

Literature update week 16 (2019)

[1] Lammi C, Sgrignani J, Roda G et al. **Inhibition of PCSK9(D374Y)/LDLR Protein-Protein Interaction by Computationally Designed T9 Lupin Peptide.** ACS medicinal chemistry letters 2019; 10:425-430.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30996774>

ABSTRACT

The inhibition of the PCSK9/LDLR protein-protein interaction is a promising strategy for developing new hypocholesterolemic agents. Familial hypercholesterolemia is linked to specific PCSK9 mutations: the D374Y is the most potent gain-of-function (GOF) PCSK9 mutation among clinically relevant ones. Recently, a lupin peptide (T9) showed inhibitory effects on this mutant PCSK9 form, being also capable to increase liver uptake of low density lipoprotein cholesterol. In this Letter, aiming to improve the potency of this peptide, the T9 residues mainly responsible for the interaction with PCSK9(D374Y) (hot spots) were computationally predicted. Then, the "non-hot" residues were suitably substituted by new amino acids capable to theoretically increase the structural complementarity between T9 and PCSK9(D374Y). The outcomes of this study were confirmed by in vitro biochemical assays and cellular investigations, showing that a new T9 analog is able to increase the LDLR expression on the liver cell surface by 84% at the concentration of 10 μ M.

[2] Reijnders D, Olson K, Liu CC et al. **Dyslipidemia and the role of the adipose tissue in early pregnancy in the BPH/5 mouse model for preeclampsia.** American journal of physiology. Regulatory, integrative and comparative physiology 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30995083>

ABSTRACT

BACKGROUND: The hypertensive pregnancy disorder preeclampsia (PE) is a leading cause of fetal/ maternal morbidity/mortality. Obesity increases the risk to develop PE, presumably via the release of inflammatory mediators from the adipose tissue, but the exact etiology remains largely unknown. **METHODS:** Using obese PE-like BPH/5 and lean gestational age-matched C57Bl6 mice, we aimed to obtain insight into differential reproductive white adipose tissue (rWAT) gene expression, circulating lipids and inflammation at the maternal-fetal interface during early pregnancy. In addition, we investigated the effect of 7 days 25% calorie restriction (CR) in early pregnancy on gene expression in rWAT and implantation sites. **RESULTS:** Compared to C57Bl6, female BPH/5 are dyslipidemic pre-pregnancy and show an amplification of rWAT mass, circulating cholesterol, free fatty acids and triacylglycerol levels throughout pregnancy. RNA sequencing showed that pregnant BPH/5 mice have elevated gene-enrichment in pathways related to inflammation and cholesterol biosynthesis at embryonic day (e)7.5. Expression of cholesterol-related HMGCS1, MVD, Cyp51a1 and DHCR was validated by qRT-PCR. CR during the first 7 days of pregnancy restored the relative mRNA expression of these genes to a level comparable to C57Bl6 pregnant females and reduced the expression of circulating leptin and pro-inflammatory prostaglandin synthase 2 (Ptgs2) in both rWAT and implantation sites in BPH/5 mice at e7.5 **Conclusion:** Our data suggest a possible role for rWAT in the dyslipidemic state and inflammatory uterine milieu that might underlie the pathogenesis of PE. Future studies should further address the physiological functioning of the adipose tissue in relation to PE-related pregnancy outcomes.

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[3] Nekrasov DA, Korotkikh AV, Blagovisnaia VA. **[Hibrid intervention for internal carotid artery stenosis and ipsilateral aneurysm of anterior communicating artery]**. Angiologiya i sosudistaia khirurgiya = Angiology and vascular surgery 2019; 25:75-78.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30994611>

ABSTRACT

The presence of an ipsilateral aneurysm in stenosis of the internal carotid artery is determined by the findings of CT angiography in 1.8-3.2% of cases. The available literature has described a wide variety of treatment for this pathology: isolated or alternate, with a method of simultaneous endovascular treatment, i. e., carotid stenting and endovascular embolization of an aneurysm, currently gaining popularity. The major difficulties associated with therapeutic decision-making in this cohort of patients include stage-wise nature, temporal parameters, the need for removal of an intracranial aneurysm, and assessment of perioperative complications. A clinical case report presented herein is an example of a method of a hybrid approach, i. e., simultaneously performing carotid endarterectomy and endovascular embolization of an aneurysm. In certain cases (anatomical variants, structure of an atherosclerotic plaque, individual peculiarities), this approach is more justified than popularity-gaining simultaneous endovascular treatment.

[4] Baran A, Kiluk P, Maciaszek M *et al.* **Liver fatty acid-binding protein might be a predictive marker of clinical response to systemic treatment in psoriasis.** Archives of dermatological research 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30993401>

ABSTRACT

Fatty acid-binding proteins play an inconclusive role in lipid metabolism and cardiometabolic diseases (CMDs) which are closely related with psoriasis. Aim of the study was to investigate the diagnostic value of serum liver fatty acid-binding protein (FABP1) level and associations with disease severity, inflammation or metabolic parameters and influence of systemic treatment in psoriatic patients. The study included thirty-three patients with active plaque-type psoriasis and eleven healthy volunteers. Blood samples were obtained before and after 12 weeks of therapy with methotrexate and acitretin. Serum FABP1 concentrations were analyzed by the enzyme-linked immunosorbent assay. Statistical analysis was performed for correlation of FABP1 with anthropometric, metabolic or inflammatory indices and treatment used. Serum liver-type FABP levels were significantly increased in psoriatic patients compared to the controls ($p < 0.001$). No statistical correlations between FABP1 and PASI ($p = 0.25$) was noted, however patients with severe psoriasis had the highest level of FABP1. No significance with metabolic parameters was obtained, beside a positive significant relation with BMI after therapy ($p = 0.03$). Liver-type FABP significantly correlated with CRP ($p = 0.01$) and morphotic blood elements. Systemic treatment combined resulted in significant decrease of FABP1 ($p = 0.04$), regardless of the drug: $p = 0.1$ in acitretin group, $p = 0.3$ in methotrexate group. Liver-type FABP might be a novel marker of psoriasis and predictor of clinical response to systemic therapy. FABP1 could be involved in CMDs risk assessment and perhaps link psoriasis with hematological disorders.

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[5] *Kitas GD, Nightingale P, Armitage J et al. Trial of atorvastatin for the primary prevention of cardiovascular events in patients with rheumatoid arthritis (TRACE RA): A multicenter, randomized, placebo controlled trial. Arthritis & rheumatology (Hoboken, N.J.)* 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30983166>

ABSTRACT

OBJECTIVE: Rheumatoid arthritis (RA) is associated with increased cardiovascular event (CVE) risk. The impact of statins in RA is not established. We assessed whether atorvastatin is superior to placebo for the primary prevention of CVE in RA patients. METHODS: Randomized, double-blind, placebo-controlled trial designed for 80% power at $p < 0.05$ to detect a 32% CVE risk reduction based on an estimated 1.8% per annum (pa) event rate. Patients aged > 50 years or with RA duration > 10 years; without clinical atherosclerosis, diabetes, or myopathy; received atorvastatin 40mg daily or matching placebo. Primary endpoint was a composite of cardiovascular death, myocardial infarction, stroke, transient ischemic attack, or any arterial revascularization. Secondary/tertiary endpoints included plasma lipids and safety. RESULTS: 3002 patients (mean age 61 years, 74% female) were followed for a median 2.51 years (IQR 1.90-3.49) [7,827 patient-years] - early termination was due to lower than expected event rate (0.77% pa). Among patients allocated atorvastatin 24/1504 (1.6%) had a primary endpoint, compared with 36/1498 (2.4%) on placebo (hazard ratio 0.66, 95%CI 0.39-1.11, $p = 0.115$); adjusted hazard ratio (0.60, 95%CI 0.32-1.15, $p = 0.127$). At trial end, patients on atorvastatin had 0.77 ± 0.04 mmol/L lower LDL-cholesterol compared to placebo ($p < 0.0001$); CRP (mg/L) was also significantly lower on atorvastatin than placebo (2.59 (0.94-6.08) vs. 3.60 (1.47-7.49) - $p < 0.0001$). CVE risk reduction per mmol/L LDLc reduction was 42% (95%CI -14%-70%). Adverse events in the atorvastatin (298 (19.8%)) and placebo (292 (19.5%)) groups were similar. CONCLUSION: Atorvastatin 40mg daily was safe and resulted in significantly greater reduction of LDLc than placebo in patients with RA. The 40% (adjusted) CVE risk reduction is consistent with the Cholesterol Treatment Trialists' Collaboration meta-analysis of statin effects in other populations. This article is protected by copyright. All rights reserved.

[6] *Cebolla JJ, Irun P, Mozas P, Giraldo P. Evaluation of two approaches to lysosomal acid lipase deficiency patient identification: An observational retrospective study. Atherosclerosis* 2019; 285:49-54.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31004967>

ABSTRACT

BACKGROUND AND AIMS: Lysosomal acid lipase deficiency (LALD) leads to the accumulation of cholesteryl esters and/or triglycerides (TG) in lysosomes due to the lack of the enzyme codified by the LIPA gene. The most common symptoms are dyslipidaemia and hypertransaminasemia, together with manifestations common to other lysosomal storage disorders (LSDs), including visceromegalies and elevated plasma biomarkers. Alteration of the lipid-liver profile (LLP) has been widely applied as a criterion for LALD screening, but the usefulness of biomarkers has not yet been explored. Our purpose was to explore the utility of plasma chitotriosidase activity (ChT) and CCL18/PARC concentration in addition to LLP to identify LALD patients in an observational retrospective study of two different sample collections. METHODS: Biological samples refining: Collection 1 (primary hypercholesterolemia suspected) included unrelated individuals with hyperlipidaemia and without LDLR, APOB and PCSK9 gene mutations (Set 1),

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and Collection 2 (LSD suspected) included individuals without definitive LSD diagnosis (Set 2). We assessed plasma LLP (total cholesterol and its fractions, TG concentration and transaminases activities), as well as plasma ChT and CCL18/PARC. All subjects with anomalous LLP and/or biomarker levels were LIPA sequenced. RESULTS: Twenty-four subjects showed altered LLP and/or biomarkers. We identified two LALD patients (one homozygous and one compound heterozygous) and one carrier of a novel LIPA variant. CONCLUSIONS: The measurement of plasma ChT and CCL18/PARC combined with LLP will be a useful approach to identifying LALD patients in retrospective LALD patient studies.

[7] *Presta V, Figliuzzi I, Miceli F et al. Achievement of low density lipoprotein (LDL) cholesterol targets in primary and secondary prevention: Analysis of a large real practice database in Italy. Atherosclerosis 2019; 285:40-48.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31003091>

ABSTRACT

BACKGROUND AND AIMS: Target and intensity of low-density lipoprotein cholesterol (LDL-C) lowering therapy should be tailored according to the individual global cardiovascular (CV) risk. We aimed at retrospectively evaluating real-life LDL-C goal attainment and predictive factors for predefined LDL-C therapeutic goals both in primary and secondary prevention. METHODS: We collected data from a large cohort of outpatients aged 40-65 years, followed by general practitioners, cardiologists and diabetologists in Italy. All data were centrally analysed for global CV risk assessment and rates of control of major CV risk factors, including LDL-C. Study population was stratified according to the presence or absence of previous CV events, including coronary artery disease (CAD), peripheral artery disease (PAD) or stroke/TIA. CV risk profile characterization was based on the European SCORE. Predefined therapeutic goals were set according to the European guidelines on dyslipidaemia: LDL-C levels <70mg/dl for very high CV risk patients in primary prevention and for those in secondary prevention; <100mg/dl LDL-C levels for high CV risk patients in primary prevention. Logistic regression analysis with clinical covariates was used to identify predictive factors for achieving these goals; lipid lowering therapy entered in the analysis as continuous (model 1) or categorical variable (model 2). RESULTS: We included 4,142 outpatients (43,7% female, age 58.0+/-5.2 years, BMI 28.5+/-5.0kg/m(2)) among whom 2,964 (71.6%) in primary and 1,178 (28.4%) in secondary prevention. In primary prevention, none of the patients at very high CV risk had LDL-C <70mg/dl and 8.9% of patients at high CV risk showed LDL-C <100mg/dl. Only 5.8% of patients in secondary prevention had LDL-C levels <70mg/dl, specifically 6.5% of patients with CAD, 2.6% of patients with PAD and 4.7% of patients with CVD (p<0.001). Beyond diabetes and lipid lowering therapy, high risk SCORE estimation resulted a strong and independent predictor for the lack of achieving all predefined therapeutic targets, including LDL-C <100mg/dl [OR: 0.806 (0.751-0.865)]; p<0.001], and LDL-C <70mg/dl [OR: 0.712 (0.576-0.880); p=0.002], in primary prevention. CONCLUSIONS: Despite high or very high SCORE risk and use of lipid lowering therapies, we observed poor achievement of LDL-C targets in this large cohort of outpatients followed in a setting of real practice in Italy.

