

Literature update week 06 (2019)

[1] Ogata A, Oho K, Matsumoto N et al. **Stabilization of vulnerable carotid plaques with proprotein convertase subtilisin/kexin type 9 inhibitor alirocumab.** *Acta neurochirurgica* 2019.
PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30729307>

ABSTRACT

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, a novel class of monoclonal antibodies, reduce low-density lipoprotein cholesterol levels and improve outcomes of myocardial infarction and stroke. However, the effects of PCSK9 inhibitors on carotid plaques remain unclear. We describe three patients treated with PCSK9 inhibitor alirocumab for progressive carotid stenosis despite lipid-lowering statin therapy. All three patients had vulnerable plaques on magnetic resonance (MR) plaque imaging. After alirocumab treatment initiation, no patients suffered stroke or adverse events, and the stabilization of the carotid plaques was observed on MR plaque imaging.

[2] Yeboyo HG, Aschmann HE, Kaufmann M, Puhan MA. **Comparative effectiveness and safety of statins as a class and of specific statins for primary prevention of cardiovascular disease: A systematic review, meta-analysis, and network meta-analysis of randomized trials with 94,283 participants.** *American heart journal* 2019; 210:18-28.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30716508>

ABSTRACT

The current guidelines of statins for primary cardiovascular disease (CVD) prevention were based on results from systematic reviews and meta-analyses that suffer from limitations. METHODS: We searched in PubMed for existing systematic reviews and individual open-label or double-blinded randomized controlled trials that compared a statin with a placebo or another, which were published in English until January 01, 2018. We performed a random-effect pairwise meta-analysis of all statins as a class and network meta-analysis for the specific statins on different benefit and harm outcomes. RESULTS: In the pairwise meta-analyses, statins as a class showed statistically significant risk reductions on non-fatal MI (risk ratio [RR] 0.62, 95% CI 0.53-0.72), CVD mortality (RR 0.80, 0.71-0.91), all-cause mortality (RR 0.89, 0.85-0.93), non-fatal stroke (RR 0.83, 0.75-0.92), unstable angina (RR 0.75, 0.63-0.91), and composite major cardiovascular events (RR 0.74, 0.67-0.81). Statins increased statistically significantly relative and absolute risks of myopathy (RR 1.08, 1.01-1.15; Risk difference [RD] 13, 2-24 per 10,000 person-years); renal dysfunction (RR 1.12, 1.00-1.26; RD 16, 0-36 per 10,000 person-years); and hepatic dysfunction (RR 1.16, 1.02-1.31; RD 8, 1-16 per 10,000 person-years). The drug-level network meta-analyses showed that atorvastatin and rosuvastatin were most effective in reducing CVD events while atorvastatin appeared to have the best safety profile. CONCLUSIONS: All statins showed statistically significant risk reduction of CVD and all-cause mortality in primary prevention populations while increasing the risk for some harm risks. However, the benefit-harm profile differed by statin type. A quantitative assessment of the benefit-harm balance is thus needed since meta-analyses alone are insufficient to inform whether statins provide net benefit.

[3] Arbel R, Hammerman A, Azuri J. **Usefulness of Ezetimibe Versus Evolocumab as Add-On Therapy for Secondary Prevention of Cardiovascular Events in Patients With Type 2 Diabetes Mellitus.** *The American journal of cardiology* 2019.

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PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30711247>

ABSTRACT

Evolocumab and ezetimibe, were both proven to significantly reduce the incidence of major adverse cardiovascular events (MACE), in type 2 diabetes patients with atherosclerotic cardiovascular disease and low-density lipoprotein (LDL) cholesterol >70 mg/dl despite statin therapy. Providing evolocumab for all such patients may be a significant burden on healthcare systems. Therefore, we analyzed the treatment cost of ezetimibe versus evolocumab to prevent 1 MACE. We extracted the number needed to treat (NNT) with evolocumab or with ezetimibe for avoiding MACE from the published FOURIER and IMPROVE-IT trials respectively. Drug costs were based on 2018 US prices. Sensitivity and scenario analyses were performed to overcome variances in terms of population risk, efficacy of therapies, and costs. In FOURIER, the 1-year NNT for avoiding MACE with evolocumab was 104 (95% confidence intervals [CI] 66 to 235). In IMPROVE-IT, the 1-year NNT with ezetimibe was 124 (95% CI 73 to 288). The annual cost of evolocumab and ezetimibe is \$6,540 and \$88, respectively. Therefore, the cost to prevent 1 MACE in the FOURIER and IMPROVE-IT trials would have been \$678,981 (95% CI \$429,810 to \$1,537,910,149) and \$10,870 (95% CI \$6,384 to \$25,322), respectively. Ezetimibe was consistently a cost-saving strategy compared with evolocumab, in all analyses performed, except for the case where evolocumab price is significantly reduced and the branded ezetimibe is used. In conclusion, treatment with ezetimibe seems to be a major cost-saving strategy for preventing MACE in this patient population.

