isolated rat hearts. Fenofibrate caused marked inhibition of the reperfusion-induced cardiac arrhythmias. The

incidence of reperfusion-induced VF decreased from 80% in the control vehicle treated animals to 33% in the fenofibrate treated animals, (P< 0.001. PVCs were also significantly (P<0.01) decreased from 223.2+/-51 in control vehicle treated animals to 136.8+/-22 in fenofibrate treated animals. Total duration of reperfusion induced VT decreased from 29.2+/-6.3 seconds in control, vehicle treated animals to 4.8+/-1.3 secs in fenofibrate treated animals, P< 0.001. Heart rate and perfusion pressure were not significantly affected by fenofibrate pretreatment. Diltiazem, a clinically used antiarrhythmic agent produced complete protection against I/R induced cardiac arrhythmias in this model reducing the incidence of VF from 80% in control, vehicle treated animals to 10% in diltiazem treated hearts. These findings indicate that fenofibrate suppresses arrhythmias in isolated rat hearts subjected to I/R- induced injury. This article is protected by copyright. All rights reserved.

[8] *Cervelli N, Tocci G, Ferri C*. **Proprotein Convertase Subtilisin-Kexin Type 9 (PCSK9) Inhibitors and Cardiovascular Risk: Does a Further Analysis of the Fourier Trial Suggest Changes in the Target of Lipid Lowering Therapy?** High blood pressure & cardiovascular prevention : the official journal of the Italian Society of Hypertension 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29305812
ABSTRACT

[9] *Canepa M, Artom N, Ameri P et al.* **Short-term effect of rosuvastatin treatment on arterial stiffness in individuals with newly-diagnosed heterozygous familial hypercholesterolemia**. International journal of cardiology 2017.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29290422
ABSTRACT

[10] *Angelini S, Rosticci M, Massimo G et al.* **Relationship between Lipid Phenotypes, Overweight, Lipid Lowering Drug Response and KIF6 and HMG-CoA Genotypes in a Subset of the Brisighella Heart Study Population**. International journal of molecular sciences 2017; 19.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29295555
ABSTRACT
The existence of genetic traits might explain the susceptibility to develop hypercholesterolemia and the inter-individual differences in statin response. This study was performed to evaluate whether individuals' polymorphisms in HMG-CoA and KIF6 genes are independently associated with hypercholesterolemia, other lipid-associated traits, and statin response in unselected individuals enrolled in the Brisighella heart study (Survey 2012). A total of 1622 individuals, of which 183 under statin medication, were genotyped for a total of five polymorphisms (KIF6 rs20455, rs9471077, rs9462535; HMG-CoA rs3761740, rs3846662). The relationships between the five loci and clinical characteristics were analyzed. The principal basic parameters calculated on 12 h fasting blood included total cholesterol (TC), High Density Lipoprotein Cholesterol (HDL-C), Low-Density Lipoprotein Cholesterol (LDL-C), and triglycerides (TG). Hypercholesterolemia was defined as a TC >200 mg/dL or use of lipid-lowering medication. 965 individuals were characterized by hypercholesterolemia; these subjects were significantly older ($p < 0.001$), with body mass index (BMI) and waist circumference significantly higher ($p < 0.001$) compared to the others. HMG-CoA rs3846662 GG genotype was significantly over-represented in the

hypercholesterolemic group (p = 0.030). HMG-CoA rs3846662 genotype was associated with the level of TC and LDL-C. Furthermore, in the same subset of untreated subjects, we observed a significant correlation between the KIF6 rs20455 and HDL-C. KIF6 variants were associated with a significantly lower (rs20455) or higher (rs9471077 and rs9462535) risk of obesity, in males only. No association between responsiveness to statins and the polymorphisms under investigation were observed. Our results showed associations between HMG-CoA rs3846662 and KIF6 rs20455 and lipid phenotypes, which may have an influence on dyslipidemia-related events. Moreover, this represents the first study implicating KIF6 variants with obesity in men, and point to the possible involvement of this genetic locus in the known gender-related differences in coronary artery disease.