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[8] Yang S, Zhang W, Xuan LL et al. **Akebia Saponin D inhibits the formation of atherosclerosis in ApoE(-/-) mice by attenuating oxidative stress-induced apoptosis in endothelial cells.**

Atherosclerosis 2019; 285:23-30.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30999121>

ABSTRACT

BACKGROUND AND AIMS: Akebia Saponin D (ASD) is a major bioactive triterpenoid saponin compound isolated from the Chinese herb *Dipsacus asper* wall (DSW). DSW has been long used as an anti-Alzheimer disease and anti-osteoporosis agent in clinics. However, anti-atherosclerotic effects of ASD have not been fully investigated. The objective of this study is to further investigate the anti-atherosclerotic activities and mechanisms of ASD in vivo and in vitro. METHODS: In in vitro experiments, ASD (50, 100, and 200µM) was used to explore the effects of preventing H₂O₂-induced endothelial cell apoptosis and the possible mechanism involved. In in vivo experiments, ApoE(-/-) mice were fed a high fat diet (HFD) and treated with atorvastatin (10mg/kg/d), ASD (50, 150, 450mg/kg/d), or the combination therapy (atorvastatin 10mg/kg/d and ASD 150mg/kg/d) for 14 weeks. RESULTS: We found that ASD reduced the generation of reactive oxygen species, inhibited mitochondrial membrane potential (MMP) impairment, diminished the expression of Bax and Caspase-3, increased Bcl-2 expression, and inhibited apoptosis in endothelial cells. ASD significantly increased the expression of anti-oxidant enzymes (GSH, SOD, and CAT) in both liver and vascular tissue, reduced blood lipid levels (TG, TC, and LDL-C), and decreased lipid deposition in the liver and atherosclerotic lesion size in ApoE(-/-) mice. CONCLUSIONS: Our study revealed that ASD inhibited atherosclerosis development in ApoE(-/-) mice by inhibiting oxidative stress-induced endothelial cell apoptosis signaling pathway, and suggested that ASD might be a potential therapeutic drug in the prevention of atherosclerosis.

[9] Zhang J, Li SF, Chen H, Song JX. **[Role of miR-106b-5p in the regulation of gene profiles in endothelial cells].** *Beijing Da Xue Xue Bao Yi Xue Ban* 2019; 51:221-227.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30996357>

ABSTRACT

OBJECTIVE: To evaluate the role of miR-106b-5p in the regulation of gene expression in endothelial cells. METHODS: The Taqman low-density microRNAs (miRNAs) array (TLDA) was used to identify miRNA expression profiles in the plasma of patients with atherosclerotic coronary artery disease (CAD) (atherosclerosis group, n=9) and individuals without atherosclerotic CAD disease (control group, n=9). A weighed and undirected miRNA coexpression network analysis was performed to investigate the interactions among miRNAs in the two groups. MiR-106b-5p, whose coexpression pattern in atherosclerosis group was most different from that of control group, was further studied. Human umbilical vein endothelial cells (HUVEC) were transfected with miR-106b-5p mimic or negative control mimic, and Affymetrix GeneChip Human Transcriptome Array 2.0 was used to screen the differential gene expression profiles after transfection. And the signal transduction pathway of differential gene profiles was further analyzed in Kyoto Encyclopedia of Genes and Genomes (KEGG) signal pathway database. After parsing the whole KEGG database, all differentially expressed genes involved pathways were extracted, and the hypergeometric distribution was used to calculate the pathway enrichment. RESULTS: The coexpression pattern of the patients with

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atherosclerosis (140 nodes, 1 154 edges) differed from that of the non-atherosclerosis control group (140 nodes, 612 edges). The analysis of array data with significant analysis of microarray (SAM) identified 746 significantly deregulated genes (fold change ≥ 1.5 and false discovery rate < 0.01) altered by overexpression of miR-106b-5p with miR-106b-5p mimic in HUVEC. By calculating the pathway enrichment, we found that multiple signaling pathways enriched in differential gene profiles were closely related to the process of formation and rupture of atherosclerotic plaque, including phosphatidylinositol-3 kinase (PI3K)/ protein kinase B (PKB, also called Akt), mammalian target of rapamycin (mTOR), transforming growth factor-beta (TGF-beta), janus kinase / signal transducer and activator of transcription (Jak-STAT), tumor necrosis factor (TNF), toll like receptor (TLR) and hypoxia-inducible factor 1alpha (HIF-1alpha) and other signal pathways. CONCLUSION: The coexpression pattern of miRNAs in plasma of patients with atherosclerosis is more significantly changed than that of individuals without atherosclerotic disease. MiR-106b-5p, which shows the most significant difference between groups, targets multiple signal pathways in vascular endothelial cells, and might play an important role in the regulatory network of atherosclerotic gene expression.

[10] *Alqarni I, Bassiouni YA, Badr AM, Ali RA. Telmisartan and/or Chlorogenic Acid Attenuates Fructose-Induced Non-Alcoholic Fatty Liver Disease in Rats: Implications of Cross-Talk between Angiotensin, the Sphingosine Kinase/Sphingosine-1-Phosphate Pathway, and TLR4 Receptors. Biochem Pharmacol* 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31004566>

ABSTRACT

Renin-angiotensin-aldosterone system (RAS) has been implicated in non-alcoholic fatty liver disease (NAFLD); the most common cause of chronic liver diseases. There is accumulating evidence that altered TLR4 and Sphingosine kinase 1(SphK1)/sphingosine1phosphate (S1P) signaling pathways are key players in the pathogenesis of NAFLD. Cross talk of the sphingosine signaling pathway, toll-4 (TLR4) receptors ,and angiotensin II was reported in various tissues. Therefore, the aim of this study was to define the contribution of these two pathways to the hepatoprotective effects of telmisartan and/or chlorogenic acid (CGA) in NAFLD. CGA is a strong antioxidant that was previously reported to inhibit angiotensin converting enzyme. Male Wistar rats were treated with either high-fructose, with or without telmisartan, CGA, telmisartan+CGA for 8 weeks. Untreated NAFL rats showed characteristics of NAFLD, as evidenced by significant increase in the body weight, insulin resistance, and serum hepatotoxicity markers (Alanine and Aspartate transaminases) and lipids as compared to the negative control group, in addition to characteristic histopathological alterations. Treatment with either telmisartan and/or CGA improved aforementioned parameters, in addition to upregulation of antioxidant enzymes (Superoxide dismutase and Glutathione peroxidase). Effect of inhibiting RAS on both sphingosine pathway and TLR4 was evident by the suppressing effect of telmisartan and/or CGA on high fructose-induced upregulation of hepatic SPK1 and S1P, in addition to concomitant up-regulation of Sphingosine-1-Phosphate receptor (S1PR)3 protein level and increased expression of S1PR1 and TLR4. As TLR4 and SPK/S1P signaling pathways play important roles in the progression of liver inflammation, the effect on sphingosine pathway and TLR4 was associated with decreased concentrations of inflammatory markers, enzyme kB kinase (IKK), nuclear factor-kB and tumor necrosis factor-alpha as compared to untreated NAFL group. In conclusion,

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the present data strongly suggests the cross-talk between angiotensin, the Sphingosine SPK/S1P Axis and TLR4 Receptors, and their role in the pathogenesis of fructose-induced NAFLD, and the protection afforded by drugs inhibiting RAS.

[11] Wang J, Li X, Pu J et al. **Association between Gamma-Glutamyl Transferase and Coronary Atherosclerotic Plaque Vulnerability: An Optical Coherence Tomography Study.** *BioMed research international* 2019; 2019:9602783.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30984786>

ABSTRACT

Background: Gamma-glutamyl transferase (GGT) has been detected in coronary plaques. However, the association between serum GGT levels and coronary atherosclerotic plaque vulnerability in patients with coronary artery disease (CAD) as detected by optical coherence tomography (OCT) has not been investigated. Methods: We performed a retrospective study of consecutively enrolled CAD patients undergoing preintervention OCT examination during coronary angiography. Plaque vulnerability was defined as the presence of ruptured plaques or thin-cap fibroatheroma (TCFA) upon OCT. The association between serum GGT levels and coronary plaque vulnerability was evaluated using multivariate logistic regression analysis. Results: A total of 142 patients were included in our analysis. OCT examination detected ruptured plaques in 16 patients, nonruptured plaques with TCFA in 17 patients, and nonruptured plaques and non-TCFA in 109 patients. Univariate analyses showed that gender, diabetes, Apolipoprotein A1 (ApoA1) and high-density lipoprotein cholesterol (HDL-c), and diagnosis of acute coronary syndrome (ACS) were associated with plaque vulnerability (P all < 0.05). Patients grouped according to serum GGT tertiles did not differ statistically in baseline characteristics or OCT findings. Results of multivariate logistic analyses showed that diabetes and diagnosis of ACS were associated with plaque rupture and TCFA (P < 0.05). Conclusions: GGT serum levels were not associated with OCT detected coronary vulnerability in our cohort of CAD patient.

[12] Aguilar-Palacio I, Malo S, Lallana M et al. **Co-prescription patterns of cardiovascular preventive treatments: a cross-sectional study in the Aragon worker' health study (Spain).**

BMJ open 2019; 9:e023571.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30987984>

ABSTRACT

OBJECTIVES: To identify cardiovascular disease (CVD) preventive treatments combinations, among them and with other drugs, and to determine their prevalence in a cohort of Spanish workers. DESIGN: Cross-sectional study. SETTING: Aragon Workers' Health Study (AWHS) cohort in Spain. PARTICIPANTS: 5577 workers belonging to AWHS cohort. From these subjects, we selected those that had, at least, three prescriptions of the same therapeutic subgroup in 2014 ($n=4605$). PRIMARY AND SECONDARY OUTCOME MEASURES: Drug consumption was obtained from the Aragon Pharmaceutical Consumption Registry (Farmasalud). In order to know treatment utilisation, prevalence analyses were conducted. Frequent item set mining techniques were applied to identify drugs co-prescription patterns. All the results were stratified by sex and age. RESULTS: 42.3% of men and 18.8% of women in the cohort received, at least, three prescriptions of a CVD preventive treatment in 2014. The most prescribed CVD

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treatment were antihypertensives (men: 28.2%, women 9.2%). The most frequent association observed among CVD preventive treatment was agents acting on the renin-angiotensin system and lipid-lowering drugs (5.1% of treated subjects). Co-prescription increased with age, especially after 50 years old, both in frequency and number of associations, and was higher in men. Regarding the association between CVD preventive treatments and other drugs, the most frequent pattern observed was lipid-lowering drugs and drugs used for acid related disorders (4.2% of treated subjects). CONCLUSIONS: There is an important number of co-prescription patterns that involve CVD preventive treatments. These patterns increase with age and are more frequent in men. Mining techniques are a useful tool to identify pharmacological patterns that are not evident in the individual clinical practice, in order to improve drug prescription appropriateness.