[4] Cannon CP, Sanchez RJ, Klimchak AC et al. **Simulation of the Impact of Statin Intolerance on the Need for Ezetimibe and/or Proprotein Convertase Subtilisin/Kexin Type 9 Inhibitor for Meeting Low-Density Lipoprotein Cholesterol Goals in a Population With Atherosclerotic Cardiovascular Disease.** *The American journal of cardiology* 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30736965>

ABSTRACT

In a population with atherosclerotic cardiovascular disease, previous research indicated that approximately 86% can achieve low-density lipoprotein cholesterol (LDL-C) of <70 mg/dL with oral lipid-lowering therapies (LLT) only, whereas 14% would require a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor. We aim to estimate these values accounting for varying levels of statin intolerance. A simulation model described previously was used to estimate the utilization of LLT needed to achieve LDL-C <70 mg/dL via an intensification algorithm which maximized statins before adding ezetimibe or a PCSK9 inhibitor. The current analysis took into account varying background rates of statin intolerance. We defined statin intolerance as either partial (inability to tolerate high-intensity statin) or full (inability to tolerate any statin). With treatment intensification and 10% of patients having partial statin intolerance, the use of ezetimibe (+/- statin +/- PCSK9 inhibitor) increased from 32.7% to 34.9%, and the need for a PCSK9 inhibitor (+ ezetimibe +/- statin) increased from 14.0% to 15.5%. If, instead, 10% were fully statin intolerant, the use of ezetimibe (+/- statin +/- PCSK9 inhibitor) increased from 32.7% to 38.5%, and the use of a PCSK9 inhibitor (+ ezetimibe +/- statin) increased from 14.0% to 19.7%. In conclusion, in our simulation-based study, partial statin intolerance increased the need for nonstatins only modestly (by an absolute 2.2%), whereas

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having 10% of patients with full statin intolerance increased the need for PCSK9 inhibitors from 14% overall to approximately 20%.

[5] Han SN, Yang WH, Yin JJ et al. **Drug Treatment of Hyperlipidemia in Chinese Patients: Focus on the Use of Simvastatin and Ezetimibe Alone and in Combination.** American journal of cardiovascular drugs : drugs, devices, and other interventions 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30714088>

ABSTRACT

Elevated serum low-density lipoprotein cholesterol (LDL-C) is a major risk factor for coronary heart disease (CHD). Many guidelines recommend LDL-C as a primary treatment target, and statins represent the cornerstone of treatment for lipid management. Recently revised guidelines recommend even more intense management of LDL-C, especially in patients at moderate and high risk. However, LDL-C levels in the Chinese population differ from those in Western populations, and the benefits and safety of the maximum allowable dose of statins have yet to be determined. Furthermore, in practice, many patients do not achieve the increasingly stringent LDL-C goals. Consequently, alternative approaches to lipid management are required. Combination therapy with ezetimibe and a statin, which have complementary mechanisms of action, is more effective than statin monotherapies, even at high doses. Several clinical studies have consistently shown that combination therapy with ezetimibe and simvastatin lowers LDL-C more potently than statin monotherapies. Moreover, the safety and tolerability profile of the combination therapy appears to be similar to that of low-dose statin monotherapies. This review discusses the role of simvastatin in combination with ezetimibe in controlling dyslipidemia in Chinese patients, particularly the efficacy and safety of combination therapy in light of recently published clinical data.

[6] Park JG, Oh GT. **Current pharmacotherapies for atherosclerotic cardiovascular diseases.** Archives of pharmacal research 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30725249>

ABSTRACT

Despite the introduction of statins for lowering LDL-C level, atherosclerotic cardiovascular disease (ASCVD) remains a leading cause of death and morbidity worldwide. Combination therapies with statin and other lipid-lowering drugs, including ezetimibe and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, have unlocked additive benefits for treatment of ASCVD, but morbidity and mortality due to ASCVD remain high. New anti-inflammatory therapies have emerged for treatment and prevention of ASCVD to address these problems. Canakinumab neutralization of interleukin-1beta (IL-1beta) is the only verified therapy, and low-dose methotrexate holds promise due to its efficacy and safety for treatment of ASCVD. However, many agonistic and antagonistic candidates within inflammation pathways have failed to develop into useful drugs for ASCVD because of the complexity of the inflammatory process in atherosclerosis. In this review, we outline current and future pharmaceutical therapies for ASCVD in terms of lipid-modifying strategies and anti-inflammation treatments.

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[7] Steffen BT, Thanassoulis G, Duprez D et al. **Race-Based Differences in Lipoprotein(a)-Associated Risk of Carotid Atherosclerosis.** *Arteriosclerosis, thrombosis, and vascular biology* 2019;Atvbaha118312267.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30727753>

ABSTRACT

Objective- Lp(a) [lipoprotein(a)] is a well-described risk factor for atherosclerosis, but Lp(a)-associated risk may vary by race/ethnicity. We aimed to determine whether race/ethnicity modifies Lp(a)-related risk of carotid atherosclerotic plaque outcomes among black, white, Chinese, and Hispanic individuals. Approach and Results- Carotid plaque presence and score were assessed by ultrasonography at baseline (n=5155) and following a median 9.4 year period (n=3380) in MESA (Multi-Ethnic Study of Atherosclerosis) participants. Lp(a) concentrations were measured by immunoassay and examined as a continuous and categorical variable using clinically-based cutoffs, 30 and 50 mg/dL. Lp(a) was related to greater risk of prevalent carotid plaque at baseline in whites alone (all P<0.001): per log unit (relative risk, 1.05); Lp(a)≥30 mg/dL (relative risk, 1.16); and Lp(a)≥50 mg/dL (relative risk, 1.20). Lp(a) levels over 50 mg/dL were associated with a higher plaque score at baseline in whites (all P<0.001) and Hispanics (P=0.04). In prospective analyses, whites with Lp(a) ≥50 mg/dL were found to have greater risk of plaque progression (relative risk, 1.12; P=0.03) and higher plaque scores (all P<0.001) over the 9.4-year follow-up. Race-based differences between whites and black participants were significant for cross-sectional associations and for carotid plaque score following the 9.4 year study period. Conclusions- Race was found to be a modifying variable in Lp(a)-related risk of carotid plaque, and Lp(a) levels may have greater influence on plaque burden in whites than in black individuals. Borderline results in Hispanics suggest that elevated Lp(a) may increase the risk of carotid plaque, but follow-up studies are needed.

