

Literature update week 29 (2018)

[1] Nikravesh H, Khodayar MJ, Mahdavinia M et al. **Protective Effect of Gemfibrozil on Hepatotoxicity Induced by Acetaminophen in Mice: the Importance of Oxidative Stress Suppression.** Advanced pharmaceutical bulletin 2018; 8:331-339.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30023335>

ABSTRACT

Purpose: Gemfibrozil (GEM) apart from agonist activity at peroxisome proliferator-activated receptor-alpha (PPAR-alpha) has antioxidant and anti-inflammatory properties. Accordingly, the present study was designed to investigate the protective effect of GEM on acute liver toxicity induced by acetaminophen (APAP) in mice. Methods: In this study, mice divided in seven groups include, control group, APAP group, GEM group, three APAP groups pretreated with GEM at the doses of 25, 50 and 100 mg/kg respectively and APAP group pretreated with N-Acetyl cysteine. GEM, NAC or vehicle were administered for 10 days. In last day, GEM and NAC were gavaged 1 h before and 1 h after APAP injection. Twenty four hours after APAP, mice were sacrificed. Serum parameters include alanine aminotransferase (ALT), aspartate aminotransferase (AST) and liver tissue markers including catalase enzyme activity, reactive oxygen species (ROS), malondialdehyde and reduced glutathione (GSH) levels determined and histopathological parameters measured. Results: GEM led to significant decrease in serum ALT and AST activities and increase in catalase activity and hepatic GSH level and reduces malondialdehyde and ROS levels in the liver tissue. In confirmation, histopathological findings revealed that GEM decrease degeneration, vacuolation and necrosis of hepatocytes and infiltration of inflammatory cells. Conclusion: Present data demonstrated that GEM has antioxidant properties and can protect the liver from APAP toxicity, just in the same pathway that toxicity occurs by toxic ROS and that GEM may be an alternative therapeutic agent to NAC in APAP toxicity.

[2] Schwalm JR, McCreedy T, Lamelas P et al. **Rationale and design of a cluster randomized trial of a multifaceted intervention in people with hypertension: The Heart Outcomes Prevention and Evaluation 4 (HOPE-4) Study.** American heart journal 2018; 203:57-66.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30015069>

ABSTRACT

BACKGROUND: Cardiovascular disease is the leading cause of death throughout the world, with the majority of deaths occurring in low- and middle-income countries. Despite clear evidence for the benefits of blood pressure reduction and availability of safe and low-cost medications, most individuals are either unaware of their condition or not adequately treated. OBJECTIVE: The primary objective of this study is to evaluate whether a community-based, multifaceted intervention package primarily provided by nonphysician health workers can improve long-term cardiovascular risk in people with hypertension by addressing identified barriers at the patient, health care provider, and health system levels. METHODS/DESIGN: HOPE-4 is a community-based, parallel-group, cluster randomized controlled trial involving 30 communities (1,376 participants) in Colombia and Malaysia. Participants ≥ 50 years old and with newly diagnosed or poorly controlled hypertension were included. Communities were randomized to usual care or to a multifaceted intervention package that entails (1) detection, treatment, and control of cardiovascular risk factors by nonphysician health workers in the community, who use tablet-based simplified management algorithms, decision support, and counseling programs; (2) free dispensation of combination antihypertensive and cholesterol-lowering medications, supervised by local physicians; and (3) support from a participant-nominated treatment supporter (either a friend or family member). The primary outcome is the change in Framingham Risk Score after 12 months

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between the intervention and control communities. Secondary outcomes including change in blood pressure, lipid levels, and Interheart Risk Score will be evaluated. SIGNIFICANCE: If successful, the study could serve as a model to develop low-cost, effective, and scalable strategies to reduce cardiovascular risk in people with hypertension.

[3] *Peterson CM, Beyl RA, Marlatt KL et al. Effect of 12 wk of resistant starch supplementation on cardiometabolic risk factors in adults with prediabetes: a randomized controlled trial. The American journal of clinical nutrition 2018.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30010698>

ABSTRACT

Background: Type 2 resistant starch (RS2) has been shown to improve glycemic control and some cardiovascular endpoints in rodent and human studies. Objective: The aim of this study was to perform one of the first randomized clinical trials in adults with prediabetes and one of the longest trials to test whether RS2 can improve cardiometabolic health. Design: 68 overweight [body mass index (BMI) ≥ 27 kg/m²] adults aged 35-75 y with prediabetes were randomized to consume 45 g/d of high-amylose maize (RS2) or an isocaloric amount of the rapidly digestible starch amylopectin (control) for 12 wk. At baseline and postintervention, ectopic fat depots (visceral adipose tissue, intrahepatic lipids, and intramyocellular lipids) were measured by magnetic resonance imaging/spectroscopy, energy metabolism by respiratory chamber, and carbohydrate metabolism by glycated hemoglobin (HbA1c), an intravenous glucose tolerance test, and a meal tolerance test. Cardiovascular risk factors-serum lipids, blood pressure, heart rate, and inflammatory markers (high-sensitivity C-reactive protein [hs-CRP], interleukin-6, and tumor necrosis factor [TNF]- α)-were also measured. The primary endpoints were insulin sensitivity, insulin secretion, ectopic fat, and markers of inflammation. Data were primarily analyzed as treatment effects via a linear mixed model both with and without the addition of covariates. Results: Relative to the control group, RS2 lowered HbA1c by a clinically insignificant 0.1 \pm 0.2% (Delta = -1 \pm 2 mmol/mol; P = 0.05) but did not affect insulin secretion, insulin sensitivity, the disposition index, or glucose or insulin areas under the curve relative to baseline (P \geq 0.23). RS2 decreased heart rate by 5 \pm 9 beats/min (P = 0.02) and TNF- α concentrations by 2.1 \pm 2.7 pg/mL (P = 0.004), relative to the control group. Ectopic fat, energy expenditure, substrate oxidation, and all other cardiovascular risk factors were unaffected (P \geq 0.06). Conclusions: 12 wk of supplementation with resistant starch reduced the inflammatory marker TNF- α and heart rate, but it did not significantly improve glycemic control and other cardiovascular disease risk factors, in adults with prediabetes. This trial was registered at clinicaltrials.gov as NCT01708694.

[4] *Jarrett KE, Lee C, De Giorgi M et al. Somatic Editing of Ldlr With Adeno-Associated Viral-CRISPR Is an Efficient Tool for Atherosclerosis Research. Arteriosclerosis, thrombosis, and vascular biology 2018.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30026278>

ABSTRACT

OBJECTIVE: Atherosclerosis studies in Ldlr knockout mice require breeding to homozygosity and congenic status on C57BL6/J background, a process that is both time and resource intensive. We aimed to develop a new method for generating atherosclerosis through somatic deletion of Ldlr in livers of adult mice. APPROACH AND RESULTS: Overexpression of PCSK9 (proprotein convertase subtilisin/kexin type 9) is currently used to study atherosclerosis, which promotes degradation of LDLR (low-density

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lipoprotein receptor) in the liver. We sought to determine whether CRISPR/Cas9 (clustered regularly interspaced short palindromic repeats-associated 9) could also be used to generate atherosclerosis through genetic disruption of Ldlr in adult mice. We engineered adeno-associated viral (AAV) vectors expressing *Staphylococcus aureus* Cas9 and a guide RNA targeting the Ldlr gene (AAV-CRISPR). Both male and female mice received either (1) saline, (2) AAV-CRISPR, or (3) AAV-hPCSK9 (human PCSK9)-D374Y. A fourth group of germline Ldlr-KO mice was included for comparison. Mice were placed on a Western diet and followed for 20 weeks to assess plasma lipids, PCSK9 protein levels, atherosclerosis, and editing efficiency. Disruption of Ldlr with AAV-CRISPR was robust, resulting in severe hypercholesterolemia and atherosclerotic lesions in the aorta. AAV-hPCSK9 also produced hypercholesterolemia and atherosclerosis as expected. Notable sexual dimorphism was observed, wherein AAV-CRISPR was superior for Ldlr removal in male mice, while AAV-hPCSK9 was more effective in female mice. **CONCLUSIONS:** This all-in-one AAV-CRISPR vector targeting Ldlr is an effective and versatile tool to model atherosclerosis with a single injection and provides a useful alternative to the use of germline Ldlr-KO mice.

[5] *Baris G, Mach F. Lipid management in ACS: Should we go lower faster? Atherosclerosis* 2018; 275:368-375.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30015301>

ABSTRACT

Low-density lipoprotein-cholesterol (LDL-C) is a well-accepted causal risk factor for athero-thrombotic cardiovascular disease, as demonstrated in large epidemiological studies, including Mendelian randomization data. Several randomized controlled trials and meta-analyses have shown that lipid lowering therapies, such as statins and more recently the non-statin agents ezetimibe and Proprotein Convertase Subtilisin Kexin type 9 (PCSK9) monoclonal antibodies (mAb), reduce cardiovascular events across a broad range of baseline LDL-C levels. Over time, the recommended target for LDL-C has become more stringent, moving from 2.6mmol/l to 1.8mmol/l in very high-risk patients. It is currently recommended to start high intensity statin treatment immediately after acute coronary syndromes (ACS) to maximally and rapidly reduce LDL-C. The novel treatment options enable the achievement of very low LDL-C levels below 1mmol/l, with no reported safety issues, in particular with regard to neurocognitive events. However, current evidence supports the use of PCSK9 mAb treatment in ACS patients only after an initial 2-3 month run-up treatment adaptation period with maximally tolerated statin. The use of PCSK9 mAb immediately in the acute phase of ACS (<1 month) remains to be studied. Some data suggest that circulating PCSK9 increases coronary plaque vulnerability, inflammation as well as platelet aggregation in the acute phase of ACS, potentially justifying earlier PCSK9 mAb treatment initiation. As the use of novel treatment combinations in ACS is further explored to widen the perspectives of a more personalized approach for the management of ACS based on individual patient risk profile and baseline LDL-C values, their relative cost-effectiveness will also need to be assessed.