[13] *Gruszka K, Rajzer M, Drozd T et al. Selected matrix metalloproteinases activity and hypertension-mediated organ damage in relation to uric acid serum level. Cardiology journal 2019.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30994184>

ABSTRACT

BACKGROUND: Atherosclerosis is as a systemic inflammatory disease associated with the activation of many mediators, including matrix metalloproteinases (MMPs), and may be amplified by abnormal high serum uric acid (UA) concentration (hyperuricemia, HU). The aim of the study was to determine the relationship between serum UA concentration and activity of MMPs and their correlation with the hypertension-mediated organ damage (HMOD) intensity. METHODS: 109 patients untreated with antihypertensive, hypolipemic or urate-lowering drugs with diagnosed stage 1-2 essential hypertension were included in this study. In all participants blood pressure (BP) was measured, carotid-femoral pulse wave velocity (PWV), intima-media thickness (IMT), echocardiography and blood tests including UA, lipids and serum concentrations of MMPs (1, 2, 3, 9) were observed. The participants were divided into hyper- and normuricemic groups. RESULTS: Uric acid concentration in the whole study group positively correlated with some HMOD parameters (IMT, PWV, left ventricular mass index, left atrial dimension). Among the studied metalloproteinases only MMP-3 activity positively correlated with serum UA concentration independently of age, body mass index and serum lipids ($R^2 = 0.11$, $p = 0.048$). Multivariate regression analysis showed positive association between IMT and BP, UA concentration and MMP-3 activity, independently of waist circumference and serum lipids ($R^2 = 0.328$, $p < 0.002$). Patients with HU were characterized by higher activity of MMP-3 than those without (19.41 [14.45; 21.74] vs. 13.98 [9.52; 18.97] ng/mL, $p = 0.016$). CONCLUSIONS: The present results may support the thesis that UA and the increased by UA activity of MMPs may take part in the development of HMOD, especially IMT.

[14] *Laimoud M, Faris F, Elghawaby H. Coronary Atherosclerotic Plaque Vulnerability Rather than Stenosis Predisposes to Non-ST Elevation Acute Coronary Syndromes. Cardiology research and practice 2019; 2019:2642740.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30984422>

ABSTRACT

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Background: Non-ST elevation acute coronary syndromes (NSTEMI-ACS) may arise from moderately stenosed atherosclerotic lesions that suddenly undergo transformation to vulnerable plaques complicated by rupture and thrombosis. Objective: Assessment and tissue characterization of the coronary atherosclerotic lesions among NSTEMI-ACS patients compared to those with stable angina. Methodology: Evaluation of IVUS studies of 312 coronary lesions was done by 2 different experienced IVUS readers, 216 lesions in 66 patients with NSTEMI-ACS (group I) versus 96 lesions in 50 patients with stable angina (group II). Characterization of coronary plaques structure was done using colored-coded iMap technique. Results: The Syntax score was significantly higher in group I compared to group II (18.7 +/- 7.8 vs. 8.07 +/- 2.5, p=0.001). Body mass index (BMI) was significantly higher in group II while triglycerides levels were higher in group I (P=0.01 & P=0.04, respectively). History of previous MI and PCI was significantly higher in group I (P=0.016 & P=0.001, respectively). The coronary lesions of NSTEMI-ACS patients had less vessel area (9.86 +/- 3.8 vs 11.36 +/- 2.9, p=0.001), stenosis percentage (54.7 +/- 14.9% vs 68.6 +/- 8.7%, p=0.001), and plaque burden (54.4 +/- 14.7 vs 67.8 +/- 9.8, p=0.001) with negative remodeling index (0.95 +/- 20 vs 1.02 +/- 0.14, p=0.008) compared to the stable angina group. On the other hand, they had more lipid content (21.8 +/- 7.03% vs 7.26 +/- 3.47%, p=0.001), necrotic core (18.08 +/- 10.19% vs 15.83 +/- 4.9%, p=0.02), and calcifications (10.4 +/- 5.2% vs 4.19 +/- 3.29%, p=0.001) while less fibrosis (51.67 +/- 7.07% vs 70.37 +/- 11.7%, p=0.001) compared to the stable angina patients. Syntax score and core composition especially calcification and lipid content were significant predictors to NSTEMI-ACS. Conclusions: The vulnerability rather than the stenotic severity is the most important factor that predisposes to non-ST segment elevation acute coronary syndromes. The vulnerability is related to the lesion characteristics especially lipidic core and calcification while lesion fibrosis favours lesion stability.

[15] Sanchez-Lopez E, Zhong Z, Stubelius A et al. **Choline Uptake and Metabolism Modulate Macrophage IL-1beta and IL-18 Production.** *Cell Metab* 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30982734>

ABSTRACT

Choline is a vitamin-like nutrient that is taken up via specific transporters and metabolized by choline kinase, which converts it to phosphocholine needed for de novo synthesis of phosphatidylcholine (PC), the main phospholipid of cellular membranes. We found that Toll-like receptor (TLR) activation enhances choline uptake by macrophages and microglia through induction of the choline transporter CTL1. Inhibition of CTL1 expression or choline phosphorylation attenuated NLRP3 inflammasome activation and IL-1beta and IL-18 production in stimulated macrophages. Mechanistically, reduced choline uptake altered mitochondrial lipid profile, attenuated mitochondrial ATP synthesis, and activated the energy sensor AMP-activated protein kinase (AMPK). By potentiating mitochondrial recruitment of DRP1, AMPK stimulates mitophagy, which contributes to termination of NLRP3 inflammasome activation. Correspondingly, choline kinase inhibitors ameliorated acute and chronic models of IL-1beta-dependent inflammation.

[16] Fiorelli S, Porro B, Cosentino N et al. **Activation of Nrf2/HO-1 Pathway and Human Atherosclerotic Plaque Vulnerability:an In Vitro and In Vivo Study.** *Cells* 2019; 8.

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PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30995787>

ABSTRACT

Reactive oxygen species (ROS) induce nuclear factor erythroid 2-related factor 2 (Nrf2) activation as an adaptive defense mechanism, determining the synthesis of antioxidant molecules, including heme-oxygenase-1 (HO-1). HO-1 protects cells against oxidative injury, degrading free heme and inhibiting ROS production. HO-1 is highly expressed in macrophages during plaque growth. Macrophages are morpho-functionally heterogeneous, and the prevalence of a specific phenotype may influence the plaque fate. This heterogeneity has also been observed in monocyte-derived macrophages (MDMs), a model of macrophages infiltrating tissue. The study aims to assess oxidative stress status and Nrf2/HO-1 axis in MDM morphotypes obtained from healthy subjects and coronary artery disease (CAD) patients, in relation to coronary plaque features evaluated *in vivo* by optical coherence tomography (OCT). We found that MDMs of healthy subjects exhibited a lower oxidative stress status, lower Nrf2 and HO-1 levels as compared to CAD patients. High HO-1 levels in MDMs were associated with the presence of a higher macrophage content, a thinner fibrous cap, and a ruptured plaque with thrombus formation, detected by OCT analysis. These findings suggest the presence of a relationship between *in vivo* plaque characteristics and *in vitro* MDM profile, and may help to identify patients with rupture-prone coronary plaque.

[17] *Wright AK, Kontopantelis E, Emsley R et al. Cardiovascular Risk and Risk Factor Management in Type 2 Diabetes: A Population-Based Cohort Study Assessing Sex Disparities. Circulation* 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30986362>

ABSTRACT

BACKGROUND: With recent changes in UK clinical practice for diabetes care, contemporary estimates of sex disparities in cardiovascular risk and risk factor management are needed. **METHODS:** In this retrospective cohort study, using the Clinical Practice Research Datalink linked to hospital and death records for people in England, we identified 79,985 patients with incident T2DM between 2006-2013 matched to 386,547 patients without diabetes. Sex-stratified Cox models were used to assess cardiovascular risk. **RESULTS:** Compared to women without T2DM, women with T2DM had a higher cardiovascular event risk (adjusted HR 1.20 [95% CI 1.12-1.28]) with similar corresponding data in men (HR 1.12 [1.06-1.19]) leading to a non-significant higher relative risk in women (risk ratio 1.07 [0.98-1.17]). However, some important sex differences in the management of risk factors were observed. Compared to men with T2DM, women with T2DM were more likely to be obese, hypertensive and have hypercholesterolaemia but were less likely to be prescribed lipid-lowering medication and ACE inhibitors, especially if they had CVD. **CONCLUSIONS:** Compared to men developing T2DM, women with T2DM do not have a significantly higher relative increase in cardiovascular risk, but ongoing sex disparities in prescribing should prompt heightened efforts to improve the standard and equity of diabetes care in women and men.

[18] *Jeendum N. Circulating PCSK9 concentrations are increased in postmenopausal women with the metabolic syndrome. Clinica chimica acta; international journal of clinical chemistry* 2019.

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PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31002780>

ABSTRACT

BACKGROUND: High PCSK9 concentrations are associated with an increased risk of cardiovascular disease (CVD). We investigated PCSK9 concentrations and their association with metabolic parameters in Thai subjects and to compare PCSK9 concentrations in pre- and postmenopausal women with and without metabolic syndrome (MetS). **METHODS:** Anthropometric data, serum lipids, fasting blood glucose (FBG), and PCSK9 concentrations were measured in 436 Thai subjects (152 men, 143 premenopausal, and 141 postmenopausal women). **RESULTS:** PCSK9 concentrations were significantly higher in women than in men ($p=.002$) and increased in subjects with an increasing number of MetS components (p for trend=.011). PCSK9 concentrations were significantly higher in postmenopausal women than in premenopausal women ($p<.001$), in the MetS group than in the non-MetS group ($p=.037$), and in postmenopausal women with MetS than in premenopausal women without MetS ($p<.001$). Serum PCSK9 concentrations were positively correlated with several metabolic parameters, including age, BMI, systolic blood pressure (SBP), total cholesterol, triglyceride, LDL-C, and FBG. **CONCLUSION:** PCSK9 concentrations are influenced by age, gender, MetS status, and menopausal status among Thai subjects. These findings suggest that an elevation in PCSK9 concentrations may increase cardiovascular risk in postmenopausal women with MetS.

[19] *Hirvensalo P, Tornio A, Neuvonen M et al. Enantiospecific pharmacogenomics of fluvastatin. Clinical pharmacology and therapeutics* 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30989645>

ABSTRACT

The aim of this study was to investigate how variability in multiple genes related to pharmacokinetics affects fluvastatin exposure. We determined fluvastatin enantiomer pharmacokinetics and sequenced 379 pharmacokinetic genes in 200 healthy volunteers. CYP2C9*3 associated with significantly increased area under the plasma concentration-time curve (AUC) of both 3R,5S- and 3S,5R-fluvastatin (by 67% and 94% per variant allele copy, $P = 3.77 \times 10^{-9}$ and $P = 3.19 \times 10^{-12}$). In contrast, SLCO1B1 c.521T>C associated with increased AUC of active 3R,5S-fluvastatin only (by 34% per variant allele copy; $P = 8.15 \times 10^{-8}$). A candidate gene analysis suggested that CYP2C9*2 also affects the AUC of both fluvastatin enantiomers and that SLCO2B1 single nucleotide variations (SNVs) may affect the AUC of 3S,5R-fluvastatin. Thus, SLCO transporters have enantiospecific effects on fluvastatin pharmacokinetics in humans. Genotyping of both CYP2C9 and SLCO1B1 may be useful in predicting fluvastatin efficacy and myotoxicity. This article is protected by copyright. All rights reserved.

[20] *Yee SW, Giacomini MM, Shen H et al. Organic Anion Transporter Polypeptide 1B1 Polymorphism Modulates the Extent of Drug-Drug Interaction and Associated Biomarker Levels in Healthy Volunteers. Clinical and translational science* 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30982223>

ABSTRACT

Understanding transporter-mediated drug-drug interactions is an integral part of risk assessment in drug development. Recent studies support the use of hexadecanedioate (HDA),

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tetradecanedioate (TDA), coproporphyrin (CP)-I, and CP-III as clinical biomarkers for evaluating organic anion-transporting polypeptide (OATP)1B1 (SLCO1B1) inhibition. The current study investigated the effect of OATP1B1 genotype c.521T>C (OATP1B1-Val174Ala) on the extent of interaction between cyclosporin A (CsA) and pravastatin, and associated endogenous biomarkers of the transporter (HDA, TDA, CP-I, and CP-III), in 20 healthy volunteers. The results show that the levels of each clinical biomarker and pravastatin were significantly increased in plasma samples of the volunteers following administration of pravastatin plus CsA compared with pravastatin plus placebo. The overall fold change in the area under the concentration-time curve (AUC) and maximum plasma concentration (C_{max}) was similar among the four biomarkers (1.8-2.5-fold, paired t-test P value < 0.05) in individuals who were homozygotes or heterozygotes of the major allele, c.521T. However, the fold change in AUC and C_{max} for HDA and TDA was significantly abolished in the subjects who were c.521-CC, whereas the respective fold change in AUC and C_{max} for pravastatin and CP-I and CP-III were slightly weaker in individuals who were c.521-CC compared with c.521-TT/TC genotypes. In addition, this study provides the first evidence that SLCO1B1 c.521T>C genotype is significantly associated with CP-I but not CP-III levels. Overall, these results suggest that OATP1B1 genotype can modulate the effects of CsA on biomarker levels; the extent of modulation differs among the biomarkers.