[8] Bea AM, Lamiquiz-Moneo I, Marco-Benedi V et al. **Lipid-lowering response in subjects with the p.(Leu167del) mutation in the APOE gene.** *Atherosclerosis* 2019; 282:143-147.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30731287>

ABSTRACT

BACKGROUND AND AIMS: The aim of this work was to compare the effect of lipid lowering drugs among familial hypercholesterolemia (FH) subjects with a functional mutation in LDLR (LDLR FH) and FH with the p.(Leu167del) mutation in APOE. METHODS: We retrospectively selected all adults with the p.(Leu167del) mutation on lipid-lowering treatment (n=22) attending the Lipid Unit at the Hospital Miguel Servet. Age and sex matched LDLR FH from the same Unit were randomly selected as a control group (n=44). RESULTS: The mean percentage reduction in LDLc was significantly higher in the p.(Leu167del) carriers (-52.1%) than in the LDLR FH (-39.7%) (p=0.040) when on high intensity statins. Similar differences between groups were observed in non-HDLc -49.4% and -36.4%, respectively (p=0.030). CONCLUSIONS: Subjects with p.(Leu167del) mutation have a higher lipid-lowering response to statins with or without ezetimibe than LDLR FH. This supports the use of genetics for a more efficient management of FH.

[9] Kim JR, Jung JA, Kim S et al. **Effect of Cilostazol on the Pharmacokinetics of Simvastatin in Healthy Subjects.** *BioMed research international* 2019; 2019:1365180.

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PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30729119>

ABSTRACT

Purpose: We evaluated potential drug-drug interactions between cilostazol and simvastatin, both CYP3A substrates, in healthy subjects. Methods: An open-label, two-period, fixed-sequence clinical study was conducted. Seventeen subjects were given a single oral dose of simvastatin 40 mg on day 1 and multiple oral doses of cilostazol 100 mg twice daily on days 2 to 5 followed by a single dose of cilostazol and simvastatin on day 6. Plasma concentrations of simvastatin and its active metabolite, simvastatin acid, were measured using liquid chromatography-tandem mass spectrometry for pharmacokinetic assessment. Moreover, serum lipid profiles under fasting conditions were determined. Results: The geometric mean ratios of the area under the plasma concentration-time curve from time zero to time infinity of simvastatin combined with cilostazol to that of simvastatin alone were 1.64 (90% CI, 1.38-1.95) for simvastatin and 1.31 (1.04-1.66) for simvastatin acid. In addition, coadministration with cilostazol significantly increased the maximum concentration of simvastatin and simvastatin acid, up to 1.8-fold and 1.6-fold, respectively. However, the effects of a single dose of simvastatin on serum lipid profiles were not affected notably when simvastatin was coadministered with cilostazol. Conclusions: Multiple doses of cilostazol increased the systemic exposure of simvastatin and simvastatin acid following a single dose of simvastatin.

[10] Landi F, Martone AM, Salini S et al. **Effects of a New Combination of Medical Food on Endothelial Function and Lipid Profile in Dyslipidemic Subjects: A Pilot Randomized Trial.** BioMed research international 2019; 2019:1970878.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30723735>

ABSTRACT

Nutritional approaches to improve dyslipidemias have been recently developed, but evidences on different medical foods are often incomplete. The main aim of our study was to evaluate the effects on endothelial function, lipid profile, and glucose metabolism of two different combinations of nutraceuticals, first one containing Bergavit (200 mg Citrus bergamia), Omega-3 (400 mg), Crominex 3+ (10 mcg trivalent chromium), and red yeast rice (100 mg; 5 mg monacolin K) and second one containing red yeast rice (200 mg; 3 mg monacolin K), Berberine (500 mg), Astaxanthin (0.5 mg), folic acid (200 mcg), Coenzyme Q10 (2 mg), and Policosanol (10 mg). Fifty subjects affected by dyslipidemia not requiring statin treatment were enrolled in this randomized, blind, controlled trial and submitted to blood sampling for lipid and glucose profiles and instrumental evaluation of endothelial function before and after 6 weeks of treatment with nutraceuticals. Both nutraceutical combinations improved the lipid profile; the nutraceutical containing 5 mg of monacolin K, 200 mg of the extract Citrus bergamia, 400 mg of Omega-3, and 10 mcg of trivalent chromium entailed a significant improvement of endothelial function with enhanced cholesterol lowering effect. In conclusion, this study confirms the positive effect of functional food on lipid profile and endothelial function in absence of major undesirable effects.