[11] *Brook RD, Kaciroti N, Bakris G et al.* **Prior Medications and the Cardiovascular Benefits From Combination Angiotensin-Converting Enzyme Inhibition Plus Calcium Channel Blockade Among High-Risk Hypertensive Patients**. Journal of the American Heart Association 2018; 7.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29301757

ABSTRACT

BACKGROUND: The ACCOMPLISH (Avoiding Cardiovascular Events Through Combination Therapy in Patients Living with Systolic Hypertension) trial demonstrated that combination therapy using amlodipine, rather than hydrochlorothiazide, in conjunction with benazepril provided greater cardiovascular risk reduction among high-risk hypertensive patients. Few trials have evaluated the effect of prior antihypertensive therapy used among participants on the study outcomes. METHODS AND RESULTS: In a post hoc observational analysis, we examined the characteristics of the drug regimens taken before trial enrollment in the context of the primary composite outcome (death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, hospitalization for angina, resuscitation after sudden cardiac death, and coronary revascularization). In the "primary subgroup" (n=4475), patients previously taking any renin-angiotensin system blockade plus either a diuretic or a calcium channel blocker alone or as part of their antihypertensive regimen, there were 206 of 2193 (9.4%) versus 281 of 2282 (12.3%) primary composite events among those randomized to combination therapy involving amlodipine versus hydrochlorothiazide, respectively (adjusted Cox proportional hazard ratio, 0.74; 95% confidence interval, 0.62-0.89; P=0.0015). All other participants (n=6975) previously taking any antihypertensive regimen not included in the primary subgroup also benefited from randomization to amlodipine plus benazepril (adjusted hazard ratio, 0.84; 95% confidence interval, 0.72-0.98; P=0.024). Outcomes among most other subgroups, including patients previously taking lipid-lowering medications or dichotomized by prior blood pressure control status, showed similar results. CONCLUSIONS: When combined with an angiotensin-converting enzyme inhibitor, amlodipine provides cardiovascular risk reduction superior to hydrochlorothiazide, largely regardless of prior medication use. These findings add further support for the initial use of this combination regimen among high-risk hypertensive patients.

[12] *Paquette M, Dufour R, Baass A*. **ABO blood group is a cardiovascular risk factor in patients with familial hypercholesterolemia**. Journal of clinical lipidology 2017.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29290540

ABSTRACT

BACKGROUND: The ABO blood group has been associated with cardiovascular disease (CVD) in observational studies. However, the effect of ABO blood group has never been studied in subjects affected by familial hypercholesterolemia (FH), a severe monogenic disease characterized by accelerated atherosclerotic plaque development. OBJECTIVE: Our aim is to investigate the effect of the ABO blood group on CVD risk in FH patients. METHODS: A total of 668 adult subjects with a heterozygous FH-causing mutation in the low density lipoprotein receptor (LDLR) gene were included in the present study. ABO blood group was determined using 2 functional single-nucleotide polymorphisms in the ABO gene (rs8176719 and rs8176746). RESULTS: Total cholesterol was significantly higher in non-O subjects compared to carriers of the O group (9.48 vs 9.14 mmol/L, P = .02). We observed a greater proportion of subjects carrying the non-O groups (73.4%) in patients with CVD compared to subjects without CVD (63.3%). In a regression model corrected for cardiovascular risk factors, the non-O group was significantly associated with an increased prevalence of CVD (odds ratio = 2.14, 95% confidence interval = 1.25-3.65, P = .005). In average, patients in the non-O blood group experienced more CVD events (0.88 per individual) than those in the O group (0.60 per individual), P = .008. CONCLUSION: Carrying a non-O blood group is associated with an independent twofold increased risk of CVD in FH patients. The ABO blood group represents a novel CVD risk factor in FH subjects that is often known by the patient and could be used to further stratify CVD risk in this population of patients.

[13] *Sun HL, Wu YR, Song FF et al.* **Role of PCSK9 in the Development of Mouse Periodontitis Before and After Treatment: A Double-Edged Sword**. The Journal of infectious diseases 2017.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29294034
ABSTRACT
Periodontitis is a highly prevalent infectious disease associated genetically with coronary heart disease (CHD). The effects of proprotein convertase subtilisin/kexin type 9 (PCSK9), a critical regulator of CHD, on periodontitis have not been studied to date. Here, we found that PCSK9 expression was increased in periodontitis patients and Porphyromonas gingivalis (Pg)-infected mice. Loss of PCSK9 attenuated Pg-induced periodontal bone loss in mice. First, PCSK9 deficiency reduced the release of inflammation-associated cytokines, such as tumor necrosis factor alpha (TNF-alpha) and interleukin 1beta, in vitro and in vivo. Second, its deficiency enhanced Pg and endotoxin clearance during Pg invasion in part by upregulating CD36 and low-density lipoprotein receptor (LDLR), respectively. However, after berberine treatment, periodontal bone regeneration in the PCSK9 knockout group was significantly lower than that in wild-type. This was because PCSK9 overexpression promoted osteogenic differentiation of periodontal ligament stem cells (PDLCs) prechallenged by TNF-alpha. Furthermore, PCSK9 could rescue PDLC osteogenesis by repressing the NF-kappaB signaling pathway by interacting with TRAF2. These results suggest that PCSK9 may be a potent drug target for treating periodontitis.