[21] *Bowman E, Funderburg NT. Lipidome Abnormalities and Cardiovascular Disease Risk in HIV Infection. Curr HIV/AIDS Rep 2019.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30993515>

ABSTRACT

PURPOSE OF REVIEW: Human immunodeficiency virus (HIV) infection and its treatment with antiretroviral therapy (ART) are associated with lipid abnormalities that may enhance cardiovascular disease risk (CVD). RECENT FINDINGS: Chronic inflammation persists in HIV+ individuals, and complex relationships exist among lipids and inflammation, as immune activation may be both a cause and a consequence of lipid abnormalities in HIV infection. Advances in mass spectrometry-based techniques now allow for detailed measurements of individual lipid species; improved lipid measurement might better evaluate CVD risk compared with the prognostic value of traditional assessments. Lipidomic analyses have begun to characterize dynamic changes in lipid composition during HIV infection and following treatment with ART, and further investigation may identify novel lipid biomarkers predictive of adverse outcomes. Developing strategies to improve management of comorbidities in the HIV+ population is important, and statin therapy and lifestyle modifications, including diet and exercise, may help to improve lipid levels and mitigate CVD risk.

[22] *Sedgeman LR, Mitchell DL, Vickers KC. Integrative roles of microRNAs in lipid metabolism and dyslipidemia. Current opinion in lipidology 2019.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30985366>

ABSTRACT

PURPOSE OF REVIEW: The purpose of the review is to discuss recent advances in microRNA (miRNA) regulation of lipid metabolism and highlight the importance of miRNA-mediated gene regulation in dyslipidemia and fatty liver disease. This article reviews examples of miRNAs that bridge disparate metabolic pathways in the liver. For example, we highlight miRNAs that are

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regulated by the sterol-sensing pathway in the liver that in turn regulate cellular or systemic cholesterol, fatty acid, and glucose levels. RECENT FINDINGS: The most widely studied of these miRNAs are miR-33a/b; however, we recently reported that miRNAs in the miR-183/96/182 cluster are also likely regulated by hepatic cholesterol content and mediate the observed glucose-lowering effects of the bile acid sequestrant colesevelam through the sterol-sensing pathway. In addition, several other hepatic and adipose miRNAs have been recently demonstrated to be key regulators of cellular lipid synthesis, storage, and catabolism, as well as systemic lipid metabolism. Moreover, many of these miRNAs are altered in fatty liver disease and dyslipidemia. SUMMARY: miRNAs are not just fine-tuners of lipid metabolism, but critical regulatory factors in lipid homeostasis and health. Loss of these miRNA regulatory modules very likely contributes to the underlying metabolic defects observed in lipid disorders.

[23] Orso E, Robenek H, Boettcher A et al. **Nonglucuronidated Ezetimibe Disrupts CD13- and CD64-Coassembly in Membrane Microdomains and Decreases Cellular Cholesterol Content in Human Monocytes/Macrophages.** *Cytometry. Part A : the journal of the International Society for Analytical Cytology* 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30994973>

ABSTRACT

Ezetimibe (EZE) and glucuronidated EZE (EZE-Glu) differentially target Niemann-Pick C1-like 1 (NPC1L1) and CD13 (aminopeptidase-N) to inhibit intestinal cholesterol absorption and cholesterol processing in other cells, although the precise molecular mechanisms are not fully elucidated. Cellular effects of EZE, EZE-Glu, and the low-absorbable EZE-analogue S6130 were investigated on human monocyte-derived macrophages upon loading with atherogenic lipoproteins. EZE and S6130, but not EZE-Glu disturbed the colocalization of CD13 and its coreceptor CD64 (Fcγ receptor I) in membrane microdomains, and decreased the presence of both receptors in detergent-resistant membrane fractions. Biotinylated cholesterol absorption inhibitor C-5 (i.e., derivative of EZE) was rapidly internalized to perinuclear tubular structures of cells, resembling endoplasmic reticulum (ER), but CD13 was detected on extracellular sites of the plasma membrane and endolysosomal vesicles. Administration of EZE, but not of EZE-Glu or S6130, was associated with decreased cellular cholesteryl ester content, indicating the sterol-O acyltransferase 1 (SOAT1)-inhibition by EZE. Furthermore, EZE decreased the expression of molecules involved in cholesterol uptake and synthesis, in parallel with increased apolipoprotein A-I-mediated cholesterol efflux and upregulation of efflux-effectors. However, NPC1L1 the other claimed molecular target of EZE, was not detected in macrophages, thereby excluding this protein as target for EZE in macrophages. Thus, EZE is very likely a CD13-linked microdomain-disruptor and SOAT1-inhibitor in macrophages leading to in vitro anti-atherosclerotic effects through a decrease of net cellular cholesterol content. (c) 2019 International Society for Advancement of Cytometry.

[24] Bengaluru Jayanna M, Robinson JG. **The extent to which statins have improved cardiovascular outcomes: Lessons from randomized trials and observational studies of "real world" practice in people with diabetes.** *Diabetes Obes Metab* 2019; 21 Suppl 1:17-27.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31002457>

ABSTRACT

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Statins are the mainstay of therapy for cardiovascular risk reduction in patients with diabetes mellitus. It is estimated that there are more than half a billion patients with diabetes mellitus worldwide and the numbers of prevalent cases of diabetes are expected to increase in both developed and developing countries in the next decade. Statins reduce risk of mortality and morbidity mainly by reducing blood low density cholesterol. Statins, along with other medical treatments, are responsible for about half of the decrease in cardiovascular mortality over the past several decades. Multiple clinical trials have found evidence for statin use in patients with diabetes, for both primary prevention and secondary prevention. The benefit of statins in patients with coronary heart disease and diabetes in terms of absolute risk reduction is twice as much as compared to the risk in patients with coronary heart disease but no diabetes. The proportion of patients with diabetes treated with statins has increased steadily over the past few decades with concurrent decrease in cardiovascular deaths in this high-risk population. However, there are significant unmet needs in cardiovascular risk reduction, due to underutilization of statins and due to residual cardiovascular risk despite maximal statin therapy. Future strategies in population risk reduction in diabetics should include maximal statin therapy, additional treatment with nonstatin therapy and new paradigms of prevention with early intervention with shorter, more intensive therapy to potentially "reverse" atherosclerosis with goals of reducing clinical cardiovascular disease later in life.

[25] *Dash S, Leiter LA. Residual cardiovascular risk among people with diabetes. Diabetes Obes Metab* 2019; 21 Suppl 1:28-38.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31002458>

ABSTRACT

Type 2 diabetes (T2D) is a growing health concern across both developed and developing countries. Cardiovascular disease (CVD) remains the major cause of increased mortality in this patient population. In recent years, effective low density lipoprotein lowering treatments and other risk reduction strategies have substantially reduced the risk of atherosclerotic CVD, yet patients with T2D continue to remain at increased risk for atherosclerotic CVD. Here, we will briefly review various proposed underlying mechanisms for this residual risk with a more in-depth focus on the potential role of triglyceride-rich lipoproteins in residual risk and potential avenues to target this pharmacologically.

[26] *Dijk W, Cariou B. Efficacy and safety of proprotein convertase subtilisin/kexin 9 inhibitors in people with diabetes and dyslipidaemia. Diabetes Obes Metab* 2019; 21 Suppl 1:39-51.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31002456>

ABSTRACT

Diabetic dyslipidaemia, characterized by quantitative, qualitative and kinetic changes in all major circulating lipids, contributes to the increased cardiovascular risk in patients with type 2 diabetes mellitus (T2DM). A promising therapeutic avenue is the inhibition of the proprotein convertase subtilisin kexin 9 (PCSK9) with human monoclonal antibodies (mAbs) that potentially reduce plasma low-density lipoprotein cholesterol (LDL-C) levels on top of statin treatment. The aim of this review is to evaluate the efficacy of PCSK9 inhibitors to lower the residual cardiovascular risk of T2DM patients and to discuss the safety of PCSK9 inhibition in these patients. PCSK9 inhibitors potentially lower plasma LDL-C levels in T2DM patients and reduce risk

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for the development of cardiovascular disease. Anti-PCSK9 mAbs are generally not more or less effective in T2DM patients compared to a general high-risk population. Nevertheless, due to their higher cardiovascular risk, the absolute risk reduction of major cardiovascular events is more significant in T2DM patients. This suggests that treatment of T2DM patients with anti-PCSK9 mAbs could be attractive from a cost-effectiveness perspective. Treatment with anti-PCSK9 mAbs did not result in significant treatment-emergent adverse effects. While genetic studies suggest a potential link between PCSK9 inhibition and glucose homeostasis, anti-PCSK9 mAbs did not worsen glycaemic control in T2DM patients, but their safety should be verified after a longer-term follow-up.

[27] *Ward NC, Page MM, Watts GF. Clinical guidance on the contemporary use of proprotein convertase subtilisin/kexin type 9 monoclonal antibodies. Diabetes Obes Metab 2019; 21 Suppl 1:52-62.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31002454>

ABSTRACT

There is now significant evidence for the benefits of lowering low-density lipoprotein cholesterol (LDL-c) to reduce the risk of atherosclerotic cardiovascular disease (ASCVD). Although statins are the most widely prescribed lipid-lowering therapy that effectively lower LDL-c, especially in combination with ezetimibe, some patients require adjunctive therapy to further lower LDL-c and mitigate attendant risk of ASCVD. The gap can be filled by proprotein convertase subtilisin/kexin type 9 (PCSK9) monoclonal antibodies whose use is currently supported by two recent cardiovascular outcome studies and new treatment guidelines. We provide an overview of extant studies investigating PCSK9 monoclonal antibodies in various patient populations, an update of the guidelines regarding their use and a case-based discussion.

[28] *Fogacci F, Ferri N, Toth PP et al. Efficacy and Safety of Mipomersen: A Systematic Review and Meta-Analysis of Randomized Clinical Trials. Drugs 2019.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30989634>

ABSTRACT

AIM: Our aim was to assess the efficacy and safety of mipomersen through a systematic review of the literature and a meta-analysis of the available clinical studies. METHODS: A systematic literature search in SCOPUS, PubMed Medline, ISI Web of Science and Google Scholar databases was conducted up to January 20, 2019, in order to identify clinical trials assessing the effect of mipomersen on lipoproteins, and the safety profile of mipomersen. Effect sizes for lipid changes were expressed as weighted mean differences (WMD) and 95% confidence intervals (CI). For safety analysis, odd ratios (OR) and 95% CI were calculated using the Mantel-Haenszel method. Data were pooled from 13 clinical studies comprising 49 arms, which included 1053 subjects overall, with 729 in the active-treated arm and 324 in the control arm. RESULTS: Meta-analysis of data suggested that mipomersen significantly reduced low-density lipoprotein cholesterol (WMD - 1.52, 95% CI - 1.85 to - 1.19; $p < 0.001$), total cholesterol (WMD - 1.55, 95% CI - 1.97 to - 1.13; $p < 0.001$), non-high-density lipoprotein cholesterol (non-HDL-C) (WMD - 1.66, 95% CI - 2.06 to - 1.27; $p < 0.001$), lipoprotein(a) (WMD - 0.99, 95% CI - 1.37 to - 0.62; $p < 0.001$), apolipoprotein B (WMD - 1.66, 95% CI - 2.04 to - 1.27; $p < 0.001$), triglycerides

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(WMD -0.61, 95% CI - 0.76 to - 0.46, $p < 0.001$), very-low-density lipoprotein cholesterol (WMD - 0.58, 95% CI - 0.73 to - 0.43; $p < 0.001$) and apolipoprotein A-I (WMD - 0.25, 95% CI - 0.51 to - 0.001; $p = 0.049$) without affecting HDL-C levels (WMD 0.11, 95% CI - 0.03 to 0.26; $p = 0.124$). However, treatment with mipomersen was positively associated with an increased risk of discontinuation of treatment (OR 3.02, 95% CI 1.96-4.65; $p < 0.001$), injection-site reaction (OR 11.41, 95% CI 7.88-16.52; $p < 0.001$), hepatic steatosis (OR 4.96, 95% CI 1.99-12.39; $p = 0.001$), hepatic enzymes elevation (OR 3.61, 95% CI 2.09-6.24; $p < 0.001$) and flu-like symptoms (OR 2.02, 95% CI 1.45-2.81; $p < 0.001$). **CONCLUSION:** Despite favourable effects on the lipid profile, some concerns are reinforced from the safety profile. As a matter of fact, mipomersen therapy is more likely discontinued and associated with increased risk of injection-site reactions, hepatic steatosis, hepatic enzyme elevation, and flu-like symptoms.