[11] Ginsberg HN, Tuomilehto J, Hovingh GK et al. **Impact of Age on the Efficacy and Safety of Alirocumab in Patients with Heterozygous Familial Hypercholesterolemia.** Cardiovascular

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drugs and therapy / sponsored by the International Society of Cardiovascular Pharmacotherapy 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30734207>

ABSTRACT

PURPOSE: This post-hoc analysis examined whether age modified the efficacy and safety of alirocumab, a PCSK9 inhibitor, in patients with heterozygous familial hypercholesterolemia (HeFH), using pooled data from four 78-week placebo-controlled phase 3 trials (ODYSSEY FH I, FH II, LONG TERM, and HIGH FH). **METHODS:** Data from 1257 patients with HeFH on maximally tolerated statin +/- other lipid-lowering therapies were analyzed by an alirocumab dose regimen and by age subgroups (18 to < 45, 45 to < 55, 55 to < 65, and >= 65 years). In the FH I and II trials, patients received 75 mg subcutaneously every 2 weeks (Q2W), with dose increase to 150 mg Q2W at week 12 if week 8 low-density lipoprotein cholesterol (LDL-C) was >= 70 mg/dl. In HIGH FH and LONG TERM, patients received 150 mg alirocumab Q2W. **RESULTS:** Baseline characteristics were similar between treatment groups across all age groups; the proportion of males decreased whereas the proportion of patients with coronary heart disease, diabetes, hypertension, and declining renal function increased with increasing age. Mean LDL-C reductions at week 24 were consistent across age groups (50.6-61.0% and 51.1-65.8% vs. placebo for the 75/150 and 150 mg alirocumab dose regimens, respectively; both non-significant interaction P-values). Treatment-emergent adverse events occurred in similar frequency in alirocumab- and placebo-treated patients regardless of age, except for injection-site reactions, which were more common in alirocumab than placebo but declined in frequency with age. **CONCLUSIONS:** Alirocumab treatment resulted in significant LDL-C reductions at weeks 12 and 24 and was generally well tolerated in patients with HeFH across all age groups studied.

[12] *Perello Camacho E. PCSK9 inhibitors: A new improvement for health. Clinica e investigacion en arteriosclerosis : publicacion oficial de la Sociedad Espanola de Arteriosclerosis* 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30737073>

ABSTRACT

It is a patient with heterozygous familial hypercholesterolemia and a personal history of acute myocardial infarction, which is referred to our lipid unit for hypocholesterolemic treatment adjustment. Since he does not reach therapeutic goals with oral medication, he starts a treatment with fortnightly sessions of LDL-apheresis, which he keeps for 8 years. With the introduction and availability of PCSK9 inhibitors, a new treatment option is possible for this patient.

[13] *Ribas N, Recasens L, Perez S et al. A new rational approach to reach LDL-cholesterol concentration objectives after an acute coronary syndrome. Clinica e investigacion en arteriosclerosis : publicacion oficial de la Sociedad Espanola de Arteriosclerosis* 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30711338>

ABSTRACT

INTRODUCTION AND OBJECTIVES: Adequate LDL cholesterol (LDLc) control after an acute coronary syndrome (ACS) is a crucial secondary prevention strategy to minimize the incidence

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of recurrent myocardial infarction and cardiovascular death. There are tables that predict the necessary dosage of lipid-lowering treatment from the initial LDLc but have not been tested in ACS. Variables associated with optimal LDLc after an ACS were analyzed and the therapeutic yield of the use of Masana's recommendations in this setting. METHODS: A total number of 326 ACS-patients were included between January-2015 and May-2016. Baseline LDLc concentration and prescribed hypolipemiant treatment at hospital discharge were registered. We analyzed the variables associated with optimal LDLc levels (<70mg/dL) control during follow-up. RESULTS: Among our patient population (72% male, age 66+/-13 years), the hypolipemiant treatment at hospital discharge fulfilled the Masana's recommendations in 196 (60%) patients. After a follow-up period of 122 [66-184] days the targeted LDLc levels were achieved in 148 (45%) patients, being this percentage greater among those in whom the Masana's recommendations were fulfilled (109/196, 56%), as compared with the remaining (39/130, 30%; P<.001). The male gender (P<.001), the absence of prior history of dyslipemia (P<.001) and the adherence to Masana's recommendations (P=.007) were independent predictors for the achievement of targeted LDLc levels during follow-up. CONCLUSIONS: In less than half of ACS-patients adequate mid-term LDLc control is obtained. The dosage of the lipid-lowering therapy according to Masana's recommendations helps to achieve this important therapeutic goal.

[14] *Schaefer EJ, Geller AS, Endress G. The biochemical and genetic diagnosis of lipid disorders. Current opinion in lipidology 2019.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30720493>

ABSTRACT

PURPOSE OF REVIEW: To examine recent advances in our knowledge on the diagnosis of lipid disorders. RECENT FINDINGS: Fasting values above the 99th percentile for direct LDL-cholesterol (LDL-C), lipoprotein(a), and triglycerides are greater than 225 mg/dl, greater than 160 mg/dl, and greater than 500 mg/dl (>5.82, >394, and >5.65 mmol/l), respectively, whereas such values for plasma lathosterol, beta-sitosterol, and cholestanol are greater than 8.0, 8.0, and 5.0 mg/l (>0.021, 0.019, and 0.013 mmol/l), respectively. Values below the first percentile for LDL-C are less than 40 mg/dl (<1.03 mmol/l) and for HDL-cholesterol (HDL-C) less than 25 mg/dl (<0.65 mmol/l) in men and less than 30 mg/dl (<0.78 mmol/l) in women, respectively. The above values can predispose to premature CVD, pancreatitis, neurologic disease, and kidney failure, and may be associated with monogenic lipid disorders. In the absence of secondary causes including diabetes or kidney, liver, or thyroid disease, consideration should be given to sequencing the following genes: ABCA1, ABCG5, ABCG8, APOA1, APOA5, APOB, APOC2, APOE, CETP, CYP27A1, GPIHBP1, LCAT, LDLR, LDLRAP1, LIPA, LIPC, LMF1, LPL, MTP, PCSK9, SCARB1, and STAP1. SUMMARY: Recent data indicate that secondary causes and a wider range of conditions need to be considered in identifying the underlying causes of hypercholesterolemia, hypertriglyceridemia, hyperalphalipoproteinemia, hypobetalipoproteinemia, and HDL deficiency. Identifying such disorders allows for a more precise assessment of prognosis and the formulation of optimal therapy.