[14] *Cacabelos R, Meyyazhagan A, Carril JC et al.* **Pharmacogenetics of Vascular Risk Factors in Alzheimer's Disease**. Journal of personalized medicine 2018; 8.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29301387
ABSTRACT

Alzheimer's disease (AD) is a polygenic/complex disorder in which genomic, epigenomic, cerebrovascular, metabolic, and environmental factors converge to define a progressive neurodegenerative phenotype. Pharmacogenetics is a major determinant of therapeutic outcome in AD. Different categories of genes are potentially involved in the pharmacogenetic network responsible for drug efficacy and safety, including pathogenic, mechanistic, metabolic, transporter, and pleiotropic genes. However, most drugs exert pleiotropic effects that are promiscuously regulated for different gene products. Only 20% of the Caucasian population are extensive metabolizers for tetragenic haplotypes integrating CYP2D6-CYP2C19-CYP2C9-CYP3A4/5 variants. Patients harboring CYP-related poor (PM) and/or ultra-rapid (UM) geno-phenotypes display more irregular profiles in drug metabolism than extensive (EM) or intermediate (IM) metabolizers. Among 111 pentagenic (APOE-APOB-APOC3-CETP-LPL) haplotypes associated with lipid metabolism, carriers of the H26 haplotype (23-TT-CG-AG-CC) exhibit the lowest cholesterol levels, and patients with the H104 haplotype (44-CC-CC-AA-CC) are severely hypercholesterolemic. Furthermore, APOE, NOS3, ACE, AGT, and CYP variants influence the therapeutic response to hypotensive drugs in AD patients with hypertension. Consequently, the implementation of pharmacogenetic procedures may optimize therapeutics in AD patients under polypharmacy regimes for the treatment of concomitant vascular disorders.

[15] *Wang F, Wang X, Ye P et al.* **High-density lipoprotein 3 cholesterol is a predictive factor for arterial stiffness: a community-based 4.8-year prospective study**. Lipids in health and disease 2018; 17:5.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29304861
ABSTRACT
BACKGROUND: Although drug trials with niacin and cholesteryl ester transfer protein inhibitors that substantially increase high-density lipoprotein-cholesterol (HDL-C) failed to reduce the risk of coronary heart disease, HDL protection of the cardiovascular system cannot be easily denied. Hence, it may be HDL subfractions that are responsible for the long-held and consistent cardioprotective association of HDL. Arterial stiffness has been increasingly recognized as a strong predictor of subclinical vascular disease, atherosclerotic disease, and cardiovascular mortality. As the association of HDL subfractions and arterial stiffness is not well characterized, we aimed to determine the relations between these two entities in a community-based longitudinal Chinese population sample. METHODS: We evaluated the associations of plasma HDL2-C and HDL3-C subfractions with arterial stiffness measured using carotid-femoral pulse wave velocity (cf-PWV) and then multivariate logistic regression in 1447 subjects (mean age 61.3 years) from a community-based population in Beijing, China. RESULTS: After a median follow-up of 4.8 years, Pearson's correlation analysis revealed that HDL3-C was negatively associated with follow-up cf-PWV (r = -0.114; P = 0.001), and there was no correlation between HDL2-C and follow-up cf-PWV (r = -0.045; P = 0.181). In the multivariate logistic regression analysis, each standard deviation (SD) increase in HDL3-C was associated with a 1.490-increased likelihood of the presence of follow-up cf-PWV [odds ratio (per SD increase in HDL3-C) 1.490; 95% confidence interval 1.021-1.470; P = 0.039), whereas there was no relation between HDL2-C and follow-up cf-PWV. CONCLUSIONS: HDL3-C subfractions were significantly and inversely

associated with arterial stiffness, suggesting that HDL subfractions are likely more important than HDL-C in preventing cardiovascular disease.

[16] *Anagnostis P, Paschou SA, Goulis DG et al.* **Dietary management of dyslipidaemias. Is there any evidence for cardiovascular benefit?** Maturitas 2018; 108:45-52.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29290214
ABSTRACT
Specific dietary strategies are the mainstay of management in most cases of dyslipidaemia, prior to or simultaneously with the initiation of a lipid-lowering agent. The exact approach differs according to the type of dyslipidaemia. In particular, a reduction in carbohydrates (mainly foods with a high glycaemic index) and their substitution with mono- and polyunsaturated fatty acids is the main strategy in patients with high levels of triglycerides (Tg) and/or low levels of high-density lipoprotein cholesterol (HDL-c). A reduction in saturated and trans fatty acids, combined with an increased intake of specific dietary components, such as plant sterols, soy protein and red yeast rice, constitutes the more efficacious dietary approach in cases where levels of total cholesterol and low-density lipoprotein cholesterol (LDL-c) are elevated. A reduction in excessive body weight is beneficial in every type of dyslipidaemia, whereas increased physical activity is mostly effective in cases with low HDL-c and high Tg levels. With respect to the potential cardiovascular benefit of these dietary interventions, there is currently evidence for the Mediterranean diet. Potential benefit may derive also from single dietary components of that diet, such as legumes, fruits, vegetables, nuts and omega-3 fatty acids, although to a lesser extent than with that general dietary pattern. The purpose of this review is to outline current knowledge regarding the recommended specific dietary pattern according to the type of dyslipidaemia and the evidence for the potential cardiovascular benefits of such approaches.