[6] *Kereiakes DJ, Lepor NE, Gerber R et al. Efficacy and safety of alirocumab in patients with or without prior coronary revascularization: Pooled analysis of eight ODYSSEY phase 3 trials. Atherosclerosis* 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30025648>

ABSTRACT

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BACKGROUND AND AIMS: Patients with atherosclerotic cardiovascular disease (ASCVD) and prior revascularization are at high risk of further cardiovascular events and may require additional lipid-lowering therapies beyond maximally tolerated statin therapy. We assessed the efficacy and safety of alirocumab, a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor, in patients with ASCVD, with or without prior coronary revascularization (percutaneous coronary intervention [PCI] or coronary artery bypass graft [CABG]). **METHODS:** Data from eight controlled (placebo/ezetimibe) phase 3 ODYSSEY trials were pooled and stratified by trial design: alirocumab 150mg or 75mg with possible dose increase to 150mg (75/150mg) every 2 weeks (Q2W) versus placebo, and alirocumab 75/150mg Q2W versus ezetimibe. Most patients received background maximally tolerated statin therapy. **RESULTS:** Among 4629 randomized patients with hypercholesterolemia, 3382 had ASCVD including 2191 with prior revascularization. Although baseline characteristics were comparable between alirocumab and control groups, revascularized patients were more likely to be male, have had prior myocardial infarction/stroke, have higher lipoprotein (a) and PCSK9 levels, and were more often treated with high-intensity statin therapy. Alirocumab significantly reduced low-density lipoprotein cholesterol (LDL-C; primary endpoint; $p < 0.0001$), lipoprotein (a), non-high-density lipoprotein cholesterol, and apolipoprotein B levels from baseline to week 24 (vs. control), regardless of stratified treatment group or revascularization status. On-treatment LDL-C levels with alirocumab ranged from 45.6 to 64.8mg/dL. Alirocumab had a similar safety profile regardless of revascularization status, and higher rates of injection-site reactions versus controls. **CONCLUSIONS:** Alirocumab is generally well-tolerated and effective with a similar safety profile in high-risk patients with or without prior revascularization (PCI/CABG).

[7] *Nguyen HN, Ahn YJ, Medina EA, Asmis R. Dietary 23-hydroxy ursolic acid protects against atherosclerosis and obesity by preventing dyslipidemia-induced monocyte priming and dysfunction. Atherosclerosis* 2018; 275:333-341.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30015296>

ABSTRACT

BACKGROUND AND AIMS: We demonstrated that dietary ursolic acid (UA) reduces atherosclerotic lesion size and improves kidney function in diabetic mice. Based on structure-function analyses of naturally occurring UA analogs, we synthesized 23-hydroxy ursolic acid (23-OHUA), a compound with structural features predicted to enhance its bioavailability and anti-atherogenic properties compared to UA. The goal of this study was to determine the anti-obesogenic and atheroprotective properties of 23-OHUA and its mechanism of action. **METHODS:** We performed chemotaxis assays to determine IC50 of phytochemicals on primed THP-1 monocytes. We fed 12-week old female LDLR(-/-) mice a high-fat diet (HFD) or a HFD supplemented with either 0.05% UA or 0.05% 23-OHUA, and measured monocyte priming, weight gain and atherosclerotic lesion size after 6 and 20 weeks. **RESULTS:** Both dietary UA and 23-OHUA prevented dyslipidemia-induced loss of MKP-1 activity, and hyper-chemotactic activity, hallmarks of blood monocytes priming and dysfunction, but they did not affect plasma lipids or blood glucose levels nor WBC and monocyte counts. After 20 weeks, mice fed 23-OHUA showed 11% less weight gain compared to HFD-fed control mice and a 40% reduction in atherosclerotic plaque size, whereas UA reduced lesion size by only 19% and did not reduce weight gain. **CONCLUSIONS:** Dietary 23-OHUA reduces weight gain and attenuates atherogenesis in mice by protecting monocytes against metabolic stress-induced priming and dysfunction. Based on its mechanism of action, 23-OHUA may represent a novel therapeutic approach for the prevention and treatment of obesity and atherosclerosis.

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[8] Tall AR. **Plasma high density lipoproteins: Therapeutic targeting and links to atherogenic inflammation.** *Atherosclerosis* 2018; 276:39-43.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30029099>

ABSTRACT

Plasma HDL levels have an inverse relationship to coronary artery disease (CAD) risk, which led to the idea that increasing HDL levels therapeutically would ameliorate atherosclerosis. Human genetic deficiency of CETP caused markedly elevated HDL and moderately reduced non-HDL cholesterol levels, suggesting that CETP inhibitors might produce cardiovascular benefit. The CETP inhibitor anacetrapib reproduced the phenotype of homozygous CETP deficiency and showed a highly significant benefit for CAD in the REVEAL trial. However, the magnitude of this effect was moderate, and the mechanism of benefit remains unclear. Insights into the mechanisms underlying macrophage cholesterol efflux and reverse cholesterol transport have come from monogenic human disorders and transgenic mouse studies. In particular, the importance of the ATP binding cassette transporters ABCA1 and ABCG1 in promoting cholesterol efflux from myeloid and other hematopoietic cells has been shown and linked to aberrant myelopoiesis and macrophage inflammation. Recent studies have shown that myeloid deficiency of ABCA1 and ABCG1 leads to macrophage and neutrophil inflammasome activation, which in turn promotes atherosclerotic plaque development and notably the formation of neutrophil extracellular traps (NETs) in plaques. In addition, clonal hematopoiesis has emerged as an important CAD risk factor, likely involving macrophage inflammation and inflammasome activation. Further elucidation of the mechanisms linking plaque accumulation of cholesterol and oxidized lipids to myeloid cell inflammation may lead to the development of new therapeutics specifically targeting atherogenic inflammation, with likely benefit for CAD.

[9] Mazza A, Lenti S, Schiavon L et al. **Effect of Monocolin K and COQ10 supplementation in hypertensive and hypercholesterolemic subjects with metabolic syndrome.** *Biomedicine & pharmacotherapy* = *Biomedecine & pharmacotherapie* 2018; 105:992-996.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30021394>

ABSTRACT

INTRODUCTION: Metabolic syndrome (MetS) is a world-wide epidemic disease with an increased risk of morbidity and mortality. Treatment strategies of MetS include pharmacologic and non-pharmacologic interventions and in this respect a relevant role has been shown for nutraceutical compounds (NCs). The aim of this study was to investigate the efficacy and safety of NCs incorporated with diet and lifestyle management versus diet alone, in lowering blood pressure (BP) values and improving lipid and glucose profile, in a group of hypertensives and hyper-cholesterolemic patients with MetS. **METHODS:** 104 subjects with MetS (mean age 57.4+/-8.8 years, 51% males) without history of cardio-vascular (CV) diseases were enrolled in the study. 52 subjects were treated with a once-daily oral formulation of a NCs containing red yeast rice and coenzyme Q10 added to their diet for 2 months and were compared with the 52 patients following a diet program. Differences in BP, serum total cholesterol (TC), low- and high-density-lipoprotein cholesterol (LDLC and HDLC), triglycerides (TG) and glucose values were compared by analysis of variance. **RESULTS:** A significant reduction of BP, TC, TG, LDLC and glucose levels was observed in both treatment groups. However, a greater reduction of systolic BP (-5.2 vs. -3.0mmHg), diastolic BP (-4.9 vs. 2.9mmHg), total cholesterol (-17.2%), LDLC (-21.8%), TG (-16.0%) and serum glucose (-3.4%) was observed in the treatment group relative to the control (p<0.001 for all); HDLC remained

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unchanged ($p=N.S.$). Gender difference was not found in either group ($p=N.S.$). **CONCLUSIONS:** In patients with MetS, NC supplementation was safe, well tolerated and effective in improving clinic BP, lipid and glucose profile.

[10] Fotso Soh J, Torres-Platas SG, Beaulieu S et al. **Atorvastatin in the treatment of Lithium-induced nephrogenic diabetes insipidus: the protocol of a randomized controlled trial.** BMC psychiatry 2018; 18:227.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30012135>

ABSTRACT

BACKGROUND: Lithium is the gold-standard treatment for bipolar disorder, is highly effective in treating major depressive disorder, and has anti-suicidal properties. However, clinicians are increasingly avoiding lithium largely due to fears of renal toxicity. Nephrogenic Diabetes Insipidus (NDI) occurs in 15-20% of lithium users and predicts a 2-3 times increased risk of chronic kidney disease (CKD). We recently found that use of statins is associated with lower NDI risk in a cross-sectional study. In this current paper, we describe the methodology of a randomized controlled trial (RCT) to treat lithium-induced NDI using atorvastatin. **METHODS:** We will conduct a 12-week, double-blind placebo-controlled RCT of atorvastatin for lithium-induced NDI at McGill University, Montreal, Canada. We will recruit 60 current lithium users, aged 18-85, who have indicators of NDI, which we defined as urine osmolality (UOsm) < 600 mOsm/kg after 10-h fluid restriction. We will randomize patients to atorvastatin (20 mg/day) or placebo for 12 weeks. We will examine whether this improves measures of NDI: UOsm and aquaporin (AQP2) excretion at 12-week follow-up, adjusted for baseline. **RESULTS:** Not applicable. **CONCLUSION:** The aim of this clinical trial is to provide preliminary data about the efficacy of atorvastatin in treating NDI. If successful, lithium could theoretically be used more safely in patients with a reduced subsequent risk of CKD, hypernatremia, and acute kidney injury (AKI). If future definitive trials confirm this, this could potentially allow more patients to benefit from lithium, while minimizing renal risk. **TRIAL REGISTRATION:** ClinicalTrials.gov NCT02967653 . Registered in February 2017.