[29] Amor AJ, Ortega E, Gimenez M et al. **Prevalence and factors associated with statin use in high-risk patients with type 1 diabetes from a specialized diabetes unit.** *Endocrinologia, diabetes y nutricion* 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31000451>

ABSTRACT

INTRODUCTION: The use of statins in non-selected type 1 diabetes (T1D) populations is low. We assessed the prevalence and factors associated with statin treatment in patients meeting criteria for this therapy for primary prevention of cardiovascular disease (CVD). **MATERIAL AND METHODS:** From 2015 to 2018, T1D patients from a tertiary hospital were selected. Inclusion criteria were: ≥ 40 years-old, diabetic nephropathy, or T1D duration ≥ 10 years with ≥ 1 cardiovascular risk factor (CVRF). A standardized cardiovascular risk evaluation protocol was performed. Prevalence of statin treatment was evaluated according to presence of several CVRFs, and multivariable models were constructed to assess independent determinants of statin use. **RESULTS:** We included 241 patients (50% women, age 48.2 \pm 9.9 years, T1D duration 26.6 \pm 9.0 years). Diabetic retinopathy and nephropathy, active smoking, and hypertension were present in 38%, 12%, 28%, and 27%, respectively. Overall, 43% of patients were on statins and 27% had LDL-cholesterol < 100 mg/dl. Statin users were older, and had higher body mass index (BMI), prevalence of kidney dysfunction, and hypertension ($p < 0.05$ for all). However, among both T1D-related and classical CVRFs, only hypertension (odds ratio [OR], 2.96; 95% confidence interval [CI] 1.48-5.91) and BMI (OR, 1.08; CI, 1.01-1.16) were independently associated with statin use in multiple regression analysis. **CONCLUSIONS:** Less than half of T1D patients from a tertiary hospital who met criteria for statin use were on treatment. Hypertension and BMI emerged as the only CVRFs independently associated with statin therapy. New strategies are needed to better address CVD prevention in this very high-risk population.

[30] Schiele F, Lemesle G, Angoulvant D et al. **Proposal for a standardized discharge letter after hospital stay for acute myocardial infarction.** *European heart journal. Acute cardiovascular care* 2019:2048872619844444.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30990337>

ABSTRACT

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In patients admitted for acute myocardial infarction, the communication and transition from specialists to primary care physicians is often delayed, and the information imparted to subsequent healthcare providers (HCPs) may be sub-optimal. A French group of cardiologists, lipidologists and diabetologists decided to establish a consensus to optimize the discharge letter after hospitalization for acute myocardial infarction. The aim is to improve both the timeframe and the quality of the content transmitted to subsequent HCPs, including information regarding baseline assessment, procedures during hospitalization, residual risk, discharge treatments, therapeutic targets and follow-up recommendations in compliance with European Society of Cardiology guidelines. A consensus was obtained regarding a template discharge letter, to be released within two days after patient's discharge, and containing the description of the patient's history, risk factors, acute management, risk assessment, discharge treatments and follow-up pathway. Specifically for post acute MI patients, tailored details are necessary regarding the antithrombotic regimen, lipid-lowering and anti-diabetic treatments, including therapeutic targets. Lastly, the follow-up pathway needs to be precisely mentioned in the discharge letter. Additional information such as technical descriptions, imaging, and quality indicators may be provided separately. A template for a standardized discharge letter based on 8 major headings could be useful for implementation in routine practice and help to improve the quality and timing of information transmission between HCPs after acute MI.

[31] *Wu J, Zhang J, Wang A et al. Association between Non-HDL Cholesterol Levels and Asymptomatic Vulnerable Carotid Atherosclerotic Plaques. European journal of neurology : the official journal of the European Federation of Neurological Societies* 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31002203>

ABSTRACT

BACKGROUND: Carotid atherosclerosis, especially rupture of plaques is related to cerebrovascular diseases (CVDs). Non-high-density lipoprotein cholesterol (non-HDL-C) is relevant with CVDs and may be a potential risk factor. We designed this study to investigate the association between non-HDL-C and prevalence of asymptomatic vulnerable carotid atherosclerotic plaques. **METHODS:** We enrolled 2888 participants who underwent carotid atherosclerotic plaques detection and non-HDL-C measurement, with no history of taking lipid-lowering agents from the Asymptomatic Polyvascular Abnormalities Community (APAC) study. We used multivariable logistic regression to estimate the association between non-HDL-C levels and the presence of asymptomatic vulnerable carotid atherosclerotic plaques. **RESULTS:** In our study, 1505 subjects had asymptomatic vulnerable carotid atherosclerotic plaques, and 1383 subjects had stable plaques. After adjustment for confounding factors, the odds ratios (95% confidence interval) for vulnerable plaques of non-HDL-C levels in middle tertile group and highest tertile group were: 1.02 (0.84-1.23), 1.50 (1.23-1.82), respectively (p trend<0.01). **CONCLUSIONS:** In our community-based, observational, and cross-sectional study, non-HDL-C level is a significant risk factor for the occurrence of asymptomatic vulnerable carotid plaques. This article is protected by copyright. All rights reserved.

[32] *Aguilar-Salinas CA, Viveros-Ruiz T. Recent advances in managing/understanding the metabolic syndrome. F1000Research* 2019; 8.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31001415>

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ABSTRACT

The metabolic syndrome (MetS) concept gathers in a single entity a set of metabolic abnormalities that have in common a close relationship with ectopic deposit of lipids, insulin resistance, and chronic low-grade inflammation. It is a valuable teaching tool to help health professionals to understand and integrate the consequences of lipotoxicity and the adverse metabolic consequences of insulin resistance. Also, it is useful to identify subjects with a high risk for having incident type 2 diabetes. Systems biology studies have gained a prominent role in understanding the interaction between adipose tissue dysfunction, insulin action, and the MetS traits and co-morbidities (that is, non-alcoholic steatohepatitis, or NASH). This approach may allow the identification of new therapeutic targets (that is, de novo lipogenesis inhibitors for NASH). Treatment targets on MetS are the adoption of a healthy lifestyle, weight loss, and the control of the co-morbidities (hyperglycemia, dyslipidemia, arterial hypertension, among others). The long-term goals are the prevention of type 2 diabetes, cardiovascular events, and other MetS-related outcomes. In the last few decades, new drugs derived from the identification of innovative treatment targets have come on the market. These drugs have positive effects on more than one MetS component (that is, hyperglycemia and weight control). New potential treatment targets are under study.

[33] *Lopez-Garcia G, Cilla A, Barbera R et al. Effect of a Milk-Based Fruit Beverage Enriched with Plant Sterols and/or Galactooligosaccharides in a Murine Chronic Colitis Model. Foods (Basel, Switzerland) 2019; 8.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30987294>

ABSTRACT

The potential anti-inflammatory effect of plant sterols (PS) enriched milk-based fruit beverages (PS, 1 g/100 mL) (MfB) with/without galactooligosaccharides (GOS, 2 g/100 mL) (MfB-G) in an experimental mice model of chronic ulcerative colitis was evaluated. Beverages were orally administered to mice every day by gavage to achieve PS and GOS doses of 35 and 90 mg/kg, respectively, and experimental colitis was induced by giving mice drinking water ad libitum containing 2% (w/v) dextran sulphate sodium (DSS) for 7 days, alternating with periods without DSS up to the end of the study (56 days). MfB beverage showed significant reduction of symptoms associated to ulcerative colitis and improved the colon shortening and mucosal colonic damage, but it was not able to reduce the increase of myeloperoxidase levels produced by DSS. MfB-G showed higher incidence of bloody feces and loss of stool consistency than MfB, as well as high levels of immune cells infiltration in colon tissue and myeloperoxidase. Therefore, PS-enriched milk-based fruit beverage could be an interesting healthy food to extend the remission periods of the diseases and the need to evaluate, in a pre-clinical model, the anti-inflammatory effect of the combination of bioactive compounds in the context of a whole food matrix.

[34] *McDivitt JD, Braun M, Kassop D. Cardiovascular Disease: Lower Extremity Peripheral Artery Disease. FP essentials 2019; 479:11-15.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30994999>

ABSTRACT

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Lower extremity peripheral artery disease (PAD) refers to atherosclerotic disease that involves the iliac, femoral, or more distal arteries of the lower extremities. This condition affects 8 to 12 million Americans. Risk factors include advanced age, hypertension, dyslipidemia, diabetes, and cigarette smoking. Approximately 10% to 30% of patients with PAD present with the classic symptom of intermittent claudication. Some patients experience symptoms such as pallor, hair loss, or nonhealing wounds, and up to half of patients are asymptomatic. There are differing recommendations from various organizations for screening of asymptomatic patients. If PAD is suspected, the ankle-brachial index is the preferred first test. Further tests, including duplex ultrasonography or angiography, may be warranted depending on the clinical situation. Therapy for patients with PAD consists of lifestyle modifications, which include diet modification, exercise programs, and smoking cessation. Medical therapy consists of antiplatelet and statin therapies for secondary prevention of vascular complications, and consideration of drugs such as cilostazol for symptom control. Patients with acute limb ischemia should be referred emergently for evaluation and possible revascularization. Patients with lifestyle-limiting claudication despite lifestyle modification and medical therapy and patients with chronic limb ischemia (eg, nonhealing wounds) should be considered for revascularization.

[35] *Gerling CJ, Mukai K, Chabowski A et al. Incorporation of Omega-3 Fatty Acids Into Human Skeletal Muscle Sarcolemmal and Mitochondrial Membranes Following 12 Weeks of Fish Oil Supplementation. Front Physiol* 2019; 10:348.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30984028>

ABSTRACT

Fish oil (FO) supplementation in humans results in the incorporation of omega-3 fatty acids (FAs) eicosapentaenoic acid (EPA; C20:5) and docosahexaenoic acid (DHA; C20:6) into skeletal muscle membranes. However, despite the importance of membrane composition in structure-function relationships, a paucity of information exists regarding how different muscle membranes/organelles respond to FO supplementation. Therefore, the purpose of the present study was to determine the effects 12 weeks of FO supplementation (3g EPA/2g DHA daily) on the phospholipid composition of sarcolemmal and mitochondrial fractions, as well as whole muscle responses, in healthy young males. FO supplementation increased the total phospholipid content in whole muscle (57%; $p < 0.05$) and the sarcolemma (38%; $p = 0.05$), but did not alter the content in mitochondria. The content of omega-3 FAs, EPA and DHA, were increased (+3-fold) in whole muscle, and mitochondrial membranes, and as a result the omega-6/omega-3 ratios were dramatically decreased (-3-fold), while conversely the unsaturation indexes were increased. Intriguingly, before supplementation the unsaturation index (UI) of sarcolemmal membranes was approximately 3 times lower ($p < 0.001$) than either whole muscle or mitochondrial membranes. While supplementation also increased DHA within sarcolemmal membranes, EPA was not altered, and as a result the omega-6/omega-3 ratio and UI of these membranes were not altered. All together, these data revealed that mitochondrial and sarcolemmal membranes display unique phospholipid compositions and responses to FO supplementation.

[36] *Akyea RK, Kai J, Qureshi N et al. Sub-optimal cholesterol response to initiation of statins and future risk of cardiovascular disease. Heart* 2019.