[17] *Pinal-Fernandez I, Casal-Dominguez M, Mammen AL*. **Statins: pros and cons**. Medicina clinica 2017.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29292104
ABSTRACT
Statins inhibit the critical step of cholesterol synthesis in which 3-hydroxy-3-methylglutaryl coenzyme A (HMGC) is transformed to mevalonate by the enzyme HMGC reductase. By doing so, they have a potent lipid-lowering effect that reduces cardiovascular risk and decreases mortality. Since the mevalonate pathway also influences endothelial function, the inflammatory response, and coagulation, the effects of statins reach well beyond their cholesterol lowering properties. As with all drugs, statins may have adverse effects; these include musculoskeletal symptoms, increased risk of diabetes, and higher rates of hemorrhagic stroke. However, the frequency of adverse effects is extremely low and, in selected patient populations, the benefits of statins considerably outweigh the potential risks.

[18] *Ferguson JJA, Stojanovski E, MacDonald-Wicks L, Garg ML*. **Curcumin potentiates cholesterol-lowering effects of phytosterols in hypercholesterolaemic individuals. A randomised controlled trial**. Metabolism 2017.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29291429

ABSTRACT
BACKGROUND: Dietary phytosterols (PS) are well-known hypocholesterolaemic agents. Curcumin elicits hypolipidaemic and anti-inflammatory effects in preclinical studies, however, consistent findings in humans are lacking. OBJECTIVE: Concurrent PS and curcumin supplementation may exhibit enhanced hypocholesterolaemic and anti-inflammatory effects to optimise cardio-protection. The objective of this trial was to investigate the effects of dietary intervention with PS with or without curcumin on blood lipids (primary outcome) in hypercholesterolaemic individuals. METHODS: A double-blinded, randomised, placebo-controlled, 2x2 factorial trial was conducted in hypercholesterolaemic individuals. Participants received either placebo (PL, no phytosterols or curcumin), phytosterols (PS, 2g/d), curcumin (CC, 200mg/d) or a combination of PS and curcumin (PS-CC, 2g/d-200mg/d respectively) for four weeks. Primary outcomes included fasting total cholesterol (TC), LDL-cholesterol, HDL-cholesterol, triglycerides (TG), TC-to-HDL-C ratio (TC:HDL-C). Secondary outcomes included anthropometrics and fasting blood glucose concentrations. RESULTS: Seventy participants with a mean (+/-SEM) fasting TC concentration of 6.57+/-0.13mmol/L completed the study (PL, n=18; PS, n=17; CC, n=18; PS-CC, n=17). PS and PS-CC supplementation significantly lowered TC, LDL-cholesterol and TC:HDL-C post-intervention ($p<0.05$). Reductions from baseline in the PS group were 4.8% and 8.1% for TC and LDL-cholesterol respectively ($p<0.05$). CC exhibited non-significant reduction (2.3% and 2.6%) in TC and LDL-C respectively, however, the PS-CC resulted in a greater reduction in TC (11.0%) and LDL-cholesterol (14.4%) than either of the treatments alone ($p<0.0001$). The reduction in the PS-CC treatment was significantly greater compared to those for CC ($p<0.05$) or PL ($p<0.01$) alone. Plasma HDL-cholesterol and TG concentrations remained unchanged across all groups. No adverse side effects were reported. CONCLUSIONS: The addition of curcumin to phytosterol therapy provides a complementary cholesterol-lowering effect that is larger than phytosterol therapy alone. Implications of these findings include the development of a single functional food containing both the active ingredients for enhanced lipid-lowering and compliance in hypercholesterolaemic individuals.