[11] Tissier F, Farhat F, Philouze C et al. **Long-term atorvastatin treatment decreases heart maximal oxygen consumption and its vulnerability to in vitro oxidative stress in WHHL rabbit.** Canadian journal of physiology and pharmacology 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30011375>

ABSTRACT

Statins are currently used in prevention of cardiovascular diseases in high risk populations, and could be considered in primary prevention. However, few studies are available on the long-term effects of low-doses of statins, especially on mitochondrial function and ROS (Reactive Oxygen Species) metabolism at cardiac level. This study aimed to determine potential effects of a long-term atorvastatin treatment, at low-dose concentration, on the myocardium mitochondrial respiration. 34 Watanabe rabbits were treated or not with atorvastatin (2.5 mg.Kg-1.Day-1) from the age of 3 to 12 months. Every three months, proton leak, basal (V_0) and maximal (V_{max}) mitochondrial respiration on cardiac permeabilized fibers were measured. Additionally, the vulnerability to ROS, cardiac enzymatic antioxidant defenses and oxidative damage (lipoperoxidation) were analyzed. Proton leak increased over the duration of the experiment (up to 60% from V_{max} at 12 month). Moreover, the statin treatment induced a decrease of V_{max} and a decrease of ROS susceptibility of cardiac mitochondria. However, the lipoperoxidation and

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the antioxidant defenses were not dependent neither on the presence of statin treatment, neither on its duration. This is the first time study showing a protective effect of long-term statins treatment against the ROS susceptibility in the cardiac muscle.

[12] Murff HJ, Roumie CL, Greevy RA et al. **Metformin use and incidence cancer risk: evidence for a selective protective effect against liver cancer.** Cancer Causes Control 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30022336>

ABSTRACT

PURPOSE: Several observational studies suggest that metformin reduces incidence cancer risk; however, many of these studies suffer from time-related biases and several cancer outcomes have not been investigated due to small sample sizes. **METHODS:** We constructed a propensity score-matched retrospective cohort of 84,434 veterans newly prescribed metformin or a sulfonylurea as monotherapy. We used Cox proportional hazard regression to assess the association between metformin use compared to sulfonylurea use and incidence cancer risk for 10 solid tumors. We adjusted for clinical covariates including hemoglobin A1C, antihypertensive and lipid-lowering medications, and body mass index. Incidence cancers were defined by ICD-9-CM codes. **RESULTS:** Among 42,217 new metformin users and 42,217 matched-new sulfonylurea users, we identified 2,575 incidence cancers. Metformin was inversely associated with liver cancer (adjusted hazard ratio [aHR] = 0.44, 95% CI 0.31, 0.64) compared to sulfonylurea. We found no association between metformin use and risk of incidence bladder, breast, colorectal, esophageal, gastric, lung, pancreatic, prostate, or renal cancer when compared to sulfonylurea use. **CONCLUSIONS:** In this large cohort study that accounted for time-related biases, we observed no association between the use of metformin and most cancers; however, we found a strong inverse association between metformin and liver cancer. Randomized trials of metformin for prevention of liver cancer would be useful to verify these observations.

[13] Kim CJ, Han EJ, Chu EH et al. **Effect of moderate-intensity statin therapy on plaque inflammation in patients with acute coronary syndrome: A prospective interventional study evaluated by 18F-FDG PET/CT of the carotid artery.** Cardiology journal 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30009378>

ABSTRACT

BACKGROUND: Asian patients with acute coronary syndrome (ACS) are frequently prescribed moderate-intensity statin in real practice, even during the early stage of ACS. Under assessment herein was the effect of moderate-intensity statin therapy on the resolution of plaque inflammation during the first month after ACS, a period with highest recurrent ischemic events, using dual time point (1)(8)F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT). **METHODS:** This prospective study included statin-naive patients with ACS and non-calcified carotid plaques ((3) 3 mm on ultrasound images). Baseline FDG PET/CT images of the carotid arteries of the patients were obtained. Then, all patients received atorvastatin (20 mg/day); follow-up FDG PET/CT images of the carotid arteries were then obtained after 1 month of therapy. The primary endpoint measurement was the change in the target-to-background ratio (TBR) of the carotid artery between the initial and follow-up FDG PET/CT scans. **RESULTS:** Thirteen ACS patients completed the initial and follow-up FDG PET/CT scans. Moderate-intensity statin therapy failed to reduce plaque inflammation at 1 month after ACS (TBR 1.60 +/- 0.20 at baseline vs. 1.50 +/- 0.40 after therapy; p = 0.422) but significantly reduced serum

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low-density lipoprotein cholesterol (LDL-C) levels (mean LDL-C 101.2 +/- 21.1 mg/dL at baseline vs. 70.7 +/- 12.4 mg/dL after therapy; $p < 0.001$). Changes in the TBR and serum LDL-C levels were not correlated ($r = -0.27$, $p = 0.243$). CONCLUSIONS: Dual time point FDG PET/CT imaging demonstrates that moderate-intensity statin therapy was insufficient in suppressed plaque inflammation within the first month after ACS in Asian patients, even though achieving target LDL levels.

[14] Moss S, Tardo D, Doyle M, Rees D. **Complex disease management of pregnant young patient with familial hypercholesterolaemia complicated by coronary artery disease and cerebrovascular disease.** Cardiovascular revascularization medicine : including molecular interventions 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30017729>

ABSTRACT

Inherited disorders of lipid metabolism may cause a heavy burden of cardiovascular disease early in life. Familial hypercholesterolaemia (FH) with abnormalities of LDL metabolism results in marked LDL elevations and accelerated, multivessel atherosclerosis presenting in teenage or young adulthood. We describe the case of a 33-year-old woman who presented with exertional angina in the setting of pregnancy who was found post-partum to have severe triple-vessel disease including left main disease on coronary angiography (Figs. 1 and 2). She was also noted to have a typical supravalvular "hourglass" [1] abnormality of the aortic root (Fig. 3), and heavy calcification of the proximal aorta precluding conventional aortic cross clamping and bypass surgery. After discussion with the multidisciplinary team, her disease was felt to be amenable to a beating-heart coronary bypass technique with an anaortic approach to minimise the possibility of cerebral embolism. Significant extracranial cerebrovascular disease, a major risk for cardiopulmonary bypass, reinforced the beating-heart technique. Her ongoing management has consisted of medical therapy with cessation of breast feeding, statins, ezetimibe, and introduction of PCSK9-inhibitor therapy. This case illustrates a number of the difficulties associated with management of widespread atherosclerotic disease associated with FH, in which an excellent outcome was achieved with the assistance of a multi-disciplinary team.

[15] Dixit A, Abrudescu A. **A Case of Atorvastatin-Associated Necrotizing Autoimmune Myopathy, Mimicking Idiopathic Polymyositis.** Case Rep Rheumatol 2018; 2018:5931046.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30026996>

ABSTRACT

Statin-induced necrotizing autoimmune myopathy (SINAM) is a rare side effect of statin use which manifests as progressive muscle weakness. Because statins are a widely prescribed medication for coronary artery disease, hyperlipidemia, and many other diseases, many patients are at risk of developing SINAM or one of the many other statin-induced myopathies. Due to identification of an antibody specific to this disease, we were able to diagnose SINAM in a patient whose symptoms had progressed to the extent that they were debilitating. Our case describes SINAM in a patient undergoing treatment with a statin for an extended period of time, diagnosis of the disease process, treatment, and resolution of symptoms.

[16] Gao CZ, Ma QQ, Wu J et al. **Comparison of the Effects of Ticagrelor and Clopidogrel on Inflammatory Factors, Vascular Endothelium Functions and Short-Term Prognosis in Patients with**

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Acute ST-Segment Elevation Myocardial Infarction Undergoing Emergency Percutaneous Coronary Intervention: a Pilot Study. *Cellular physiology and biochemistry : international journal of experimental cellular physiology, biochemistry, and pharmacology* 2018; 48:385-396.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30016801>

ABSTRACT

BACKGROUND/AIMS: Acute ST-segment elevation of myocardial infarction (STEMI) is the most severe type of acute coronary syndrome (ACS). Particular attention has been focused on studying the pathogenesis of STEMI, and how to prevent thrombosis, reduce inflammatory reaction, stabilize plaques and improve vascular endothelial functions to preserve the survived myocardium. This study aimed to compare the anti-inflammatory endothelium-protective effects, clinical prognosis, and relevant bleeding risks of ticagrelor versus clopidogrel in patients with STEMI who underwent urgent percutaneous coronary intervention (PCI) and provide certain experimental evidence and a theoretical basis for the selection of safe and effective drugs and their proper dosage, thereby further guiding clinical medication. **METHODS:** We sequentially enrolled 193 patients (104 males and 89 females) admitted to hospital due to acute STEMI. These patients underwent urgent PCI between December 2013 and May 2015 and met the inclusion criteria. They were assigned (1: 1) into two groups according to different treatments, 97 patients in the ticagrelor group (treatment group), and 96 patients in the clopidogrel group (control group). Levels of hypersensitive C-reactive protein (hs-CRP), interleukin-6 (IL-6), and endothelial cell-specific molecule 1 (ESM-1) taken at admission and 24 h, 4 days, and 7 days after administration, as well as the correlation between the levels of IL-6, hs-CRP, and ESM-1, were determined in the two groups. At the same time, the effects of treatment with ticagrelor and clopidogrel on the efficacy endpoint events (ischemic and safety) were explored. **RESULTS:** No statistically significant difference was found in the levels of hs-CRP, IL-6, or ESM-1 at admission between the two groups ($P > 0.05$); Their levels were significantly elevated 24 h after administration, with statistical differences between two groups ($P < 0.05$). Furthermore, a downward trend with statistically significant differences was found on Day 4 and Day 7 ($P < 0.05$); ESM-1 levels increased along with increases of hs-CRP and IL-6 levels, indicating ESM-1 was positively correlated with hs-CRP ($r=0.523$, $P < 0.001$) and IL-6 ($r=0.431$, $P < 0.001$); and the occurrence rates of ischemic endpoint events at 30 days were lower in the treatment group than in the control group. The occurrence of safety endpoint events was higher than in the control group; however, no statistically significant difference was found ($P > 0.05$). **CONCLUSIONS:** Compared with clopidogrel, ticagrelor appears to rapidly reduce the prevalence of inflammatory reactions and stabilize the functions of vascular endothelium to improve the stability of atherosclerotic plaque and decrease the occurrence rate of thrombosis as well as ischemic outcome events without any obvious increase in the risk of bleeding in patients with acute STEMI receiving urgent PCI. This renders it a potential drug for clinical practice. At the same time, measurement of ESM-1, a new biological marker for vascular endothelial function disorder, could possibly become a simple, effective, and practical new method for clinical evaluation of risk stratification of patients with acute STEMI at admission.