[15] *Ortega-Loubon C, Fernandez-Molina M, Singh G, Correa R. Obesity and its cardiovascular effects. Diabetes/metabolism research and reviews 2019:e3135.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30715772>

ABSTRACT

Obesity is described in terms of body-fat percentage or body mass index (BMI), despite the fact that these measures do not give full insight about the body fat-distribution. It is presently a consistently growing universal challenge since it has tripled in the last 10 years, killing approximately 28 million people each year. In this review, we want to clarify the different results of obesity on the working and physiology of the cardiovascular system and to reveal changes in the obesity "paradox" - a variety of cardiovascular outcomes in typical/overweight people. Central fat builds up in ordinary/overweight populaces has been related to expanded occurrences of Myocardial Infarction, Heart Failure or all-cause mortality when contrasted with the obese populace. These discoveries are additionally clarified as the abundance and prolonged vulnerability to free fatty acids (FFAs) in obesity. This has been believed to cause the myocardial substrate to move from glucose to FFAs digestion, which causes lipid gathering in cardiomyocytes, spilling over to other lean tissues, prompting a general atherogenic impact. This cardiomyocyte lipid aggregation has been demonstrated to cause insulin resistance, cardiovascular hypertrophy, and lessened the heart functions generally. There is proof backing the fact that fat tissue is not only an energy reservoir, it also coordinates hormones and pro-inflammatory cytokines, and deals with the energy transition of the body by putting away abundant lipids in diverse tissues.

[16] *Elsheikh E, Henry LL, Younossi ZM. Current management of patients with nonalcoholic fatty liver disease. Expert review of endocrinology & metabolism* 2013; 8:549-558.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30736139>

ABSTRACT

Nonalcoholic fatty liver disease (NAFLD) and its progressive form, nonalcoholic steatohepatitis (NASH) are the most common causes of chronic liver disease in industrialized countries. NAFLD has also been strongly associated with type II diabetes and cardiovascular diseases. This study was a multipurposed review, which included discussion of recent studies investigating the cellular and genetic basis of these diseases, the pathogenesis of NAFLD and the current treatment and management of nonalcoholic steatohepatitis. Currently, maintaining a healthy weight through dietary changes and exercise, the use of insulin-modulating pharmacologic agents for diabetes control and the use of lipid-lowering, anti-oxidants have been the most widely recommended treatments. Inclusion of pathogenic mechanisms in treatment design will allow future therapies to target-specific pathways involved in NAFLD pathogenesis.

[17] *Morimoto K, Itoh H, Watanabe M. Developments in understanding bile acid metabolism. Expert review of endocrinology & metabolism* 2013; 8:59-69.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30731653>

ABSTRACT

Bile acids (BAs) are not only facilitators participating in the absorption of dietary lipids and soluble vitamins, but are also important signaling molecules exerting versatile biophysiological effects. Three major signaling pathways, including the MAPK pathways, the nuclear hormone receptor farnesoid X receptor α -mediated pathways and the G protein-coupled receptor TGR5/M-BAR-mediated pathways, have been identified to be the targets of BAs. BAs, the biologically many-sided and toxic molecules, regulate the homeostasis of themselves via these

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signaling pathways. BAs also affect diverse metabolic status including glucose metabolism, lipid metabolism, energy expenditure, immunity and others. BAs and their related signaling mechanisms are attractive therapeutic targets of various diseases such as metabolic syndrome.

[18] *Chow CK, Brieger D, Ryan M et al. Secondary prevention therapies in acute coronary syndrome and relation to outcomes: observational study. Heart Asia* 2019; 11:e011122.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30728864>

ABSTRACT

Objective: To ascertain the use of secondary prevention medications and cardiac rehabilitation after an acute coronary syndrome (ACS) and the impact on 2-year outcomes. Methods: CONCORDANCE (Cooperative National Registry of Acute Coronary care, Guideline Adherence and Clinical Events) is a prospective, observational registry of 41 Australian hospitals. A representative sample of 6859 patients with an ACS and 6 months' follow-up on 31 May 2016 were included. The main outcome measure was use of $\geq 75\%$ of indicated medications ($\geq 4/5$ (or $\geq 3/4$ if contraindicated) of angiotensin-converting enzyme (ACE) inhibitor/angiotensin receptor blocker, beta-blocker, lipid-lowering therapy, aspirin and other antiplatelet). Major adverse cardiovascular events (MACE) included myocardial infarction, stroke or cardiovascular death. Results: The mean age was 65 ± 13 years, 29% were women, and the mean Global Registry of Acute Coronary Events (GRACE) score was 106 ± 30 . At discharge, 92% were on aspirin, 93% lipid-lowering therapy, 78% beta-blocker, 74% ACE/angiotensin receptor blocker and 73% a second antiplatelet; 89% were taking $\geq 75\%$ of medications at discharge, 78% at 6 months and 66% at 2 years. At 6 months, 38% attended cardiac rehabilitation, 58% received dietary advice and 32% of smokers reported quitting. Among 1896 patients followed to 2 years, death/MACE was less frequent among patients on $\geq 75\%$ vs $< 75\%$ of medications (8.3% vs 13.9%; adjusted OR 0.75, 95% CI 0.56 to 0.99), and was less frequent in patients who attended versus who did not attend cardiac rehabilitation (4.6% vs 13.4%; adjusted OR 0.44, 95% CI 0.31 to 0.62). Conclusions: Use of secondary prevention therapies diminishes over time following an ACS. Patients receiving secondary prevention had decreased rates of death and MACE at 2 years.