[19] *Chang SF, Yeh CC, Chen PJ, Chang HI*. **The Impact of Lipid Types and Liposomal Formulations on Osteoblast Adiposity and Mineralization**. Molecules (Basel, Switzerland) 2018; 23.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29301300

ABSTRACT
Recent studies have demonstrated that fat accumulation in bone cells is detrimental to bone mass. Both adipocytes and osteoblasts are derived from common multipotent mesenchymal stem cells (MSCs) and hence the presence of fat may increase adipocyte proliferation, differentiation and fat accumulation while inhibiting osteoblast differentiation and bone formation. Lipids are common constituents in supramolecular vesicles (e.g., micelles or liposomes) that serve as drug delivery systems. Liposomal formulations such as Meriva((R)) were proven to decrease joint pain and improve joint function in osteoarthritis (OA) patients. In this study, we evaluated how lipid types and liposomal formulations affect osteoblast behavior including cell viability, differentiation, mineralization and inflammation. Various liposomal formulations were prepared using different types of lipids, including phosphatidylcholine (PC), 1,2-dioleoyl-sn-glycero-3-phospho-ethanolamine (DOPE), cholesterol (Chol), 3beta-[N-(N',N'-

dimethylaminoethane)-carbamoyl] cholesterol hydrochloride (DC-cholesterol HCl), and 1,2-dioleoyl-3-trimethylammonium-propane chloride salt (DOTAP) to investigate the impact on osteoblast differentiation and inflammation. The results indicated that cationic lipids, DC-cholesterol and DOTAP, presented higher dose-dependent cytotoxicity and caused high level of inflammatory responses. Due to the natural properties of lipids, all the lipids can induce lipid droplet formation in osteoblasts but the level of lipid droplet accumulation was different. In comparison with cationic lipids, neutral lipids induced less adiposity, and maintained high osteoblast mineralization. Similar to previous researches, we also confirmed an inverse relationship between lipid droplet formation and osteoblast mineralization in 7F2 mouse osteoblasts. Importantly, PC containing liposomes (PC only and PC/DOTAP) suppressed IL-1beta-induced gene expression of COX-2 and MMP-3 but not Chol/DOTAP liposomes or DC-Chol/DOPE liposomes. Taken together, we suggested that PC contained liposomes could provide the best liposomal formulation for the treatment of bone diseases.

[20] *Kumar A, Palfrey HA, Pathak R et al.* **The metabolism and significance of homocysteine in nutrition and health**. Nutrition & metabolism 2017; 14:78.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29299040
ABSTRACT
An association between arteriosclerosis and homocysteine (Hcy) was first demonstrated in 1969. Hcy is a sulfur containing amino acid derived from the essential amino acid methionine (Met). Hyperhomocysteinemia (HHcy) was subsequently shown in several age-related pathologies such as osteoporosis, Alzheimer's disease, Parkinson's disease, stroke, and cardiovascular disease (CVD). Also, Hcy is associated with (but not limited to) cancer, aortic aneurysm, hypothyroidism and end renal stage disease to mention some. The circulating levels of Hcy can be increased by defects in enzymes of the metabolism of Met, deficiencies of vitamins B6, B12 and folate or by feeding Met enriched diets. Additionally, some of the pharmaceuticals currently in clinical practice such as lipid lowering, and anti-Parkinsonian drugs are known to elevate Hcy levels. Studies on supplementation with folate, vitamins B6 and B12 have shown reduction in Hcy levels but concomitant reduction in certain associated pathologies have not been definitive. The enormous importance of Hcy in health and disease is illustrated by its prevalence in the medical literature (e.g. > 22,000 publications). Although there are compelling data in favor of Hcy as a modifiable risk factor, the debate regarding the significance of Hcy mediated health effects is still ongoing. Despite associations between increased levels of Hcy with several pathologies being well documented, whether it is a causative factor, or an effect remains inconclusive. The present review though not exhaustive, is focused on several important aspects of Hcy metabolism and their relevance to health.

[21] *Arpon A, Milagro FI, Razquin C et al.* **Impact of Consuming Extra-Virgin Olive Oil or Nuts within a Mediterranean Diet on DNA Methylation in Peripheral White Blood Cells within the PREDIMED-Navarra Randomized Controlled Trial: A Role for Dietary Lipids**. Nutrients 2017; 10.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29295516
ABSTRACT
DNA methylation could be reversible and mouldable by environmental factors, such as dietary exposures. The objective was to analyse whether an intervention with two Mediterranean

diets, one rich in extra-virgin olive oil (MedDiet + EVOO) and the other one in nuts (MedDiet + nuts), was influencing the methylation status of peripheral white blood cells (PWBCs) genes. A subset of 36 representative individuals were selected within the PREvencion con DIeta MEDiterranea (PREDIMED-Navarra) trial, with three intervention groups in high cardiovascular risk volunteers: MedDiet + EVOO, MedDiet + nuts, and a low-fat control group. Methylation was assessed at baseline and at five-year follow-up. Ingenuity pathway analysis showed routes with differentially methylated CpG sites (CpGs) related to intermediate metabolism, diabetes, inflammation, and signal transduction. Two CpGs were specifically selected: cg01081346-CPT1B/CHKB-CPT1B and cg17071192-GNAS/GNASAS, being associated with intermediate metabolism. Furthermore, cg01081346 was associated with PUFAs intake, showing a role for specific fatty acids on epigenetic modulation. Specific components of MedDiet, particularly nuts and EVOO, were able to induce methylation changes in several PWBCs genes. These changes may have potential benefits in health; especially those changes in genes related to intermediate metabolism, diabetes, inflammation and signal transduction, which may contribute to explain the role of MedDiet and fat quality on health outcomes.