[17] *Paulin N, Viola JR, Maas SL et al. Double-Strand DNA Sensing Aim2 Inflammasome Regulates Atherosclerotic Plaque Vulnerability. Circulation* 2018; 138:321-323.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30012706>

ABSTRACT

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[18] Marzal D, Rodriguez Padial L, Arnaiz JA et al. **Use of the cardiovascular polypill 40mg in secondary cardiovascular prevention.** Clinica e investigacion en arteriosclerosis : publicacion oficial de la Sociedad Espanola de Arteriosclerosis 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30017176>

ABSTRACT

Controlling cardiovascular risk factors (CV) is essential for patients with cardiovascular disease. The CV polypill contains aspirin 100mg, atorvastatin 20mg or 40mg, and ramipril 2.5mg, 5mg or 10mg in a fixed combination pill. The objective was to review the evidence on the secondary prevention of cardiovascular disease, to establish the eventual patient profiles suitable to consider the use of CV polypill with atorvastatin 40mg in secondary CV prevention (P40PS), and to define the priority situations most adequate for the use of P40PS. A bibliographic review was carried out, which was complemented with the clinical opinion of 19 specialists. During hospitalization and discharge, P40PS is an option for patients admitted because of an atherothrombotic event, peripheral arterial disease, or other causes, and with the indication of the monocomponents. Its priority use is proposed in: prior intolerance to the highest dose of atorvastatin (80mg), age > 75 years, low weight, stage 3 of chronic renal failure, hypothyroidism, drug interactions and Asian origin. Outside the hospital setting, the P40PS is a therapeutic alternative in patients with a need for secondary CV prevention and with indication to receive the monocomponents. The priority situations to receive the P40PS are: to be taking the three components separately, to require polypharmacy, lack of adherence or understanding of the treatment, and lack of control of CV risk factors. This work is the first with proposals for the use of P40PS and can facilitate the treatment of patients with cardiovascular disease in secondary prevention.

[19] Abdelhamid AS, Martin N, Bridges C et al. **Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease.** The Cochrane database of systematic reviews 2018; 7:Cd012345.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30019767>

ABSTRACT

BACKGROUND: Evidence on the health effects of total polyunsaturated fatty acids (PUFA) is equivocal. Fish oils are rich in omega-3 PUFA and plant oils in omega-6 PUFA. Evidence suggests that increasing PUFA-rich foods, supplements or supplemented foods can reduce serum cholesterol, but may increase body weight, so overall cardiovascular effects are unclear. **OBJECTIVES:** To assess effects of increasing total PUFA intake on cardiovascular disease and all-cause mortality, lipids and adiposity in adults. **SEARCH METHODS:** We searched CENTRAL, MEDLINE and Embase to April 2017 and clinicaltrials.gov and the World Health Organization International Clinical Trials Registry Platform to September 2016, without language restrictions. We checked trials included in relevant systematic reviews. **SELECTION CRITERIA:** We included randomised controlled trials (RCTs) comparing higher with lower PUFA intakes in adults with or without cardiovascular disease that assessed effects over 12 months or longer. We included full texts, abstracts, trials registry entries and unpublished data. Outcomes were all-cause mortality, cardiovascular disease mortality and events, risk factors (blood lipids, adiposity, blood pressure), and adverse events. We excluded trials where we could not separate effects of PUFA intake from other dietary, lifestyle or medication interventions. **DATA COLLECTION AND ANALYSIS:** Two review authors independently screened titles and abstracts, assessed trials for inclusion, extracted data, and assessed risk of bias. We wrote to authors of included trials for further data. Meta-analyses used random-effects analysis, sensitivity analyses included fixed-effects and limiting to low summary risk of bias. We assessed

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GRADE quality of evidence. MAIN RESULTS: We included 49 RCTs randomising 24,272 participants, with duration of one to eight years. Eleven included trials were at low summary risk of bias, 33 recruited participants without cardiovascular disease. Baseline PUFA intake was unclear in most trials, but 3.9% to 8% of total energy intake where reported. Most trials gave supplemental capsules, but eight gave dietary advice, eight gave supplemental foods such as nuts or margarine, and three used a combination of methods to increase PUFA. Increasing PUFA intake probably has little or no effect on all-cause mortality (risk 7.8% vs 7.6%, risk ratio (RR) 0.98, 95% confidence interval (CI) 0.89 to 1.07, 19,290 participants in 24 trials), but probably slightly reduces risk of coronary heart disease events from 14.2% to 12.3% (RR 0.87, 95% CI 0.72 to 1.06, 15 trials, 10,076 participants) and cardiovascular disease events from 14.6% to 13.0% (RR 0.89, 95% CI 0.79 to 1.01, 17,799 participants in 21 trials), all moderate-quality evidence. Increasing PUFA may slightly reduce risk of coronary heart disease death (6.6% to 6.1%, RR 0.91, 95% CI 0.78 to 1.06, 9 trials, 8810 participants) and stroke (1.2% to 1.1%, RR 0.91, 95% CI 0.58 to 1.44, 11 trials, 14,742 participants, though confidence intervals include important harms), but has little or no effect on cardiovascular mortality (RR 1.02, 95% CI 0.82 to 1.26, 16 trials, 15,107 participants) all low-quality evidence. Effects of increasing PUFA on major adverse cardiac and cerebrovascular events and atrial fibrillation are unclear as evidence is of very low quality. Increasing PUFA intake slightly reduces total cholesterol (mean difference (MD) -0.12 mmol/L, 95% CI -0.23 to -0.02, 26 trials, 8072 participants) and probably slightly decreases triglycerides (MD -0.12 mmol/L, 95% CI -0.20 to -0.04, 20 trials, 3905 participants), but has little or no effect on high-density lipoprotein (HDL) (MD -0.01 mmol/L, 95% CI -0.02 to 0.01, 18 trials, 4674 participants) or low-density lipoprotein (LDL) (MD -0.01 mmol/L, 95% CI -0.09 to 0.06, 15 trials, 3362 participants). Increasing PUFA probably causes slight weight gain (MD 0.76 kg, 95% CI 0.34 to 1.19, 12 trials, 7100 participants). Effects of increasing PUFA on serious adverse events such as pulmonary embolism and bleeding are unclear as the evidence is of very low quality. AUTHORS' CONCLUSIONS: This is the most extensive systematic review of RCTs conducted to date to assess effects of increasing PUFA on cardiovascular disease, mortality, lipids or adiposity. Increasing PUFA intake probably slightly reduces risk of coronary heart disease and cardiovascular disease events, may slightly reduce risk of coronary heart disease mortality and stroke (though not ruling out harms), but has little or no effect on all-cause or cardiovascular disease mortality. The mechanism may be via lipid reduction, but increasing PUFA probably slightly increases weight.

[20] *Riksen NP, Stienstra R. Metabolism of innate immune cells: impact on atherosclerosis. Current opinion in lipidology* 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30020200>

ABSTRACT

PURPOSE OF REVIEW: It is increasingly recognized that profound metabolic changes occur in activated myeloid cells, which shape their inflammatory phenotype and cellular functions. The purpose of this review is to summarize the accumulating evidence that major metabolic adaptations occur in monocytes and macrophages in the context of atherosclerosis ultimately modulating atherosclerotic plaque formation. RECENT FINDINGS: Plaque macrophages show a profound metabolic reprogramming which is driven by atherogenic factors in the plaque microenvironment, such as damage associated molecular patterns, modified lipoproteins, and hypoxia. In addition, systemic atherogenic factors modulate metabolism of circulating monocytes and their bone marrow progenitors. Activation of glycolysis, the pentose phosphate pathway, and fatty acid synthesis, a reduction of fatty acid oxidation accompanied by complex changes in the lysosomal handling of lipids all appear to facilitate atherogenesis. These processes also drive the development of trained immunity, a phenomenon describing the persistent

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pro-inflammatory phenotype that develops after brief stimulation of monocytes with pro-atherogenic stimuli. SUMMARY: A pro-atherosclerotic environment reprograms the metabolism of myeloid cells in the various developmental phases of atherosclerosis. Knowledge of these metabolic programs facilitates the development of novel drugs to prevent atherosclerotic cardiovascular disease.

[21] *Generoso G, Bensenor IM, Santos IS et al. Diabetes alters the association between high-density lipoprotein subfractions and carotid intima-media thickness: The Brazilian Longitudinal Study of Adult Health (ELSA-Brasil).* Diabetes & vascular disease research 2018:1479164118788080.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30024274>

ABSTRACT

INTRODUCTION: High-density lipoprotein cholesterol comprises a group of heterogeneous subfractions that might have differential effects on atherosclerosis. Moreover, prior investigations suggest that the presence of diabetes (T2D) modifies the impact of some subfractions on atherosclerosis. In this study, we aimed to evaluate the association between high-density lipoprotein cholesterol subfractions and carotid intima-media thickness in the baseline assessment of the Brazilian Longitudinal Study of Adult Health participants from the Sao Paulo investigation centre. METHODS: We evaluated 3930 individuals between 35 and 74 years without previous cardiovascular disease not using lipid-lowering drugs. High-density lipoprotein cholesterol subfractions (HDL2-C and HDL3-C) were measured by vertical ultracentrifugation (vertical auto profile). The relationship between each high-density lipoprotein cholesterol subfraction and carotid intima-media thickness was analysed by multiple linear regression models. RESULTS: Total high-density lipoprotein cholesterol, as well as HDL2-C and HDL3-C, was negatively associated with carotid intima-media thickness after adjustment for demographic data (all $p < 0.001$) and traditional risk factors (all $p < 0.05$). When stratified by T2D status, the HDL2-C/HDL3-C ratio showed a negative association with carotid intima-media thickness in participants with T2D ($p = 0.032$), even after fully controlling for confounding variables, including total high-density lipoprotein cholesterol. CONCLUSION: HDL2-C, HDL3-C and HDL2/HDL3-C ratio are inversely associated with carotid intima-media thickness after adjustment for traditional risk factors. Association of the HDL2-C/HDL3-C ratio is modified by the presence of diabetes, being more pronounced in diabetic individuals.