[19] *Honda A, Tanaka A, Kaneko T et al. Bezafibrate improves GLOBE and UK-PBC scores and long-term outcomes in patients with primary biliary cholangitis. Hepatology* 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30737815>

ABSTRACT

In Japan, bezafibrate (BF) is a second-line agent for primary biliary cholangitis (PBC) that is refractory to ursodeoxycholic acid (UDCA) treatment. From a retrospective cohort (n=873) from the Japan PBC Study Group, we enrolled 118 patients who had received UDCA monotherapy for ≥ 1 year followed by combination therapy with UDCA+BF for ≥ 1 year. GLOBE and UK-PBC scores after UDCA monotherapy (that is, immediately before UDCA+BF combination therapy) were compared with those after 1 year of UDCA+BF combination therapy. The real outcomes of enrolled patients estimated by Kaplan-Meier analysis were compared with the predicted outcomes calculated using GLOBE and UK-PBC scores. In addition, the hazard ratio of BF treatment was calculated using propensity score analysis. The mean GLOBE score before the combination therapy was 0.504 ± 0.080 , which improved significantly to 0.115 ± 0.085

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($p < 0.0001$) after 1 year of combination therapy. The real liver transplant-free survival of enrolled patients was significantly better than that predicted by GLOBE score before introducing BF. Combination therapy did not significantly improve the real rates of liver transplantation or liver-related death compared with those predicted by UK-PBC risk score before introducing BF, but the predicted risk was significantly reduced by the addition of BF ($p < 0.0001$). Cox regression analysis with inverse probability of treatment weighting showed that the addition of BF significantly reduced the hazard of liver transplant or liver-related death in patients who, after 1 year of UDCA monotherapy, had normal serum bilirubin (adjusted hazard ratio 0.09, 95% CI 0.01-0.60, $p = 0.013$). Conclusion: Addition of BF to UDCA monotherapy improves not only GLOBE and UK-PBC scores but also the long-term prognosis of PBC patients, especially those with early-stage PBC. This article is protected by copyright. All rights reserved.

[20] Lee HR, Jo MK, Park KY et al. **Anti-TNF effect of combined pravastatin and cilostazol treatment in an in vivo mouse model.** *Immunopharmacology and immunotoxicology* 2019;1-6.
PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30714456>

ABSTRACT

OBJECTIVES: Pravastatin and cilostazol are used as lipid-lowering and antiplatelet agents, respectively. Regarding their well-known anti-inflammatory effects, the additive effect of the two drugs on anti-TNF functions has not yet been investigated. In the present investigation, the beneficial effect of combined pravastatin and cilostazol on their anti-TNF activities was assessed using an in vivo mouse model. **METHODS:** Mice were pretreated with pravastatin and/or cilostazol (40 mg/kg of each), orally once two hour prior to an LPS (5 mg/kg, i.p.) challenge. One hour post challenge, blood and descending aorta were collected for serum TNF levels and immune cell infiltration analyses. For survival analysis, pravastatin and/or cilostazol (40 mg/kg of each) were administered 30 minutes prior to d-galactosamine administration (700 mg/kg, i.p.) and TNF (10 microg/kg, i.p.) challenge and mice survival was monitored. We also examined the effect of either drug or the combination of drugs on TNF-mediated MAPK and NF-kappaB signaling, using Western blot analysis. **RESULTS:** Combined treatment of pravastatin and cilostazol significantly decreased serum TNF release and immune cell infiltration in the descending aorta following LPS administration, compared to each single treatment. Additionally, the combined drugs significantly decreased TNF-mediated mouse mortality and downregulated TNF-induced MAPK and NF-kappaB activation. **CONCLUSIONS:** These findings suggest that combined pravastatin and cilostazol is more effective for reducing TNF-driven inflammation through their anti-TNF activity than monotherapy.

[21] Dutta A, Sharma-Walia N. **Curbing Lipids: Impacts ON Cancer and Viral Infection.** *International journal of molecular sciences* 2019; 20.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30717356>

ABSTRACT

Lipids play a fundamental role in maintaining normal function in healthy cells. Their functions include signaling, storing energy, and acting as the central structural component of cell membranes. Alteration of lipid metabolism is a prominent feature of cancer, as cancer cells must modify their metabolism to fulfill the demands of their accelerated proliferation rate. This aberrant lipid metabolism can affect cellular processes such as cell growth, survival, and

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migration. Besides the gene mutations, environmental factors, and inheritance, several infectious pathogens are also linked with human cancers worldwide. Tumor viruses are top on the list of infectious pathogens to cause human cancers. These viruses insert their own DNA (or RNA) into that of the host cell and affect host cellular processes such as cell growth, survival, and migration. Several of these cancer-causing viruses are reported to be reprogramming host cell lipid metabolism. The reliance of cancer cells and viruses on lipid metabolism suggests enzymes that can be used as therapeutic targets to exploit the addiction of infected diseased cells on lipids and abrogate tumor growth. This review focuses on normal lipid metabolism, lipid metabolic pathways and their reprogramming in human cancers and viral infection linked cancers and the potential anticancer drugs that target specific lipid metabolic enzymes. Here, we discuss statins and fibrates as drugs to intervene in disordered lipid pathways in cancer cells. Further insight into the dysregulated pathways in lipid metabolism can help create more effective anticancer therapies.