[22] *Chen IC, Tseng WK, Li YH et al.* **Effect of cilostazol on plasma levels of proprotein convertase subtilisin/kexin type 9**. Oncotarget 2017; 8:108042-108053.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29296222
ABSTRACT
The protein complex proprotein convertase subtilisin/kexin type 9 (PCSK9) serves as an important target for the prevention and treatment of atherosclerosis and lipid homeostasis. This study investigated the effect of cilostazol on plasma PCSK9 concentrations. We performed a post hoc analysis of two prospective, double-blind, randomized controlled trials including 115 patients of whom 61 received cilostazol 200 mg/day and 54 received placebo for 12 weeks. Linear regression analysis was performed to determine the associations between several parameters and changes in PCSK9 levels. Use of cilostazol, but not placebo, significantly increased plasma PCSK9 concentrations, high-density lipoprotein cholesterol levels, and number of circulating endothelial progenitor cells (EPCs), and decreased triglyceride levels with a trend toward an increase in total cholesterol (TC) levels. A reduction in hemoglobin A1C and an increase in plasma vascular endothelial growth factor and adiponectin levels with cilostazol treatment were also found. Changes in the number of circulating EPCs were positively correlated and the TC concentrations were inversely correlated with changes in the PCSK9 levels. After adjusting for changes in levels of TC and numbers of circulating EPCs and history of metabolic syndrome, use of cilostazol remained independently associated with changes in plasma PCSK9 levels. In conclusion, cilostazol treatment was significantly and independently associated with an increase in plasma PCSK9 levels in patients with peripheral artery disease or at a high risk of cardiovascular disease regardless of background statin use and caused an improvement in some metabolic disorders and levels of vasculo-angiogenic biomarkers.

[23] *Jiang S, Venners SA, Li K et al.* **Effect modification by region in the associations of LEP G2548A and LEPR Q223R polymorphisms with statin-induced CK elevation**. Oncotarget 2017; 8:107565-107576.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29296187

ABSTRACT
We investigated the associations of LEP G2548A and LEPR Q223R polymorphisms with statin-induced creatine kinase (CK) elevation among Chinese patients with hyperlipidemia. A total of587 enrolled individuals were treated with 20 mg/d oral simvastatin for 8 consecutive weeks. Genotyping of LEP G2548A and LEPR Q223R were conducted using PCR-RFLP. Multiple regression analyses showed that, in the Dongzhi region only, patients carrying the LEP AA genotype had a significantly greater increase in CK levels compared to those carrying the AG+GG genotypes after four weeks (P = 0.004) and eight weeks (P < 0.001) consecutive simvastatin treatment. Patients were further divided into three groups based on the tertiles of the CK distribution. Compared to subjects in the lowest tertile of CK elevation, the adjusted relative odds of having the AG+GG genotypes among subjects in the highest tertile was 0.5 (95% CI, 0.3 to 0.7) and 0.4 (95% CI, 0.2 to 0.6) after the fourth and eighth weeks, respectively. The interaction terms between the Beijing or Dongzhi region and the LEP GA+AA genotypes were marginally significant for CK elevation at the fourth week (P = 0.057) and significant for CK elevation at the eighth week (P = 0.002). The adverse effect of the LEP G2548A polymorphism on increasing CK levels may be dependent on the environmental milieu. It suggests that lifestyle interventions might offset the side effects of simvastatin therapy among those with genetic susceptibility. Further research is needed to identify specific individual-level factors for clinical practice that modify the effect of genotype.