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PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30988003>

ABSTRACT

OBJECTIVE: To assess low-density lipoprotein cholesterol (LDL-C) response in patients after initiation of statins, and future risk of cardiovascular disease (CVD). **METHODS:** Prospective cohort study of 165 411 primary care patients, from the UK Clinical Practice Research Datalink, who were free of CVD before statin initiation, and had at least one pre-treatment LDL-C within 12 months before, and one post-treatment LDL-C within 24 months after, statin initiation. Based on current national guidelines, <40% reduction in baseline LDL-C within 24 months was classified as a sub-optimal statin response. Cox proportional regression and competing-risks survival regression models were used to determine adjusted hazard ratios (HRs) and sub-HRs for incident CVD outcomes for LDL-C response to statins. **RESULTS:** 84 609 (51.2%) patients had a sub-optimal LDL-C response to initiated statin therapy within 24 months. During 1 077 299 person-years of follow-up (median follow-up 6.2 years), there were 22 798 CVD events (12 142 in sub-optimal responders and 10 656 in optimal responders). In sub-optimal responders, compared with optimal responders, the HR for incident CVD was 1.17 (95% CI 1.13 to 1.20) and 1.22 (95% CI 1.19 to 1.25) after adjusting for age and baseline untreated LDL-C. Considering competing risks resulted in lower but similar sub-HRs for both unadjusted (1.13, 95% CI 1.10 to 1.16) and adjusted (1.19, 95% CI 1.16 to 1.23) cumulative incidence function of CVD. **CONCLUSIONS:** Optimal lowering of LDL-C is not achieved within 2 years in over half of patients in the general population initiated on statin therapy, and these patients will experience significantly increased risk of future CVD.

[37] *Essid SM, Bevington A, Brunskill NJ. Proinsulin C-Peptide Enhances Cell Survival and Protects against Simvastatin-Induced Myotoxicity in L6 Rat Myoblasts. International journal of molecular sciences 2019; 20.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30987105>

ABSTRACT

The repair capacity of progenitor skeletal muscle satellite cells (SC) in Type 1 diabetes mellitus (T1DM) is decreased. This is associated with the loss of skeletal muscle function. In T1DM, the deficiency of C-peptide along with insulin is associated with an impairment of skeletal muscle functions such as growth, and repair, and is thought to be an important contributor to increased morbidity and mortality. Recently, cholesterol-lowering drugs (statins) have also been reported to increase the risk of skeletal muscle dysfunction. We hypothesised that C-peptide activates key signaling pathways in myoblasts, thus promoting cell survival and protecting against simvastatin-induced myotoxicity. This was tested by investigating the effects of C-peptide on the L6 rat myoblast cell line under serum-starved conditions. Results: C-peptide at concentrations as low as 0.03 nM exerted stimulatory effects on intracellular signaling pathways-MAP kinase (ERK1/2) and Akt. When apoptosis was induced by simvastatin, 3 nM C-peptide potently suppressed the apoptotic effect through a pertussis toxin-sensitive pathway. Simvastatin strongly impaired Akt signaling and stimulated the reactive oxygen species (ROS) production; suggesting that Akt signaling and oxidative stress are important factors in statin-induced apoptosis in L6 myoblasts. The findings indicate that C-peptide exerts an important protective effect against death signaling in myoblasts. Therefore, in T1DM, the deficiency of C-

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peptide may contribute to myopathy by rendering myoblast-like progenitor cells (involved in muscle regeneration) more susceptible to the toxic effects of insults such as simvastatin.

[38] *Lebeau PF, Byun JH, Platko K et al. Diet-induced hepatic steatosis abrogates cell-surface LDLR by inducing de novo PCSK9 expression in mice. The Journal of biological chemistry* 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31004037>

ABSTRACT

The worldwide prevalence of non-alcoholic fatty liver disease (NAFLD) is increasing rapidly. Although this condition is generally benign, accumulating evidence now suggests that patients with NAFLD are also at increased risk of cardiovascular disease (CVD); the leading cause of death in developed nations. Despite the well-established role of the liver as a central regulator of circulating low-density lipoprotein (LDL) cholesterol levels, a known driver of CVD, the mechanism(s) by which hepatic steatosis contributes to CVD remains elusive. Interestingly, a recent study has shown that circulating proprotein convertase subtilisin/kexin type 9 (PCSK9) levels correlate positively with liver steatosis grade. Given that PCSK9 degrades the LDL receptor (LDLR) and prevents the removal of LDL from the blood into the liver, in the present study we examined the effect of hepatic steatosis on LDLR expression and circulating LDL cholesterol levels. We now report that in a manner consistent with findings in human patients, diet-induced steatosis increases circulating PCSK9 levels as a result of de novo expression in mice. We also report the novel finding that steatosis abrogates hepatic LDLR expression and increases circulating LDL levels in a PCSK9-dependent manner. These findings provide important mechanistic insights as to how hepatic steatosis modulates lipid regulatory genes like PCSK9 and the LDLR, and also highlights a novel mechanism by which liver disease may contribute to CVD.

[39] *Bahrambeigi S, Rahimi M, Yousefi B, Shafiei-Irannejad V. New potentials for 3-hydroxy-3-methyl-glutaryl-coenzymeA reductase inhibitors: Possible applications in retarding diabetic complications. Journal of cellular physiology* 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31004363>

ABSTRACT

The prevalence of diabetes mellitus is increasing all over the world and it is apparent that treatment of diabetic complications has the same importance as primary diabetes treatment and glycemic control. Diabetic complications occur as a result of prolonged hyperglycemia and its consequences, such as advanced glycation end products and reactive oxygen species. Impairment of lipid profile is also contributed to worsening diabetic complications. Therefore, it seems that the application of lipid-lowering agents may have positive effects on reversing diabetic complications besides glycemic control. Statins, a group of lipid-lowering compounds, have been shown to exert antioxidant, immunomodulatory, anti-inflammatory, and antiproliferative properties beyond their lipid-lowering effects. Furthermore, they have been reported to improve diabetic complications with different pathways. In this review, we will discuss the clinical importance, molecular biology of the most important microvascular/macrovascular diabetic complications, possible application of statins and their mechanism of action in retarding these complications.

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[40] Zhou AL, Ward RE. **Milk polar lipids modulate lipid metabolism, gut permeability, and systemic inflammation in high-fat-fed C57BL/6J ob/ob mice, a model of severe obesity.**

Journal of dairy science 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30981495>

ABSTRACT

Dynamic interactions between lipid metabolism, gut permeability, and systemic inflammation remain unclear in the context of obesity. Milk polar lipids, lipids derived from the milk fat globule membrane, could positively affect the aforementioned obesity-related endpoints. This study aimed to test the hypotheses that milk polar lipids will reduce gut permeability, systemic inflammation, and liver lipid levels, and differentially affect the hepatic expression of genes associated with fatty acid synthesis and cholesterol regulation in preexisting obesity. We fed 3 groups of C57BL/6J ob/ob mice (n = 6 per group) for 2 wk: (1) a modified AIN-93G diet (CO) with 34% fat by energy; (2) CO with milk gangliosides (GG) at 0.2 g/kg of diet; and (3) CO with milk phospholipids (PL) at 10 g/kg of diet. The GG and PL were provided as semi-purified concentrates and replaced 2.0% and 7.2% of dietary fat by energy. The GG and PL did not affect total food intake, weight gain, fasting glucose, or gut permeability. The PL decreased liver mass and the mesenteric fat depot compared with the CO. The GG increased tight junction protein occludin in colon mucosa compared with the CO. The GG and PL decreased tight junction protein zonula occludens-1 in jejunum mucosa compared with the CO. Plasma endotoxin increased during the study but was unaffected by the treatments. Compared with the CO and GG, the PL increased plasma sphingomyelin and plasma IL-6. The GG and PL differentially regulated genes associated with lipid metabolism in the liver compared with the CO. Regarding general effects on lipid metabolism, the GG and PL decreased lipid levels in the liver and the mesenteric depot, and increased lipid levels in the plasma. Diet consumption decreased significantly when the ob/ob mice were kept in metabolic cages, which were not big enough and resulted in unwanted animal deaths. Future studies may keep this in mind and use better metabolic equipment for ob/ob mice. In conclusion, dietary milk polar lipids may have limited beneficial effects on gut barrier integrity, systemic inflammation, and lipid metabolism in the context of severe obesity.

[41] Liang JX, Zhang QQ, Huang YF et al. **Comprehensive chemical profiling of monascus-fermented rice and screening of lipid-lowering compounds other than monacolins.** *Journal of ethnopharmacology* 2019:111879.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30991138>

ABSTRACT

ETHNOPHARMACOLOGICAL RELEVANCE: Monascus-fermented rice product (MFRP) has been regarded as a dietary supplement and traditional medicine with circulation-promoting effects in China and other countries for centuries. AIM OF THE STUDY: This study was carried out to profile the chemical components in MFRP, and provide available information for elucidating the potential lipid-lowering compounds other than monacolins. MATERIALS AND METHODS: High-performance liquid chromatography coupled with quadrupole time-of-flight mass spectrometry (HPLC-QTOF MS) and gas chromatography coupled with mass spectrometry (GC-MS) methods were applied to comprehensive analysis of chemical components in MFRP. Potential small molecules were identified by comparing with reference standards, or tentatively characterized

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by comparing their retention time and high-resolution mass spectral data with previous literatures. The lipid-lowering properties of ten major non-monacolin compounds were evaluated in cholesterol-fed zebrafish larvae. And one with optimum lipid-lowering activity was subsequently evaluated in high fat diet-fed C57BL/6J mice, with the dyslipidemia and ectopic lipid deposition being investigated. RESULTS: A total of 99 compounds were characterized in MFRP, including 38 monacolins, 5 decalins, 6 isoflavones, 13 pigments, 8 azaphilones, 11 amino acids, 4 nucleosides, 9 lipid acids, 4 phytosterols and glycerol. The preliminary screening showed that ergosterol remarkably reduced cholesterol levels in zebrafish larvae. Moreover, ergosterol delayed body weight gain and decreased circulating total cholesterol, triglyceride, low density lipoprotein cholesterol levels in high fat diet-fed mice. Ectopic lipid accumulation was also ameliorated in the liver and heart of obese mice. CONCLUSION: Global analysis of chemical components and screening of lipid-lowering non-monacolin compounds in MFRP have improved our understanding of its therapeutic material basis.

[42] *Bonaccio M, Di Castelnuovo A, Costanzo S et al. Impact of combined healthy lifestyle factors on survival in an adult general population and in high-risk groups: prospective results from the Moli-sani Study. Journal of internal medicine* 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30993789>

ABSTRACT

BACKGROUND: There is poor knowledge on the association between combined lifestyles with mortality risk among individuals at high risk, and little is known on the biological mechanisms that could be on the pathway. METHODS: Longitudinal analysis on 22 839 individuals from the Moli-sani Study (Italy, 2005-2010). Among them, we identified 5200 elderly individuals (≥ 65 year), 2127 subjects with diabetes and 1180 with cardiovascular disease (CVD) at baseline. A healthy lifestyle score (HLS) was calculated, allocating 1 point for each of the following: abstention from smoking; adherence to Mediterranean diet; physical activity; absence of abdominal obesity. Hazard ratios (HR) with 95% confidence intervals (95%CI) were calculated by multivariable Cox regression and competing risk models. RESULTS: During 8.2 years of follow-up, 1237 deaths occurred. In the general population, adherence to all four healthy lifestyles, compared with none or 1, was associated with lower risk of all-cause (HR = 0.53; 95%CI:0.39-0.72), CVD (HR = 0.54; 0.32-0.91), cancer (HR = 0.62; 0.39-1.00) and mortality from other causes (HR = 0.39; 0.19-0.81). A 1-point increase in HLS was associated with 20%, 22% and 24% lower risk of total mortality among the elderly, in subjects with diabetes or CVD, respectively. Traditional (e.g. blood lipids), inflammatory (e.g. C-reactive protein) and novel biomarkers (e.g. markers of cardiac damage) accounted for up to 24% of the association of HLS with all-cause mortality risk in the general population. CONCLUSIONS: The impact of combined four healthy lifestyles on survival was considerable, both in the general population and among high-risk subgroups. Inflammatory and novel biomarkers of CVD risk explained a substantial proportion of this association.