[22] *Butterworth RF, Canbay A. Hepatoprotection by L-Ornithine L-Aspartate in Non-Alcoholic Fatty Liver Disease.* Dig Dis 2018:1-6.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30016770>

ABSTRACT

BACKGROUND: Non-alcoholic fatty liver disease (NAFLD) is the leading chronic hepatic condition worldwide and new approaches to management and treatment are limited. SUMMARY: L-ornithine L-aspartate (LOLA) has hepatoprotective properties in patients with fatty liver of diverse etiology and results of a multicenter randomized clinical trial reveal that 12 weeks treatment with oral LOLA (6-9 g/d) results in a dose-related reduction in activities of liver enzymes and triglycerides together with significant improvements of liver/spleen CT ratios. A preliminary report described improvements of hepatic microcirculation in patients with non-alcoholic steatohepatitis (NASH) following treatment with LOLA. Mechanisms responsible for the beneficial effects of LOLA in NAFLD/NASH involve, in addition to its established ammonia-lowering effect, metabolic transformations of the LOLA-constituent amino acids L-ornithine and L-aspartate into L-glutamine, L-arginine, and glutathione. These metabolites have

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well-established actions implicated in the prevention of lipid peroxidation, improvement of hepatic microcirculation in addition to anti-inflammatory, and anti-oxidant properties. Key Messages: (1) LOLA is effective for the treatment of key indices in NAFLD/NASH. (2) Mechanisms other than LOLA's ammonia-lowering action have been postulated. (3) Further assessments in the clinical setting are now required.

[23] Kosmas CE, Munoz Estrella A, Sourlas A et al. **Inclisiran: A New Promising Agent in the Management of Hypercholesterolemia.** Diseases (Basel, Switzerland) 2018; 6.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30011788>

ABSTRACT

The discovery of proprotein convertase subtilisin-kexin type 9 (PCSK9), a serine protease which binds to the low-density lipoprotein (LDL) receptors and targets the receptors for lysosomal degradation, offered an additional route through which plasma LDL-cholesterol (LDL-C) levels can be controlled. Initially, the therapeutic approaches to reduce circulating levels of PCSK9 were focused on the use of monoclonal antibodies. To that effect, evolocumab and alirocumab, two human monoclonal antibodies directed against PCSK9, given on a background of statin therapy, have been shown to markedly decrease LDL-C levels and significantly reduce cardiovascular risk. The small interfering RNA (siRNA) molecules have been used recently to target the hepatic production of PCSK9. siRNA interferes with the expression of specific genes with complementary nucleotide sequences by affecting the degradation of mRNA post-transcription, thus preventing translation. Inclisiran is a long-acting, synthetic siRNA directed against PCSK9 and it has been shown to significantly decrease hepatic production of PCSK9 and cause a marked reduction in LDL-C levels. This review aims to present and discuss the current clinical and scientific evidence pertaining to inclisiran, which is a new promising agent in the management of hypercholesterolemia.

[24] Vavlukis M, Vavlukis A. **Adding ezetimibe to statin therapy: latest evidence and clinical implications.** Drugs in context 2018; 7:212534.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30023003>

ABSTRACT

Background: Statins are the hypolipemic treatment of choice for hyperlipidemia with confirmed atherosclerotic cardiovascular disease (ASCVD) protective effect, proven even in normolipemic patients. But in rare situations, even with a high-dose treatment regimen, or maximally tolerated statin dose treatment, treatment targets of low-density lipoprotein cholesterol (LDL-C), according to the risk profile of the patient, cannot be achieved. Combination therapy with ezetimibe is an effective treatment choice, as it is one of the few hypolipemic drugs with proven ASCVD protective effect. Aim: In this review, we address the question of therapeutic efficacy and safety of ezetimibe in combination therapy with statins, as expressed through its hypolipemic and vasoprotective effects and its potential side effects. Methods: We conducted a literature review of English articles through PubMed, PubMed Central, and Cochrane for randomized clinical trials, retrospective analyses, meta-analyses, and review articles by using key words: ezetimibe, statins, combination therapy, adverse effects. We analyzed data on ezetimibe-statin combination therapy in terms of hypolipemic efficacy, ASCVD risk reduction, and adverse effects. Results: Statins have been proven to be very effective in reducing ASCVD risk, with no apparent threshold at which LDL-C lowering is not associated with reduced risk. Yet, a significant on-treatment residual risk of major cardiovascular (CV) events still exists according to meta-analyses of

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statin trials. Findings like this point to the unmet needs of the patients on statin treatment. The unmet needs in terms of LDL-C targets and ASCVD risk reduction raise the question of statin combination therapy. Ezetimibe is a cholesterol-lowering drug from the class of cholesterol absorption inhibitors, with the potency to decrease LDL-C by about 10-18% and Apo B by 11-16%, while in combination therapy with statins, an additional LDL-C lowering of 25% or total LDL-C lowering of 34-61% is observed. The effects on LDL-C and other lipoprotein (LP) fractions are translated by ASCVD risk reduction. Ezetimibe is one of the few hypolipemic medications that leads to additional ASCVD risk reduction when added to statin therapy. Present data on ezetimibe support the existence of pleiotropic anti-inflammatory and antioxidative effects, in addition to its hypolipemic effect, which are responsible for this added ASCVD risk reduction on top of statin monotherapy. Ezetimibe, in combination therapy with a maximal or maximally tolerated statin therapy, is used in patients who fail to achieve target LDL-C levels with statin monotherapy. In combination with low-to-moderate statin dose treatment, or with second- or third-line statins, ezetimibe is used in situations of statin-associated muscle symptoms. The combination therapy is relatively safe. Conclusion: Ezetimibe add-on to statin combination therapy is an effective treatment option that leads to additional LDL-C lowering - recommended in situations where, with a maximal or maximally tolerated statin monotherapy treatment regimen, LDL-C targets cannot be achieved. It leads to additional ASCVD risk reduction, without raising significant safety concerns.

[25] Bougarne N, Weyers B, Desmet SJ et al. **Molecular actions of PPARalpha in lipid metabolism and inflammation.** Endocrine reviews 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30020428>

ABSTRACT

Peroxisome proliferator-activated receptor alpha (PPARalpha) is a nuclear receptor of clinical interest as a drug target in various metabolic disorders. PPARalpha also exhibits marked anti-inflammatory capacities. The first generation PPARalpha agonists, the fibrates, have however been hampered by drug-drug interaction issues, statin drop-in and ill-designed cardiovascular intervention trials. Notwithstanding, understanding the molecular mechanisms by which PPARalpha works will enable control of its activities as a drug target for metabolic diseases with an underlying inflammatory component. Given its role in reshaping the immune system, the full potential of this nuclear receptor subtype as a versatile drug target with high plasticity becomes increasingly clear, and a novel generation of agonists may pave the way for novel fields of applications.

[26] Jankovic SM, Tesic D, Kostic M. **Profile of evolocumab and its cost-effectiveness in patients with high cardiovascular risk: literature review.** Expert review of pharmacoeconomics & outcomes research 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30014724>

ABSTRACT

INTRODUCTION: Evolocumab is fully human monoclonal antibody which binds to proprotein convertase subtilisin/kexin type 9 (PCSK9), and prevents its blocking effect on recycling of liver low-density-lipoprotein (LDL) receptors. Areas covered: The aim of this review was to assess efficacy, safety and cost-effectiveness of evolocumab in adult patients with high cardiovascular risk. Major research databases MEDLINE, EBSCO and CENTRAL were systematically searched for relevant study reports. Expert commentary: Even when given in full doses, statins augmented with ezetimibe and cholesterol-

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binding resins could not reduce cholesterol baseline level for more than 66%, while evolocumab reduces cholesterol level for 75% or even more. Up to now, evolocumab showed good safety profile, and patients tolerate it very well. The abovementioned advantages of evolocumab made it almost ideal drug for hypercholesterolemia, and probably in the future the best drug for secondary prevention of major cardiovascular events. Evolocumab is borderline cost-effective for the treatment of patients with high cardiovascular risk in European countries, while in the USA it is under debate where the underlying assumption (risk of cardiovascular disease events) determine the true value.

[27] *Leporowski A, Godman B, Kurdi A et al. Ongoing activities to optimize the quality and efficiency of lipid-lowering agents in the Scottish National Health System: influence and implications. Expert review of pharmacoeconomics & outcomes research 2018.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30014725>

ABSTRACT

INTRODUCTION AND AIMS: Prescribing of lipid lowering agents (LLAs) has increased worldwide including in Scotland with increasing prevalence of coronary heart disease, and higher dose statins have been advocated in recent years. There have also been initiatives to encourage prescribing of generic versus patented statins to save costs without compromising care. There is a need to document these initiatives and outcomes to provide future direction. METHOD: Assessment of utilization (items dispensed) and expenditure of key LLAs (mainly statins) and expenditure between 2001 and 2015 in Scotland alongside initiatives. RESULTS: Multiple interventions over the years have increased international non-proprietary name (INN) prescribing (99% for statins) and preferential prescribing of generic versus patented statins, and reduced inappropriate prescribing of ezetimibe. This resulted in a 50% reduction in expenditure of LLAs between 2001 and 2015 despite a 412% increase in utilization, increased prescribing of higher dose statins (71% in 2015) especially atorvastatin following generic availability, and reduced prescribing of ezetimibe (reduced by 72% between 2010 and 2015). As a result, the quality of prescribing has improved. CONCLUSION: Generic availability coupled with multiple measures has resulted in appreciable shifts in statin prescribing behavior and reducing ezetimibe prescribing, resulting in improvements in both the quality and efficiency of prescribing.