[24] *Haghighatdoost F, Hariri M*. **Effect of resveratrol on lipid profile: An updated systematic review and meta-analysis on randomized clinical trials**. Pharmacological research : the official journal of the Italian Pharmacological Society 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29305228

ABSTRACT
BACKGROUND: New studies indicate that resveratrol can significantly reduce plasma lipids, but the result of randomized clinical trials (RCTs) on resveratrol effect and the serum lipid profile are contradictory. Our objective was to conduct a systematic review and meta-analysis on RCTs assessed the effect of resveratrol on lipids. MATERIAL AND METHODS: PubMed, ISI Web of Science, Scopus and Google scholar data bases were searched up to Jun 2017. RCTs which assessed resveratrol effects on lipid profile among adult participants were chosen. TREATMENT: effects were considered as weighted mean difference (WMD) and the corresponding standard error (SE) in concentrations of serum lipids. To estimate the overall summary effect, we used random-effects model. The protocol was registered with PROSPERO (No. CRD42017072365). RESULT: This meta-analysis was performed on twenty-one trials. Our results indicated that resveratrol can significantly reduce total cholesterol (TC) (WMD=-0.26 Mmol/L, 95% CI: -0.40, -0.12; P<0.0001, I(2)=93.4%), but its effects on triacylglycerol (TG) (WMD: -0.02mmol/L, 95%CI: -0.08, 0.04; P=0.467, I(2)=79.4%), low-density lipoprotein (LDL-C) (WMD: 0.01mmol/L, 95% CI: -0.15, 0.17; P=0.898, I(2)=94.6%), and high density lipoprotein (HDL-C) (WMD: 0.00mmol/l, 95% CI: -0.02, 0.03; P=0.878, I(2)=64.2%) were non-significant. In cross-over trials, resveratrol could significantly increase HDL-C. We also found that sex, age, BMI, resveratrol dosage, and intervention duration could not change the results. CONCLUSION: Resveratrol might be able to change TC and HDL-C, but for confirming the results, more studies exclusively on dyslipidemia patients and considering the intake of lipid lowering agents as exclusion criteria is necessary.

[25] *Simental-Mendia LE, Simental-Mendia M, Sanchez-Garcia A et al.* **Effect of fibrates on glycemic parameters: A systematic review and meta-analysis of randomized placebo-controlled trials**. Pharmacological research : the official journal of the Italian Pharmacological Society 2017.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29292213
ABSTRACT
AIMS: The aim of this meta-analysis of randomized placebo-controlled clinical trials was to assess the effect of fibrates on glycemic parameters. MATERIALS AND METHODS: Only randomized placebo-controlled trials investigating the impact of fibrate treatment on glucose homeostasis markers were searched in PubMed-Medline, SCOPUS, Web of Science and Google Scholar databases (from inception to April 11, 2017). A random-effects model and generic inverse variance method were used for quantitative data synthesis. Sensitivity analysis was conducted using the leave-one-out method. A weighted random-effects meta-regression was performed to evaluate the impact of potential confounders on glycemic parameters. RESULTS: This meta-analysis of data from 22 randomized placebo-controlled clinical trials involving a total of 11,402 subjects showed that fibrate therapy significantly decreased fasting plasma glucose (WMD: -0.28mmol/L, 95% CI: -0.42, -0.14, p<0.001), insulin levels (WMD: -3.87pmol/L, 95% CI: -4.97, -2.78, p<0.001) and insulin resistance (HOMA-IR, WMD: -1.09, 95% CI: -1.71, -0.47, p=0.001), but with no effect on HbA1c (WMD: 0.01%, 95% CI: -0.18, 0.19, p=0.955). All analyses were robust in the leave-one-out sensitivity analysis except for insulin levels that showed a non-significant result (WMD: -0.84pmol/L, 95% CI: -6.36, 4.68, p=0.766) following omission of one of the included trials. CONCLUSION: This meta-analysis has shown that fibrate treatment significantly decreases fasting plasma glucose, insulin levels, and HOMA-IR indicating additional clinical therapeutic benefits.

[26] *Qasimi MI, Nagaoka K, Watanabe G*. **Feeding of phytosterols reduced testosterone production by modulating GnRH and GnIH expression in the brain and testes of male Japanese quail (Coturnix coturnix japonica)**. Poultry science 2017.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29294112
ABSTRACT
Phytosterols (PS), or plant sterols used as cholesterol-lowering agents, have been shown to act as endocrine-disrupting chemicals in some laboratory animals. Moreover, dietary PS efficiently pass through the blood-brain barrier and accumulate in brain cell membranes. We asked whether the accumulation of PS affects reproduction through the hypothalamic-pituitary-gonadal axis. Thirty male quail chicks were randomly divided into 3 groups (control, 80 mg/kg BW, and 800 mg/kg BW), and daily single doses of PS or vehicle were gavaged into the crop sac from 15 to 100 d of age. At the end of the entire period, half of each group was injected intramuscularly with either 10 mug of chicken gonadotropin-releasing hormone 1 (cGnRH-1) or phosphate-buffered saline solution (PBS) as the vehicle. Blood was collected before and 30 min after cGnRH-1 challenge by jugular venipuncture and decapitation, respectively. The results indicated that testosterone concentrations were low ($P < 0.05$) before (800 mg/kg BW) and after GnRH challenge in PS-treated quails compared with controls ($P < 0.001$). However, luteinizing hormone (LH) levels were not different among the groups before cGnRH-1 challenge.