[22] *Gyanwali B, Shaik MA, Tan BY et al. Risk Factors for and Clinical Relevance of Incident and Progression of Cerebral Small Vessel Disease Markers in an Asian Memory Clinic Population. Journal of Alzheimer's disease : JAD 2019.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30714960>

ABSTRACT

BACKGROUND: Cerebral small vessel disease (SVD) is one of the major contributors to cognitive impairment and dementia. However, data on the incidence and progression of SVD in an Asian population are lacking. **OBJECTIVE:** The present study aims to investigate the incidence, progression, associated risk factors, and clinical relevance of SVD in a memory clinic setting. **METHODS:** A prospective case-control study, where 346 patients underwent repeated brain MRI with a mean interval of 24.5 months, accessing white matter hyperintensities (WMH), lacunes and cerebral microbleeds (CMBs). Severity of cognitive impairment was assessed using Clinical Dementia Rating scale and change in clinical diagnosis. Data on demographics, vascular risk factors, and clinical history were collected at baseline. **RESULTS:** The prevalence of significant WMH (Fazekas ≥ 2) was 56.6% at baseline which progressed to 59.0% at follow-up. Overall prevalence of CMBs increased from 42.2% to 47.4% (9% new cases) and lacunes increased from 31.8% to 33.2% (2.1% new cases). Hypertension was associated with WMH progression (OR: 1.78, 95% CI: 1.01, 2.99) and increasing age was associated with incident CMBs (OR: 1.04, 95% CI: 1.01, 1.08). Moreover, the use of lipid-lowering medications decreased the incidence of lacunes (OR: 0.15, 95% CI: 0.04, 0.61). The major risk factor for incident SVD was baseline SVD lesion load. WMH progression was associated with increased severity of cognitive impairment (OR: 1.95, 95% CI: 1.16, 3.23). **CONCLUSION:** Vascular risk factors and baseline severity of SVD lesion load were associated with progression of SVD. Furthermore, WMH progression was linked with increased severity of cognitive impairment. Future studies should be aimed to slow cognitive deterioration by preventing SVD related brain damage by targeting vascular risk factors.

[23] *McDonnell RP, JV OD, Earley B et al. Effect of supplementation with n-3 polyunsaturated fatty acids and/or beta-glucans on performance, feeding behaviour and immune status of*

Holstein Friesian bull calves during the pre- and post-weaning periods. Journal of animal science and biotechnology 2019; 10:7.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30719285>

ABSTRACT

Background: Previous research in both calves and other species has suggested n-3 polyunsaturated fatty acids (PUFA) and beta-glucans may have positive effects on immune function. This experiment measured performance, behaviour, metabolite and immunological responses to pre-weaning supplementation of dairy bull calves with n-3 PUFA in the form of fish oil and beta-glucans derived from seaweed extract. 44 Holstein Friesian bull calves, aged 13.7 +/- 2.5 d and weighing 48.0 +/- 5.8 kg were artificially reared using an electronic feeding system. Each calf was offered 5 L (120 g/L) per day of milk replacer (MR) and assigned to one of four treatments included in the MR, (1) Control (CON); (2) 40 g n-3 PUFA per day (FO); (3) 1 g beta-glucans per day (GL) and (4) 40 g n-3 PUFA per day & 1 g/d beta-glucans (FOGL) in a 2 x 2 factorial design. Milk replacer and concentrate was offered from d 0-62 (pre-weaning), while concentrate provision continued for a further 31 d post-weaning period. Individual daily feed intake and feeding behaviour was recorded throughout, while bodyweight and blood analyte data were collected at regular intervals. Results: Overall mean concentrate DMI from d 0-93 was 1.39, 1.27, 1.00 and 0.72 kg/d for CON, FO, GL and FOGL calves, respectively (SEM = 0.037; P < 0.0001). Calves supplemented with GL were significantly lighter (P < 0.0001) at both weaning (d 62) and turnout to pasture (d 93) than un-supplemented calves, with a similar effect (P < 0.0001) evident for calves receiving FO compared to un-supplemented contemporaries. Supplementation with GL reduced the number of unrewarded visits where milk was not consumed (P < 0.0001) while supplementation with FO increased mean drinking speed (P < 0.0001). Supplementation with GL resulted in greater concentrations of haptoglobin (P = 0.034), greater serum osmolality (P = 0.021) and lower lymphocyte levels (P = 0.027). In addition, cells from GL supplemented calves exhibited a lower response than un-supplemented contemporaries to both Phytohaemagglutinin A stimulated IFN-gamma (P = 0.019) and Concanavalin A stimulated IFN-gamma (P = 0.012) following in vitro challenges. Conclusions: Pre-weaning supplementation of bull calves with either n-3 PUFA or beta-glucan resulted in reduced voluntary feed intake of concentrate and consequently poorer pre-weaning calf performance. There was no evidence for any beneficial effect of either supplementation strategy on calves' immune responses.