[28] *Ibanez B, Castellano JM, Fuster V. Polypill strategy at the heart of cardiovascular secondary prevention. Heart 2018.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30030331>

ABSTRACT

[29] *Green DM, Wang M, Krasin MJ et al. Serum ALT elevations in survivors of childhood cancer. A report from the St. Jude Lifetime Cohort Study. Hepatology 2018.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30016547>

ABSTRACT

Background and Rationale for Study: To define the prevalence of and risk factors for elevated serum alanine aminotransferase (ALT) level among adult childhood cancer survivors (CCS). PATIENTS AND METHODS: 2751 CCS from the St. Jude Lifetime Cohort Study (>10 years post-diagnosis, age >/=18

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years). Serum ALT level graded using the Common Terminology Criteria for Adverse Events v 4.03. Modified Poisson regression models were used to estimate relative risks (RR) and 95% confidence intervals (CI) for the association between demographic and clinical factors and grades 1 - 4 ALT on the selected models. MAIN RESULTS: 1339 (48.7%) of CCS were female; 2271 (82.6%) were non-Hispanic white. Median age at evaluation was 31.4 years (Interquartile Range (IQR) = 25.8 - 37.8); median elapsed time from diagnosis to evaluation was 23.2 years (IQR = 17.6 - 29.7). 1137 (41.3%) had ALT > Upper Limit of Normal [Common Terminology Criteria for Adverse Events v 4.03 - Grade 1 - 1058 (38.5%); Grade 2 - 56 (2.0%); Grade 3 - 23 (0.8%); Grade 4 - none]. Multivariable models demonstrated non-Hispanic white race/ethnicity, age at evaluation in years, being overweight or obese, presence of the metabolic syndrome, current treatment with atorvastatin or rosuvastatin or simvastatin, hepatitis C virus infection, prior treatment with busulfan or thioguanine, history of hepatic surgery, and the percentage of liver treated with ≥ 10 Gray, ≥ 15 Gray, or ≥ 20 Gray were associated with elevated ALT. CONCLUSION: Grade 3 or 4 hepatic injury is infrequent in CCS. Mild hepatic injury in this group may be amenable to lifestyle modifications. This article is protected by copyright. All rights reserved.

[30] *Ikdahl E, Wibetoe G, Rollefstad S et al. Guideline recommended treatment to targets of cardiovascular risk is inadequate in patients with inflammatory joint diseases. International journal of cardiology 2018.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30007486>

ABSTRACT

OBJECTIVES: Patients with inflammatory joint diseases (IJD) have an increased risk of cardiovascular disease (CVD). Our goal was to examine indications for, and use of, lipid-lowering therapy (LLT) and antihypertensive treatment (AntiHT) in patients with IJD. Furthermore, to investigate the frequency of low-density lipoprotein cholesterol (LDL-c) and blood pressure (BP) goal attainment among IJD patients. METHODS: The cohort was derived from the NORwegian Collaboration on Atherosclerosis in patients with Rheumatic joint diseases (NOCAR). Indications for AntiHT were: systolic/diastolic BP $\geq 140/90$ mmHg, self-reported hypertension or AntiHT. CVD risk was estimated by the systematic coronary risk evaluation (SCORE) algorithm. LDL-c goals were < 2.6 mmol/L in case of diabetes, total cholesterol > 8 mmol/L or a SCORE estimate $\geq 5\%$, and < 1.8 mmol/L for those with established CVD or SCORE $\geq 10\%$. Comparisons across IJD entities were performed using age and sex adjusted logistic regression. RESULTS: In total, 2277 patients (rheumatoid arthritis: 1376, axial spondyloarthritis: 474, psoriatic arthritis: 427) were included. LLT and AntiHT were indicated in 36.1% and 52.6% of the patients, of whom 37.6% and 47.0% were untreated, respectively. LDL-c and BP targets were obtained in 26.2% and 26.3%, respectively. Guideline recommended treatment and/or corresponding treatment targets were not initiated or obtained in approximately 50%. Rheumatoid arthritis patients were particularly likely to be undertreated with LLT, whereas hypertension undertreatment was most common in psoriatic arthritis. CONCLUSIONS: Inadequate CVD prevention encompasses all the three major IJD entities. The unmet need for CVD preventive measures is not only prevalent in RA, but exists across all the major IJD entities.

[31] *Pitha J. Improved management of patients after acute coronary syndrome: using nonalcoholic fatty liver disease fibrosis score and ezetimibe? International journal of cardiology 2018.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30017528>

ABSTRACT

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[32] Mehta S, Jackson R, Pylypchuk R et al. **Development and validation of alternative cardiovascular risk prediction equations for population health planning: a routine health data linkage study of 1.7 million New Zealanders.** International journal of epidemiology 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30010781>

ABSTRACT

Background: Cardiovascular disease (CVD) risk prediction equations are primarily used in clinical settings to inform individual risk management decisions. We sought to develop and validate alternative equations derived solely from linked routinely collected national health data that could be applied countrywide to inform population health planning. Methods: Individual-level linkage of eight administrative health datasets identified all New Zealand residents aged 30-74 years in contact with publicly funded health services during 2006 with no previous hospitalizations for CVD or heart failure, and with complete data on eight pre-specified predictors. The linked health datasets encompassed demographic characteristics, hospitalizations, outpatient visits, primary care enrolment, primary care reimbursement, community laboratory requests, community pharmaceutical dispensing and mortality. Sex-specific Cox models were developed to estimate the risk of CVD death or hospitalization within 5 years and included sex, age, ethnicity, level of deprivation, diabetes, previous hospitalization for atrial fibrillation and baseline preventive pharmacotherapy (blood-pressure-lowering, lipid-lowering and antiplatelet/anticoagulant medications) as predictors. Calibration and discrimination were assessed in the whole cohort, in 15-year age bands, in different ethnic groups, in quintiles of deprivation, according to baseline dispensing of pharmacotherapy, and in regional sub-populations. Results: The First CVD events occurred in 62 031 of the 1 746 695 people during 8 526 024 person-years of follow-up (mean = 4.8 years). Median 5-year CVD risk was 1.1% in women and 2.6% in men. In both sexes, the risk equations were well calibrated throughout the risk range and had good risk discrimination in the national, regional and ethnic populations, within 15-year age bands, in deprivation quintiles and according to baseline medication dispensing. Conclusions: Robust policy-focused CVD risk equations can be developed solely from administrative health data to inform population health planning, and will complement CVD primary prevention at the individual level using clinical risk tools. Similar policy-focused equations could be replicated in countries and regions with linked administrative health datasets.

[33] Rosenson RS, Hegele RA, Fazio S, Cannon CP. **The Evolving Future of PCSK9 Inhibitors.** Journal of the American College of Cardiology 2018; 72:314-329.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30012326>

ABSTRACT

Variants in proprotein convertase subtilisin/kexin type 9 (PCSK9) provide insights into mechanisms regulating low-density lipoprotein (LDL) levels. Human monoclonal antibodies that target PCSK9 lower LDL cholesterol (LDL-C) levels by 55% to 72% in different high-risk patient groups. Clinical trials with PCSK9 inhibitors have demonstrated reductions in atherosclerotic cardiovascular disease events, particularly in patients with recent acute coronary syndrome, multivessel coronary artery disease, or peripheral arterial disease. Commonly observed profound reductions in LDL-C to levels <25 mg/dl have been accompanied by even lower rates of atherosclerotic cardiovascular disease events, thus supporting the concept that there may be no lower limit for LDL-C. Aggressive LDL-C lowering with fully human PCSK9 monoclonal antibodies has been accompanied by a safety profile that has been very favorable.

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On the basis of clinical trial evidence, LDL lowering with PCSK9 inhibitors is recommended for high-risk patients with LDL-C levels ≥ 70 mg/dl on maximally tolerated oral therapies including statins and/or ezetimibe.

[34] *Lupo MG, Ferri N. Angiopietin-Like 3 (ANGPTL3) and Atherosclerosis: Lipid and Non-Lipid Related Effects. Journal of cardiovascular development and disease 2018; 5.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30011918>

ABSTRACT

Genetic and clinical studies have demonstrated that loss-of-function variants in the angiopoietin-like 3 (ANGPTL3) gene are associated with decreased plasma levels of triglycerides (TGs), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C), which leads to a significant reduction in cardiovascular risk. For this reason, ANGPTL3 is considered an important new pharmacological target for the treatment of cardiovascular diseases (CVDs) together with more conventional lipid lowering therapies, such as statins and anti proprotein convertase subtilisin/kexin type 9 (PCSK9) monoclonal antibodies. Experimental evidence demonstrates that anti-ANGPTL3 therapies have an important anti-atherosclerotic effect. Results from phase I clinical trials with a monoclonal anti-ANGPTL3 antibody (evinacumab) and anti-sense oligonucleotide (ASO) clearly show a significant lipid lowering effect. In addition, from the analysis of the protein structure of ANGPTL3, it has been hypothesized that, beyond its inhibitory activity on lipoprotein and endothelial lipases, this molecule may have a pro-inflammatory, pro-angiogenic effect and a negative effect on cholesterol efflux, implying additional pro-atherosclerotic properties. In the future, data from phase II clinical trials and additional experimental evidence will help to define the efficacy and the additional anti-atherosclerotic properties of anti-ANGPTL3 therapies beyond the already available lipid lowering therapies.

[35] *Krishna R, Gheyas F, Corr C et al. Pharmacokinetics and Pharmacodynamics of Anacetrapib in Black and White Healthy Subjects. Journal of clinical pharmacology 2018.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30029292>

ABSTRACT

Anacetrapib is a cholesteryl ester transfer protein inhibitor intended for the treatment of dyslipidemia. A phase 1 study was conducted to examine the pharmacokinetics and pharmacodynamics of multiple doses of anacetrapib in black compared to white healthy subjects. Although there was no apparent race-related pharmacokinetic effect, attenuation of the lipid response was observed in black subjects. Specifically, high-density lipoprotein cholesterol percentage increased 18.1% (absolute percentage points) less in black subjects (89.9%) when compared to increases in white subjects (108.0%). Similarly, the decrease in low-density lipoprotein cholesterol was 17.8% (absolute percentage points) less in blacks (-21.2%) relative to whites (-39.0%). In contrast, there were no apparent race-related differences in cholesteryl ester transfer protein mass or activity. Anacetrapib was generally well tolerated in this study. The results of this study suggest that there may be race-related differences in pharmacodynamics of anacetrapib independent of pharmacokinetics.