In addition, PS-gavaged animals failed to manifest increased LH levels after cGnRH-1 injection ($P < 0.01$). The same trends were observed in pituitary LH levels at 800 mg/kg BW PS after cGnRH-1 injection ($P < 0.05$). Real-time PCR results revealed that PS (800 mg/kg BW) feeding reduced expression of GnRH-1 in the brain and testes compared to controls. However, gonadotropin-inhibitory hormone (GnIH) expression was significantly elevated before and after GnRH-1 challenges in the brain and testes. Collectively, these results suggest that brain-mediated effects of PS on gonadal function occurs via the induction of GnIH gene expression, and these indirect effects are less potent than direct effects.

[27] *Choi JY, Ryu J, Kim HJ et al.* **Therapeutic Effects of Targeted PPAR Activation on Inflamed High-Risk Plaques Assessed by Serial Optical Imaging In Vivo**. Theranostics 2018; 8:45-60.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29290792

ABSTRACT

Rationale: Atherosclerotic plaque is a chronic inflammatory disorder involving lipid accumulation within arterial walls. In particular, macrophages mediate plaque progression and rupture. While PPARgamma agonist is known to have favorable pleiotropic effects on atherogenesis, its clinical application has been very limited due to undesirable systemic effects. We hypothesized that the specific delivery of a PPARgamma agonist to inflamed plaques could reduce plaque burden and inflammation without systemic adverse effects. Methods: Herein, we newly developed a macrophage mannose receptor (MMR)-targeted biocompatible nanocarrier loaded with lobeglitazone (MMR-Lobe), which is able to specifically activate PPARgamma pathways within inflamed high-risk plaques, and investigated its anti-atherogenic and anti-inflammatory effects both in in vitro and in vivo experiments. Results: MMR-Lobe had a high affinity to macrophage foam cells, and it could efficiently promote cholesterol efflux via LXRalpha-, ABCA1, and ABCG1 dependent pathways, and inhibit plaque protease expression. Using in vivo serial optical imaging of carotid artery, MMR-Lobe markedly reduced both plaque burden and inflammation in atherogenic mice without undesirable systemic effects. Comprehensive analysis of en face aorta by ex vivo imaging and immunostaining well corroborated the in vivo findings. Conclusion: MMR-Lobe was able to activate PPARgamma pathways within high-risk plaques and effectively reduce both plaque burden and inflammation. This novel targetable PPARgamma activation in macrophages could be a promising therapeutic strategy for high-risk plaques.

[28] *Vogt K, Mahajan-Thakur S, Wolf R et al.* **Release of Platelet-Derived Sphingosine-1-Phosphate Involves Multidrug Resistance Protein 4 (MRP4/ABCC4) and Is Inhibited by Statins**. Thrombosis and haemostasis 2018; 118:132-142.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29304533

ABSTRACT

Sphingosine-1-phosphate (S1P) is a potent lipid mediator released from activated platelets by an adenosine triphosphate (ATP)-dependent export mechanism. A candidate transport protein is the multidrug resistance protein 4 (MRP4/ABCC4), an ATP-dependent transporter highly expressed in platelets. Furthermore, several statins are known to affect platelet functions and exhibit antithrombotic properties. This study determines the involvement of MRP4 in the transport of S1P and a possible interference by statins. Transport studies in membrane vesicles

of Sf9 cells containing recombinant human MRP4 revealed that MRP4 mediates ATP-dependent transport of fluorescein- and tritium-labelled S1P. Also, ATP-dependent S1P transport in platelet membrane vesicles containing endogenous MRP4 was inhibited by the MRP inhibitor MK571 and the MRP4-selective compound Ceefourin-1. Confocal microscopy using fluorescein-labelled S1P as well as boron-dipyrromethene (BODIPY)-labelled sphingosine indicated association of S1P and MRP4 in human platelets. In MRP4-deficient mice, agonist-induced S1P secretion was reduced compared with matched wild-type C57Bl/6 mice and platelet S1P concentrations were lower. Fluvastatin and rosuvastatin interfered with MRP4 function inhibiting ATP-dependent cGMP (cyclic guanosine monophosphate) uptake into MRP4-containing vesicles, inhibited MRP4-mediated S1P transport in vitro and significantly attenuated endogenous S1P release from agonist-activated platelet ex vivo. These data suggest that release of S1P from platelets depends on MRP4 and statins can interfere with this transport process. Potentially, this may be relevant for the pleiotropic anti-inflammatory effects of statins and their effect on modulating atherothrombosis.