[43] *Rawther T, Tabet F. Biology, pathophysiology and current therapies that affect lipoprotein (a) levels. Journal of molecular and cellular cardiology* 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30986377>

ABSTRACT

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Lipoprotein (a) [Lp(a)] has recently emerged as a causal, independent and genetic risk factor for cardiovascular disease and calcific aortic valve disease. Given the high incidence of elevated Lp(a) among the general population, significant gaps in the knowledge of Lp(a) biology, pathophysiology and current therapies affecting Lp(a) reduction exist. As plasma Lp(a) levels are genetically determined and insensitive to diet, exercise and life-style changes, lipid-lowering therapies seem to be the solution to lower elevated Lp(a) levels. This review summarises the current knowledge of Lp(a) structure, metabolism, catabolism, pathophysiology, and Lp(a) response to statins, lipid apheresis, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, cholesterol esterase transferase protein (CETP) inhibitors and antisense oligonucleotides (ASOs).

[44] Walker ME, Matthan NR, Solano-Aguilar G et al. **A Western-type dietary pattern and atorvastatin induce epicardial adipose tissue interferon signaling in the Ossabaw pig.** The Journal of nutritional biochemistry 2019; 67:212-218.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30981985>

ABSTRACT

Epicardial adipose tissue (EAT) inflammation is thought to potentiate the development of coronary artery disease (CAD). Overall diet quality and statin therapy are important modulators of inflammation and CAD progression. Our objective was to examine the effects and interaction of dietary patterns and statin therapy on EAT gene expression in the Ossabaw pig. Pigs were randomized to 1 of 4 groups; Heart Healthy diet (high in unsaturated fat, unrefined grain, fruits/vegetables [HHD]) or Western diet (high in saturated fat, cholesterol, refined grain [WD]), with or without atorvastatin. Diets were fed in isocaloric amounts for 6 months. A two-factor edge R analysis identified the differential expression of 21 genes. Relative to the HHD, the WD resulted in a significant 12-fold increase of radical s-adenosyl methionine domain containing 2 (RSAD2), a gene induced by interferon signaling. Atorvastatin led to the significant differential expression of 17 genes predominately involved in interferon signaling. Results were similar using the Porcine Translational Research Database. Pathway analysis confirmed the up-regulation of interferon signaling in response to the WD and atorvastatin independently. An expression signature of the largely interferon related differentially expressed genes had no predictive capability on a histological assessment of atherosclerosis in the underlying coronary artery. These results suggest that a WD and atorvastatin evoke an interferon mediated immune response in EAT of the Ossabaw pig, which is not associated with the presence of atherosclerosis.

[45] Hammad MA, Syed Sulaiman SA, Aziz NA, Mohamed Noor DA. **Prescribing statins among patients with type 2 diabetes: The clinical gap between the guidelines and practice.** Journal of research in medical sciences : the official journal of Isfahan University of Medical Sciences 2019; 24:15.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30988683>

ABSTRACT

Background: Statins are recommended for cardiovascular protection for people with diabetes (high-risk groups). This study aimed to evaluate the gap between the guidelines of statin utilization and clinical practice among outpatients with type 2 diabetes regarding the patient's

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age and gender, to assess if this preventive drug is being satisfactorily utilized or not. Materials and Methods: In this cross-sectional study, patients aged <40 or >75 years, pregnant patients, and patients with type 1 diabetes, human immunodeficiency virus, or liver cirrhosis were excluded. Demographics, laboratory parameters, and prevalence of exposure to statin therapy were evaluated. This study was guided by the 2013 American College of Cardiology/American Heart Association cholesterol guidelines. IBM SPSS software was used for data management. Results: The study cohort involved 576 patients, with age being 58.3 +/- 8.9 years. There were 50.5% of females and 49.5% of males. Overall 81.1% of patients aged 58.8 +/- 8.8 years were statin users and 18.9% of patients aged 56.2 +/- 9 years were statin nonusers. About 83.2% of females and 78.9% of males were prescribed statins. Statin medications included simvastatin 79.2%, atorvastatin 11.6%, lovastatin 5.8%, rosuvastatin 2.1%, and pravastatin 1.3%. Statin users' and nonusers' adherence was 56.5%, and 41.3% (P = 0.004), respectively. The adherence to medication plan of females and males was 55.7% and 51.6%, respectively (P = 0.004). Conclusion: Patients with diabetes who are at high risk of cardiovascular events, exposure to statin treatment is significantly less than perfect position both in females and males. Nearly one-fifth of the patients with type 2 diabetes are not using statins despite therapeutic necessities.

[46] *Snarska A, Wysocka D, Rytel L. Effect of Simvastatin on Thrombopoiesis in Porcine Bone Marrow. Journal of veterinary research 2019; 63:117-121.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30989143>

ABSTRACT

Introduction: Statins are pharmacological agents commonly used to lower serum cholesterol level. The aim of the experiment was to investigate the effect of the statin simvastatin on thrombopoiesis in the porcine model because it is the closest to the human one regarding physiological and genetic similarities. Material and Methods: The study was conducted on a group of 32 pigs randomly divided into two equal groups: control and experimental. The pigs were treated for 28 and 56 days with simvastatin in a dose of 40 mg per day per animal. Cytological evaluation of bone marrow smears was performed to assess the average number of all types of cells during thrombopoiesis as was analysis of haematological parameters to assess PLT and MPV. Results: During the course of the experiment statistically significant changes in the number of promegakaryocytes were observed. Other parameters also showed some fluctuations during the study. However, these changes were not statistically significant. Conclusion: The obtained results clearly indicate a toxic influence of simvastatin on the process of thrombopoiesis and prove that statins reduce mean platelet volume, thus affecting the process of clot formation through the period of administration in a duration-dependent manner.

[47] *Korneva VA, Kuznetsova TY, Tihova GP. [Lipid Lowering Therapy with Statins in Patients with Heterozygous Familial Hypercholesterolemia]. Kardiologija 2019; 59:27-35.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30990138>

ABSTRACT

AIM: to analyze adherence of FH patients with familial hypercholesterolemia (FH) to the statin therapy and reveal factors, which influence it; to assess the degree of target level of low-

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density lipoprotein cholesterol (LDLCH) achievement by FH patients on statin therapy. Materials and methods. We included in this study 203 FH patients aged ≥ 18 years (mean age 50.0 \pm 1.1 years, 82 men). Definite FH was diagnosed in 96 persons, in the other patients FH was considered possible. For evaluating the adherence to therapy with statins we used the Morisky-Green questionnaire. Results. Among patients with definite FH 57 % were adherent to lipid-lowering therapy, 16 % were partially adherent, and 27 % - not adherent. Target LDLCH levels were achieved in 22.6 % and 12.5 % of patients with definite and possible FH, respectively. Smoking and gender were not associated with adherence to statin therapy. Factors associated with higher adherence were age ($p=0.000003$), arterial hypertension (odds ratio [OR] 1.90, 95 % confidence interval [CI] 1.02 to 3.55), $p=0.044$), ischemic heart disease (IHD) (OR=2.99, 95 %CI 1.50 to 5.97, $p=0.002$), history of myocardial infarction (MI) (OR 5.26, 95 %CI 2.03 to 13.60, $p=0.0006$), history of myocardial revascularization (OR 20.3, 95 %CI 2.64 to 156.11, $p=0.004$) and the fact of achieving target LDLCH level (OR 19.93, 95 %CI 7.03 to 56.50, $p<0.0001$). The main reason for the refuse from statin therapy in 87 % of patients was fear of side effects. Main reasons for stopping of ongoing therapy were: myalgia, an increase in transaminases, skin rashes, and high cost in 12, 35, 12, and 6 % of patients, respectively. The decision to withdraw therapy with statins was made by 29 % of patients by themselves. CONCLUSION: In this study 57 % of patients with definite FH were adherent to statin therapy. Factors associated with increased adherence were age, hypertension, IHD, history of MI, history of myocardial revascularization, achievement of target LDLCH level. Target LDLCH levels were achieved by 22.6 and 12.5 % of patients with definite and possible FH, respectively.

[48] *Pigarevsky PV, Snegova VA, Nazarov PG. [Macrophages and Their Role in Destabilization of an Atherosclerotic Plaque]. Kardiologiya 2019; 59:88-91.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31002045>

ABSTRACT

The modern data on structure and the functional activity of macrophages are presented in the review. It is shown that they are the nonhomogeneous cell population. Two of their main subpopulations are presented as M1 and M2 phenotypes which perform opposite functions at inflammation development. The main attention in the review is paid to a role of macrophages in pathogenesis of atherosclerosis and, first, in formation of unstable atherosclerotic plaques which are the cause of the most severe complications of the disease. It is shown that main subpopulations of macrophages play different roles in formation of unstable and stable atherosclerotic plaques. Macrophages of M1 phenotype in the vascular wall carry out pro-atherogenic role and influence destabilization of an atherosclerotic plaque, while M2 macrophages perform atheroprotective function.

[49] *Alzoubi KH, Mayyas F, Abu Zamzam HI. Omega-3 fatty acids protects against chronic sleep-deprivation induced memory impairment. Life sciences 2019.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30998938>

ABSTRACT

AIMS: The current study aims to evaluate the possible protective effect of omega-3 fatty acids on memory impairment induced by sleep-deprivation in rats. MATERIALS AND METHODS: Animals were chronically sleep deprived using the modified multiple platform model (8h/day

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for 8 weeks). Omega-3 fatty acids were administered as fish oil via oral gavage at a daily dose of 100mg omega-3 PUFA/100g BWT. The spatial learning and memory were evaluated using the radial arm water maze (RAWM). Additionally, the following oxidative stress biomarkers were measured in the hippocampus: glutathione (GSH), oxidized glutathione (GSSG), GSH/GSSG, glutathione peroxidase (GPx), catalase, superoxide dismutase (SOD), and thiobarbituric acid reactive substance (TBARS). **KEY FINDINGS:** Animals in the SD group committed significantly more errors in both short- and long- term memory tests of the RAWM compared to other groups. On the other hand, animals that were sleep deprived and treated with omega-3 fatty acids committed similar number of errors compared to the control group. This indicates that SD impaired both short- and long- term memories, and that chronic omega-3 fatty acids administration prevented these effects. Omega-3 fatty acids also prevented the decreases in hippocampal GPx, catalase and GSH/GSSG ratio and normalized the increases in GSSG levels, which were impaired by SD model. No changes were observed on hippocampal TBARS levels, or activity of SOD among experimental groups. **SIGNIFICANCE:** In conclusion, a protective effect of omega-3 fatty acids administration has been observed against chronic SD-induced memory impairment probably via improving hippocampus antioxidant effects.

[50] *Huang D, Zhou Q, Chao YQ, Zou CC. Clinical features and genetic analysis of childhood sitosterolemia: Two case reports and literature review. Medicine (Baltimore) 2019; 98:e15013.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30985648>

ABSTRACT

RATIONALE: Sitosterolemia is a rare autosomal recessive disorder of dyslipidemia due to mutations of genes ABCG5 and ABCG8, leading to highly elevated plasma levels of plant sterols and expanded body pools of cholesterol. **PATIENT CONCERNS:** We present a 9-year-old and a 7-year-old Chinese boy with hypercholesterolemia and xanthomas of sitosterolemia due to ABCG5 gene mutations. We also make a literature review of another 30 sitosterolemic children cases that have been reported with virulence ABCG5 gene mutations. **DIAGNOSIS:** We took peripheral blood samples from 2 patients and their parents to conduct genetic analysis by next-generation sequencing (NGS) technologies. **INTERVENTIONS:** The 2 patients received dietary modifications without pharmaceuticals treatment. **OUTCOMES:** A c.1166G>A (Arg389His) homozygosis mutation in exon 9 was observed in case 1, whereas a c.751C>T (Gln251*) homozygosis mutation in exon 6 was found in case 2. Literature review found another 30 pediatric cases with sitosterolemia due to ABCG5 gene mutation. The lipid profile was normalized and xanthomas got smaller with combined therapy of a combined low-cholesterol and low-phytosterols diet. **LESSONS:** These suggested that in patients (especially Asian patients) with multiple xanthomas, severe hypercholesterolemia, or elevated low-density lipoprotein-cholesterol, sitosterolemia should be considered in the differential diagnosis. Early diagnosis is important, and restriction of both cholesterol and phytosterols diet should suggested for these patients.