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[36] *Gutierrez-Casado E, Khraiwesh H, Lopez-Dominguez JA et al. The impact of aging, calorie restriction and dietary fat on mitochondrial ultrastructure, dynamics and autophagy markers in mouse skeletal muscle. J Gerontol A Biol Sci Med Sci 2018.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30010806>

ABSTRACT

Loss of skeletal muscle mass and function is a hallmark of aging. This phenomenon has been related to a dysregulation of mitochondrial function and proteostasis. Calorie restriction (CR) has been demonstrated to delay aging and preserve function until late in life, particularly in muscle. Recently, we reported the type of dietary fat plays an important role in determining lifespan extension with 40% CR in male mice. In these conditions, lard fed mice showed an increased longevity compared to mice fed soybean or fish oils. In this paper, we analyze the effect of 40% CR on muscle mitochondrial mass, autophagy and mitochondrial dynamics markers in mice fed these diets. In CR fed animals, lard preserved muscle fibers structure, mitochondrial ultrastructure and fission/fusion dynamics and autophagy, not only compared to control animals, but also compared with CR mice fed soybean and fish oils as dietary fat. We focus our discussion on dietary fatty acid saturation degree as an essential predictor of lifespan extension in CR mice.

[37] *Liu M, Jiang S, Ma Y et al. Peripheral-blood gene expression profiling studies for coronary artery disease and its severity in Xinjiang population in China. Lipids in health and disease 2018; 17:154.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30021655>

ABSTRACT

BACKGROUND: Alterations in gene expression in peripheral blood cells play a curtail role in the presence and extent of coronary artery disease (CAD), but its severity reflected by gene expression alterations in peripheral blood cells is still unknown in Xinjiang population in China. **METHODS:** Global gene expression profiling in peripheral blood was used to explore differentially expressed genes in coronary artery stenosis patients. RNA was extracted from peripheral blood of 9 controls without coronary stenosis and 21 cases with angiographically CAD. The extent of CAD severity was categorized angiographically as no CAD, mild CAD (20 to 50% luminal diameter stenosis [LDS]), moderate CAD (50 to 75% LDS) and severe CAD (\geq 75% LDS). Differentially expressed genes related with CAD severity from peripheral blood cells were screened by linear mixed effects analysis using the lme4 package in R. Then the differentially expressed genes that gradually up-regulated or down-regulated were enriched by Gene Ontology (GO) functional annotation and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis. **RESULTS:** The most significantly enrichments were toll-like receptor signaling pathway, immune responses, translational processes, cellular growth, inflammation and metabolic processes. Combined with NCBI-GenerIF and PubMed analysis, we focused on the 12 genes associated with toll-like receptor signaling pathway in the extent of coronary artery stenosis patients. Receiver operating characteristic (ROC) analysis of 12 genes associated with toll-receptor signaling pathway in the 236 CAD patients from GEO database demonstrated that 12 genes expression could predict severe CAD with an area under the curve of 0.67, sensitivity of 77.65% and specificity of 51.52%. **CONCLUSION:** These results suggest that 12 genes associated with toll-like receptor signaling pathway in peripheral-blood cells reflect the presence and extent of CAD severity in Xinjiang population in China.

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[38] Yu Q, Wang F, Meng X et al. **Shortterm use of atorvastatin affects glucose homeostasis and suppresses the expression of LDL receptors in the pancreas of mice.** Molecular medicine reports 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30015940>

ABSTRACT

Lowdensity lipoprotein receptors (LDLRs) may serve a role in the diabetogenic effect of statins; however, the effects of statins on LDLR expression and its regulation in the pancreas and islets have yet to be determined. To exclude the longterm effects of treatment with atorvastatin, which allows mice to adapt, male C57BL/j and apolipoprotein Edeficient mice were acutely treated with oral atorvastatin for 6 weeks, and glucose homeostasis and LDLR expression in the pancreas and islets were examined. In the present study, it was observed that the shortterm use of atorvastatin affected insulin sensitivity in normal mice and glucose tolerance in hyperlipidemic mice. Furthermore, it was identified that 6 weeks of treatment with atorvastatin suppressed LDLR expression in the pancreas and pancreatic islets in C57BL/j mice, and an increase in proprotein convertase subtilisin/kexin type 9 expression was additionally observed in the pancreas. However, 6 weeks of treatment with atorvastatin did not affect LDLR expression in the pancreas of hyperlipidemic mice. It may be concluded that the shortterm use of atorvastatin disturbs glucose homeostasis and suppresses LDLR expression in the pancreas and pancreatic islets in C57BL/j mice, suggesting that the role of LDLR in the diabetogenic effect of statins requires further investigation.

[39] Cozzolino M, Bolasco P, Ronco C et al. **Clinical Management of Chronic Kidney Disease Patients in Italy: Results from the IRIDE Study.** Nephron 2018:1-9.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30016767>

ABSTRACT

BACKGROUND: Lack of adequate management of chronic kidney disease (CKD) often results in delayed diagnosis and inadequate treatment. This study assessed the clinical management and outcome of stages 1-5 CKD patients. METHODS: Patients were prospectively followed for 3 years in 25 nephrology centers across Italy. Clinical characteristics were measured at baseline and every 6 months. Outcome measures included CKD staging, presence of comorbidities, treatment, mineral bone disorder (MBD) parameters, and patient outcomes. RESULTS: Of 884 enrolled patients (59.7% males, aged 66.2 +/- 14.6 years), 587 (66.4%) completed the study. The majority of patients were referred by a general practitioner (44.7%) and had stage 3 or 4 CKD (40.9 and 23.8% respectively). Data reveal that 91.3% of patients had at least 1 concomitant disease, most frequently hypertension (80.1%) and dyslipidemia (42.5%); 94.6% of patients were receiving cardiovascular medication and 52.6% were receiving lipid-lowering medication. Approximately 40% of patients had proteinuria and intact parathyroid hormone levels outside the normal range. As expected, stages 4 and 5 CKD patients had a higher prevalence of proteinuria (68 and 74%), MBD (59 and 88%) and anemia (28 and 73%), as well as a higher risk of hospitalization (34.3 and 51.9%) and need for dialysis (69.5 and 70%). The overall probability of survival over 36 months was 90.6%. CONCLUSIONS: This is the first Italian prospective study performed with a large cohort of CKD patients over a 3-year period. Considering the multifactorial burden of diseases associated with CKD patients, the need for greater attention to CKD and related disorders is paramount.

[40] Liu JJ, Hezghia A, Shaikh SR et al. **Regulation of monoamine transporters and receptors by lipid microdomains: implications for depression.** Neuropsychopharmacology 2018.

Literature update week 29 (2018)

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30022062>

ABSTRACT

Lipid microdomains ("rafts") are dynamic, nanoscale regions of the plasma membrane enriched in cholesterol and glycosphingolipids, that possess distinctive physicochemical properties including higher order than the surrounding membrane. Lipid microdomain integrity is thought to affect neurotransmitter signaling by regulating membrane-bound protein signaling. Among the proteins potentially affected are monoaminergic receptors and transporters. As dysfunction of monoaminergic neurotransmission is implicated in major depressive disorder and other neuropsychiatric conditions, interactions with lipid microdomains may be of clinical importance. This systematic review evaluates what is known about the molecular relationships of monoamine transporter and receptor regulation to lipid microdomains. The PubMed/MeSH database was searched for original studies published in English through August 2017 concerning relationships between lipid microdomains and serotonin, dopamine and norepinephrine transporters and receptors. Fifty-seven publications were identified and assessed. Strong evidence implicates lipid microdomains in the regulation of serotonin and norepinephrine transporters; serotonin 1A, 2A, 3A, and 7A receptors; and dopamine D1 and beta2 adrenergic receptors. Results were conflicting or more complex regarding lipid microdomain associations with the dopamine transporter, D2, D3, and D5 receptors; and negative with respect to beta1 adrenergic receptors. Indirect evidence suggests that antidepressants, lipid-lowering drugs, and polyunsaturated fatty acids may exert effects on depression and suicide by altering the lipid milieu, thereby affecting monoaminergic transporter and receptor signaling. The lipid composition of membrane subdomains is involved in localization and trafficking of specific monoaminergic receptors and transporters. Elucidating precise mechanisms whereby lipid microdomains modulate monoamine neurotransmission in clinical contexts can have critical implications for pharmacotherapeutic targeting.

[41] Wang YL, Yu W. **Association of circulating microRNA-122 with presence and severity of atherosclerotic lesions.** *PeerJ* 2018; 6:e5218.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30013851>

ABSTRACT

Objective: MicroRNA (miR)-122 is highly expressed in the liver, where it has been implicated as a regulator of fatty-acid metabolism. A recent study reported that miR-122 plays a role in pathogenesis of atherosclerosis; however, whether it connects with severity of atherosclerotic lesion is still controversial. We therefore investigated the association between miR-122 expression and presence and severity of coronary atherosclerotic plaque. Methods: During January-November 2017, we included 300 patients with coronary heart disease (CHD) and 100 subjects as the control group. MiR-122 content was detected by quantitative real-time polymerase chain reaction. MiR-122 level was identified in all subjects, and the Spearman correlation between miR-122 and severity of atherosclerosis was analyzed. Results: Patients with CHD had higher miR-122 expression than in control group (2.61, 0.91-8.86 vs. 1.62, 0.71-3.45, $p < 0.001$). Gensini score was significantly associated with miR-122 expression ($r = 0.7964$, $p < 0.001$). The odds ratio of miR-122 solely was 0.12 (95% CI [0.05-0.43]) and factors such as cholesterol, triglyceride together with miR-122 level were closely associated with atherosclerosis (all $p < 0.001$). Conclusions: The serum level of miR-122 may be used to differentiate between mild and severe coronary atherosclerotic lesion. Use of this marker might allow non-invasive diagnosis the degree of coronary atherosclerosis.

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[42] Liu N, Yang G, Hu M et al. **Association of ABCC2 polymorphism and gender with high-density lipoprotein cholesterol response to simvastatin.** Pharmacogenomics 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30024814>

ABSTRACT

AIM: The clinical benefits of lipid-lowering therapy with statins are widely recognized. However, the lipid-lowering efficacy of statins shows significant differences between individuals. ABCC2 has been demonstrated to contribute to the transmembrane transport of the substrate compounds. The ABCC2 SNPs may be important factors that affect individual differences in clinical drug response. The aim of this study was to evaluate the association of rs717620 of ABCC2 with treatment response to simvastatin in a Chinese Han population. METHODS: A total of 318 subjects were medicated with simvastatin 20 mg/day for 12 weeks after enrollment. Venous blood was obtained before and after simvastatin treatment for measurement of blood lipid profile. Subjects were classified into high-response and low-response groups depending on whether their lipid profile change was higher or lower than median change values. The ABCC2 SNP rs717620 was genotyped from blood samples with a snapshot assay. RESULTS: A total of 12 weeks of treatment with simvastatin significantly decreased low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), triglycerides (TGs) and significantly increased high-density lipoprotein cholesterol (HDL-C; $p < 0.05$). In multivariate analysis, there were no significant genetic effects of SNP rs717620 on the incidence of high- or low-response patients among TC, TG and LDL-C groups. However, rs717620 A-allele and female gender are significantly associated with the risk of low-response of HDL-C elevation after simvastatin treatment. CONCLUSION: ABCC2 rs717620 and female gender may be related to the low-effect of simvastatin treatment on the HDL-C level in the Chinese Han population. Female Chinese patients with hyperlipidemia carrying rs717620 GA/AA genotypes might have reduced benefit from simvastatin treatment.

[43] Fiorucci S, Biagioli M, Distrutti E. **Future trends in the treatment of non-alcoholic steatohepatitis.** Pharmacological research : the official journal of the Italian Pharmacological Society 2018; 134:289-298.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30021122>

ABSTRACT

With an estimated prevalence of approximately 25% in Western and Asian countries, non alcoholic fatty liver disease (NAFLD), caused by chronic excessive caloric intake, is emerging as the most prevalent liver disorder worldwide. NAFLD exists in two clinical entities, non-alcoholic fatty liver disease (NAFL), a relative benign disease that carries on minimal risk of liver-related morbidity but significant risk of cardiovascular complications, and non-alcoholic steatohepatitis (NASH), a progressive liver disorder with a significant risk for development of liver-related morbidities and mortality. While, liver injury in NASH is contributed by lipid overload in hepatocytes, lipotoxicity, the main determinant of disease progression is an inflammation-driven fibrotic response. Here, we review the landscape of emerging pharmacological interventions in the treatment of NAFL and NASH. A consensus exists that, while treating the liver component of NASH requires development of novel pharmacological approaches, the future therapy of NASH needs to be tailored to the single patient and most likely will be a combination of agents acting on specific pathogenic mechanisms at different disease stage.

Literature update week 29 (2018)

[44] *Tajmohammadi A, Razavi BM, Hosseinzadeh H. Silybum marianum (milk thistle) and its main constituent, silymarin, as a potential therapeutic plant in metabolic syndrome: A review. Phytotherapy research : PTR 2018.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30015401>

ABSTRACT

Metabolic syndrome describes a complex metabolic risk factors including obesity, hypertension, dyslipidemia, and diabetes. This syndrome is diagnosed by medical conditions such as weight gain, high blood pressure, high blood glucose, and disturbance in lipid profile. Metabolic syndrome has become as an important and increasing global health problem, so finding potentially novel solutions with less adverse effects is favorable for health problems. Herbal therapy plays an important role for treatment of different diseases. *Silybum marianum* is a plant that is used for centuries as a herbal treatment in liver and biliary tract diseases. Silymarin is the main component of *S. marianum* and derived from fruits and seeds of *S. marianum* (milk thistle). *S. marianum* has been found to exhibit antioxidant, lipid-lowering, antihypertensive, antidiabetic, antiatherosclerotic, anti-obesity, and hepatoprotective effects. Therefore, the aim of this review is to summarize different animal and human studies regarding the effect of *S. marianum* in metabolic syndrome and to identify the underlying mechanisms of action.

[45] *Auguet T, Aragones G, Colom M et al. Targeted metabolomic approach in men with carotid plaque. PLoS one 2018; 13:e0200547.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30011297>

ABSTRACT

BACKGROUND: The aim of the study was to analyse the presence of several metabolites related to atherosclerosis in the plasma of patients with unstable carotid plaque and in the plasma of healthy subjects. MATERIALS AND METHODS: We included 20 patients who had undergone carotid endarterectomy and 20 healthy subjects as a control group. All the subjects recruited were male. We used a metabolomic approach with liquid chromatography coupled to mass spectrometry to evaluate plasma metabolite levels in the metabolic pathway involved in the progression of atherosclerotic plaque. RESULTS: We observed that circulating levels of 20-HETE were significantly higher in patients with atheroma plaque than in healthy subjects ($p = 0.018$). No differences were found with regard to the other metabolites analysed. We also conducted a random forest analysis and found that 20-HETE was the main differentiator in the list of selected metabolites. In addition, plasma levels of 20-HETE correlated positively with body mass index ($r = 0.427$, $p = 0.007$) and diastolic blood pressure ($r = 0.365$, $p = 0.028$). CONCLUSION: This study confirms that of all the molecules studied only 20-HETE is related to carotid plaque. Further studies are needed to compare patients with stable carotid plaque vs. patients with unstable carotid plaque in order to confirm that 20-HETE could be a potential factor related to carotid plaque.

[46] *Wybraniec MT, Filipecki A, Chudek J, Mizia-Stec K. Atorvastatin facilitates protection against contrast-induced nephropathy in patients undergoing coronary angiography via humoral mediators rather than altered renal hemodynamics. Postępy w kardiologii interwencyjnej = Advances in interventional cardiology 2018; 14:191-194.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30008773>

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ABSTRACT

[47] *Jeyapal S, Kona SR, Mullapudi SV et al. Substitution of linoleic acid with alpha-linolenic acid or long chain n-3 polyunsaturated fatty acid prevents Western diet induced nonalcoholic steatohepatitis. Scientific reports 2018; 8:10953.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30026586>

ABSTRACT

Imbalance in the n-6 polyunsaturated fatty acids (PUFA) and n-3 PUFA in the Western diet may increase the risk of nonalcoholic fatty liver disease (NAFLD). This study investigates the impact of substitution of linoleic acid with alpha-linolenic acid (ALA) or long chain (LC) n-3 PUFA and hence decreasing n-6:n-3 fatty acid ratio on high fat, high fructose (HFHF) diet induced nonalcoholic steatohepatitis (NASH). Male Sprague-Dawley rats were divided into four groups and fed control diet, HFHF diet (n-6:n-3 ratio of 200), HFHF diet with ALA (n-6:n-3 ratio of 2) or HFHF diet with LC n-3 PUFA (n-6:n-3 ratio of 5) for 24 weeks. Rats fed HFHF diet with n-6:n-3 ratio of 200 resulted in hepatic steatosis, induced glucose intolerance, insulin resistance and oxidative stress accompanied by increase in markers of inflammation, plasma lipids and aminotransferase levels. Histopathological examination of liver further confirmed the establishment of NASH. ALA and LC n-3 PUFA supplementation prevented hepatic steatosis and dyslipidemia by inhibiting lipogenesis and increasing insulin sensitivity. Furthermore, n-3 PUFA supplementation attenuated hepatic oxidative stress by restoring antioxidant status, decreased inflammation and preserved hepatic architecture. These findings suggest that decreasing n-6:n-3 ratio prevented HFHF induced NASH by attenuating oxidative stress and inflammation.

[48] *Ma S, Motevalli SM, Chen J et al. Precise theranostic nanomedicines for inhibiting vulnerable atherosclerotic plaque progression through regulation of vascular smooth muscle cell phenotype switching. Theranostics 2018; 8:3693-3706.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30026877>

ABSTRACT

Coronary heart disease is a prevalent and fatal killer caused by vulnerable atherosclerotic plaques (VASPs). However, the precise detection and treatment of VASPs remains a difficult challenge. Here, we present the development of noninvasive human serum albumin (HSA)-based theranostic nanomedicines (NMs) for the specific diagnosis and effective therapy of VASPs. Methods: The ICG/SRT@HSA-pept NMs were formulated to contain payloads of the near-infrared (NIR) fluorescent dye indocyanine green (ICG) and the sirtuin 1 (Sirt1) activator SRT1720, and modified with a peptide moiety targeting osteopontin (OPN). The in vivo atherosclerotic mouse model was established with the high-fat diet (HFD). The in vitro vascular smooth muscle cells (VSMCs) phenotypic switching was induced using the ox-LDL stimulation. Results: Due to the overexpression of OPN in activated VSMCs and VASPs, the targeted NMs specifically accumulated within the VASPs region after intravenous injection into the atherosclerotic mice, achieving the precise detection of VASPs. In addition, in the presence of SRT1720, the NMs could activate intracellular Sirt1 and activate an antiatherogenesis effect by inhibiting the phenotypic switching of VSMCs, which is an essential contributor to the vulnerability and progression of atherosclerotic plaques. After therapeutic administration of the ICG/SRT@HSA-pept NMs for two weeks, the physiological sizes and plaque compositions of VASPs were markedly improved. Furthermore, ICG/SRT@HSA-pept NMs-treated mice presented a more favorable plaque phenotype than that was observed in free SRT1720-

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treated mice, suggesting the enhanced delivery of pharmaceutical agents to the atherosclerotic lesions and improved therapeutic efficacy of NMs compared with free SRT1720. Conclusions: The theranostic ICG/SRT@HSA-pept NMs showed great potential for the precise identification and targeted treatment of atherosclerotic diseases.