[51] *Halade GV, Kain V, Tourki B, Jadapalli JK. Metabolism 2019.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30999004>

ABSTRACT

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BACKGROUND: After myocardial infarction (MI), delayed progression or reversal of cardiac remodeling is a prime target to limit advanced chronic heart failure (HF). However, the temporal kinetics of lipidomic and systemic metabolic signaling is unclear in HF. There is no consensus on metabolic and lipidomic signatures that influence structure, function, and survival in HF. Here we use genetic knock out model to delineate lipidomic, and metabolic changes to describe the role of lipoxygenase in advancing ischemic HF driven by leukocyte activation with signs of non-resolving inflammation. Bioactive lipids and metabolites are implicated in acute and chronic HF, and the goal of this study was to define the role of lipoxygenase in temporal kinetics of lipidomic and metabolic reprogramming in HF. **MATERIALS AND METHODS:** To address this question, we used a permanent coronary ligation mouse model which showed profound metabolic and lipidomic reprogramming in acute HF. Additionally, we defined the lipoxygenase-mediated changes in cardiac pathophysiology in acute and chronic HF. For this, we quantitated systemic metabolic changes and lipidomic profiling in infarcted heart tissue with obvious structural remodeling and cardiac dysfunction progressing from acute to chronic HF in the survival cohort. **RESULTS:** After MI, lipoxygenase-derived specialized pro-resolving mediators were quantitated and showed lipoxygenase-deficient mice (12/15LOX(-/-)) biosynthesize epoxyeicosatrienoic acid (EETs; cyproins) to facilitate cardiac healing. Lipoxygenase-deficient mice reduced diabetes risk biomarker 2-aminoadipic acid with profound alterations of plasma metabolic signaling of hexoses, amino acids, biogenic amines, acylcarnitines, glycerophospholipids, and sphingolipids in acute HF, thereby improved survival. **CONCLUSION:** Specific lipoxygenase deletion alters lipidomic and metabolic signatures, with modified leukocyte profiling that delayed HF progression and improved survival. Future studies are warranted to define the molecular network of lipidome and metabolome in acute and chronic HF patients.

[52] *El-Zailik A, Cheung LK, Wang Y et al. Longitudinal Impacts of Gastric Bypass Surgery on Pharmacodynamics and Pharmacokinetics of Statins. Obesity surgery* 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31004269>

ABSTRACT

PURPOSE: Undergoing Roux-en-Y gastric bypass (RYGB) is expected to affect orally administered drug absorption. Statins are commonly prescribed to patients with obesity for the prevention of atherosclerotic cardiovascular diseases by lowering cholesterol. This is the first longitudinal prospective study on impacts of RYGB on weight loss, pharmacodynamics, and pharmacokinetics of atorvastatin, rosuvastatin, and simvastatin, and their active metabolites, up to 1-year post-surgery. **METHODS:** Forty-six patients were recruited, five patients on atorvastatin, twelve on rosuvastatin, nine on simvastatin, and twenty on no statin. The concentrations of atorvastatin, rosuvastatin, and simvastatin with their active metabolites were monitored. **RESULTS:** Mean plasma concentrations of atorvastatin and metabolites and rosuvastatin normalized by the unit dose [(nM)/(mg/kg)] decreased by 3- to 6-month post-surgery. Conversely, simvastatin and its metabolite concentrations increased up to 6-month post-surgery, then declined to preoperative levels by 1-year post-surgery. The metabolisms of atorvastatin to hydroxyl-metabolites and simvastatin to simvastatin acid were decreased after RYGB. The weight loss and PD outcomes were comparable between statin and non-statin groups suggesting the key impacts were from RYGB. The discontinuation or reduction of dose of

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atorvastatin or rosuvastatin post-RYGB exhibited rebounds of LDL levels in some subjects, but the rebound was not apparent with patients on simvastatin pre-surgery. **CONCLUSION:** Discontinuations of statin dosing post-RYGB require LDL monitoring and reducing the dose to half seems to have better results. Patients on statin treatment post-RYGB should be followed-up closely based on our pharmacokinetic findings, to ensure therapeutic effects of the treatment with minimal adverse effects.

[53] Nyariki JN, Ochola LA, Jillani NE et al. **Oral administration of Coenzyme Q10 protects mice against oxidative stress and neuro-inflammation during experimental cerebral malaria.**

Parasitology international 2019; 71:106-120.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30981893>

ABSTRACT

In animal model of experimental cerebral malaria (ECM), the genesis of neuropathology is associated with oxidative stress and inflammatory mediators. There is limited progress in the development of new approaches to the treatment of cerebral malaria. Here, we tested whether oral supplementation of Coenzyme Q10 (CoQ10) would offer protection against oxidative stress and brain associated inflammation following *Plasmodium berghei* ANKA (PbA) infection in C57BL/6J mouse model. For this purpose, one group of C57BL/6 mice was used as control; second group of mice were orally supplemented with 200mg/kg CoQ10 and then infected with PbA and the third group was PbA infected alone. Clinical, biochemical, immunoblot and immunological features of ECM was monitored. We observed that oral administration of CoQ10 for 1month and after PbA infection was able to improve survival, significantly reduced oedema, TNF-alpha and MIP-1beta gene expression in brain samples in PbA infected mice. The result also shows the ability of CoQ10 to reduce cholesterol and triglycerides lipids, levels of matrix metalloproteinases-9, angiopoietin-2 and angiopoietin-1 in the brain. In addition, CoQ10 was very effective in decreasing NF-kappaB phosphorylation. Furthermore, CoQ10 supplementation abrogated Malondialdehyde, and 8-OHdG and restored cellular glutathione. These results constitute the first demonstration that oral supplementation of CoQ10 can protect mice against PbA induced oxidative stress and neuro-inflammation usually observed in ECM. Thus, the need to study CoQ10 as a candidate of antioxidant and immunomodulatory molecule in ECM and testing it in clinical studies either alone or in combination with antimalaria regimens to provide insight into a potential translatable therapy.

[54] Krysiak R, Kowalcze K, Bednarska-Czerwinska A, Okopien B. **The effect of atorvastatin on cardiometabolic risk factors in women with non-classic congenital adrenal hyperplasia: A pilot study.** *Pharmacological reports* : PR 2019; 71:417-421.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31003151>

ABSTRACT

BACKGROUND: Individuals with non-classic congenital adrenal hyperplasia (NC-CAH) often show evidence of hyperandrogenism, including premature pubarche, accelerated linear growth velocity, short final height, hirsutism, acne, alopecia, impaired ovulation, menstrual dysfunction and subfertility. Although statins were found to reduce elevated levels of androgens in subjects with this disorder, no previous study has investigated whether 3-hydroxy-3-methylglutaryl-CoA reductase inhibitors affect cardiometabolic risk factors in patients with NC-CAH. **METHODS:** We

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studied 12 women with NC-CAH, 6 of whom because of coexisting hypercholesterolemia received atorvastatin (20-40 mg daily). Circulating levels of lipids, glucose homeostasis markers, plasma levels of androgens, 17-hydroxyprogesterone, high-sensitivity C-reactive protein (hsCRP), uric acid, fibrinogen, homocysteine and 25-hydroxyvitamin D, as well as urinary albumin-to-creatinine ratio (UACR) were determined at the beginning of the study and 12 weeks later. RESULTS: Beyond affecting plasma lipids, atorvastatin reduced circulating levels of testosterone, dehydroepiandrosterone sulphate, androstenedione and 17-hydroxyprogesterone, and decreased free androgen index. Moreover, atorvastatin caused a decrease in plasma levels/urinary loss of uric acid, hsCRP, homocysteine and UACR, and insignificantly increased circulating levels of 25-hydroxyvitamin D. The drug produced no effect on plasma fibrinogen. The effect of atorvastatin on hsCRP, uric acid, homocysteine, 25-hydroxyvitamin D and UACR correlated with the magnitude of reduction in 17-hydroxyprogesterone and androgens. CONCLUSION: Our results suggest that statin therapy reduces cardiometabolic risk in women with NC-CAH.

[55] *Cordero A, Facila L, Galve E, Gonzalez Juanatey JR. Estimated Percentage of Patients With Stable Coronary Heart Disease Candidates for PCSK9 Inhibitors. Revista espanola de cardiologia (English ed.)* 2019.

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ABSTRACT

[56] *Chyzyhyk V, Brown AS. Familial chylomicronemia syndrome: A rare but devastating autosomal recessive disorder characterized by refractory hypertriglyceridemia and recurrent pancreatitis. Trends in cardiovascular medicine* 2019.

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ABSTRACT

Familial Chylomicronemia Syndrome (FCS) is a rare autosomal recessive lipid disorder characterized by severe hypertriglyceridemia and recurrent pancreatitis. Because the disorder is often misdiagnosed or not diagnosed and because traditional triglyceride lowering medications are often ineffective, the disease leads to a tremendous physical, social and emotional burden on afflicted patients and their caretakers. Mutations in 5 different genes have been implicated in the development of FCS, all of which have an effect on the activity of lipoprotein lipase. Lipoprotein lipase (LPL) is responsible for removing triglycerides from chylomicrons and other triglyceride rich lipoproteins in the circulation, breaking them down into free fatty acids for use as energy. Patients with FCS have loss of function of their LPL leading to severely elevated chylomicrons in the circulation and hence, severe hypertriglyceridemia. The principle treatment for FCS is to reduce chylomicron formation in the gut by placing the patient on an extremely low fat diet. New medications in development hold significant promise for improving the quality of life for FCS patients.

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PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30982448>

ABSTRACT

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INTRODUCTION: Oral statins reduce intimal hyperplasia (IH) after arterial injury by only approximately 25%. Alternative drug delivery systems have gained attention as carriers for hydrophobic drugs. We studied the effects of simvastatin (free vs hyaluronic acid-tagged polysialic acid-polycaprolactone micelles) on vascular smooth muscle cell (VSMC) migration, VSMC proliferation and intimal hyperplasia. We hypothesized both free and micelle containing simvastatin would inhibit VSMC chemotaxis and proliferation, and local statin treatment would be more effective than oral in reducing IH in rats following carotid balloon injury. **METHODS:** VSMCs pretreated with free simvastatin (20 minutes or 20 hours) or simvastatin-loaded micelles underwent chemotaxis and proliferation to platelet-derived growth factor. Next, rats that underwent balloon injury of the common carotid artery received statin therapy- intraluminal simvastatin-loaded micelles prior to injury, periadventitial pluronic gel following injury, or combinations of gel, micelle, and oral simvastatin. After 14 days, morphometric analysis determined the -intimal to medial ratio. Findings were compared to controls receiving oral simvastatin or no statin therapy. Statistical analysis was by analysis of variance for the in vitro experiments and a factorial general linear model for the in vivo experiments. **RESULTS:** The simvastatin-loaded micelles and free simvastatin inhibited VSMC chemotaxis (54%-60%). IH was induced in all injured vessels. Simvastatin in pluronic gel or micelles reduced IH compared to untreated controls (0.208 +/- 0.04 or 0.160 +/- 0.03 vs 0.350 +/- 0.03, respectively); however, neither gel nor simvastatin-loaded micelles were superior to oral statins (0.261 +/- 0.03). Addition of oral statins or combining both local therapies did not provide additional benefit. Micelles were the single greatest contributing factor in IH attenuation. **CONCLUSIONS:** Intraluminally or topically delivered statins reduced IH. The efficacy of single-dose, locally delivered statin alone may lead to novel treatments to prevent IH. The different routes of administration may allow for treatment during endovascular procedures, without the need for systemic therapy.

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PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30989939>

ABSTRACT

In the background of the high incidence and high mortality of cardiovascular diseases, atherosclerosis is the main pathological feature of cardiovascular diseases and the core pathological basis for disease progression. In the evolution of atherosclerotic plaques, the rupture of unstable plaques, plaque shedding and formation of thrombosis are the most dangerous parts. In this process, the formation of plaque fibrosis is the core mechanism regulating plaque stability. Additionally, fibrosis reflects dynamic changes in the inflammatory processes and pathological changes. In view of the inflammation regulation and fibrosis regulation, this paper clarified the process of atherosclerotic plaque, explained the roles of relevant inflammatory cells and cytokines in plaque stability, and summed up drug researches related with stable plaque in recent years. In the future, improving the fibrosis will be a new idea for stabilizing plaque in atherosclerosis drug development.

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