[24] *Hsu H, Hsu P, Cheng MH et al. Lipoprotein Subfractions and Glucose Homeostasis in Prediabetes and Diabetes in Taiwan.* Journal of atherosclerosis and thrombosis 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30726792>

ABSTRACT

AIMS: Prediabetes and diabetes are associated with increased insulin resistance and decreased insulin production, dyslipidemia, and increased cardiovascular disease (CVD) risk. Our goals were to assess lipoprotein subfractions using novel assays in such subjects. METHODS: Fasting normal, prediabetic, and diabetic Taiwanese men and women (n=2,049) had their serum glucose, glycosylated hemoglobin, insulin, total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), HDL3-C, apolipoprotein E-HDL-C, direct low-density lipoprotein cholesterol (LDL-C), small dense LDL-C (sdLDL-C), LDL-TG, and remnant lipoprotein cholesterol

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(RLP-C) levels measured using novel assays. HDL2-C, LDL-C, and large-buoyant LDL-C (lLDL-C) were calculated. RESULTS: Prediabetic male and female subjects had significantly higher levels of TG, RLP-C, sdLDL-C, the sdLDL-C/LDL-C ratio, and LDL-TG than normal subjects, and statin treatment abolished this effect in men, but not in women. Diabetic male and female subjects had significantly higher TG and sdLDL-C/LDL-C ratios, and significantly lower levels of HDL-C, HDL2-C, HDL3-C, and apoE HDL-C than normal subjects, as did prediabetic women. Median direct LDL-C levels were 100 mg/dL in all groups, even in those receiving statin therapy. Calculated LDL-C significantly underestimated direct LDL-C by 10% in diabetic subjects. CONCLUSIONS: Our data indicate that prediabetic subjects were more likely to have significantly elevated RLP-C, sdLDL-C, and LDL-TG, while diabetic subjects were more likely to have significantly decreased HDL-C, HDL2-C, HDL3-C, and apoE HDL-C than normal subjects, and calculated LDL-C significantly underestimated their direct LDL-C. In our view, direct LDL-C and sdLDL-C should be measured and optimized in both diabetic and prediabetic subjects to reduce CVD risk.

[25] *Voelker DR, Numata M. Phospholipid regulation of innate immunity and respiratory viral infection. The Journal of biological chemistry* 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30733339>

ABSTRACT

Toll-like receptors (TLRs) coupled to intracellular signaling cascades function as central elements of innate immunity that control transcription of numerous pro-inflammatory genes. Two minor anionic phospholipids present in the pulmonary surfactant complex, palmitoyl-oleoyl-phosphatidylglycerol (POPG) and phosphatidylinositol (PI), antagonize the cognate ligand activation of TLRs 2 and 4. The lipids block recognition of activating ligands by the TLRs, either directly, or via the TLR4 co-receptors, CD14 and MD2. Antagonism of TLR activation results in inhibition of the initiating step of the pro-inflammatory signaling pathways. Evidence for this mechanism of action comes from direct binding studies between CD14 and MD2 with POPG and PI. Additional evidence for this mechanism of antagonism also comes from monitoring the reduction of protein phosphorylation events that characterize the intracellular signaling by activated TLRs. The pathogenesis of Respiratory Syncytial Virus (RSV) and Influenza A Virus (IAV) have been linked to TLR4 activation and we examined the action of POPG and PI, as potential antagonists of the pathology of these viruses. Surprisingly, POPG and PI dramatically curtail infection, in addition to inhibiting inflammatory sequelae associated with RSV and IAV infections. The mechanism of action by the lipids is disruption of virus particle binding to host cell plasma membrane receptors, required for viral uptake. The antagonism of activation of TLRs and virus binding to the alveolar epithelium by resident constituents of the pulmonary surfactant system suggests that POPG and PI function in homeostasis, to prevent inflammatory processes that result in reductions in gas exchange within the alveolar compartment.

[26] *Chang CY, Tung YT, Lin YK et al. Effects of Caloric Restriction with Protein Supplementation on Plasma Protein Profiles in Middle-Aged Women with Metabolic Syndrome-A Preliminary Open Study. Journal of clinical medicine* 2019; 8.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30736312>

ABSTRACT

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BACKGROUND: Clinical studies have demonstrated that higher protein intake based on caloric restriction (CR) alleviates metabolic abnormalities. However, no study has examined the effects of plasma protein profiles on caloric restriction with protein supplementation (CRPS) in metabolic syndrome (MetS). Therefore, using a proteomic perspective, this pilot study investigated whether CRPS ameliorated metabolic abnormalities associated with MetS in middle-aged women. **METHODS:** Plasma samples of middle-aged women with MetS in CR (n = 7) and CRPS (n = 6) groups for a 12-week intervention were obtained and their protein profiles were analysed. Briefly, blood samples from qualified participants were drawn before and after the dietary treatment. Anthropometric, clinical, and biochemical variables were measured and correlated with plasma proteomics. **RESULTS:** In results, we found that body mass index, total body fat, and fasting blood glucose decreased significantly after the interventions but were not different between the CR and CRPS groups. After liquid chromatography(-)tandem mass spectrometry analysis, the relative plasma levels of alpha-2-macroglobulin (A2M), C4b-binding protein alpha chain (C4BPA), complement C1r subcomponent-like protein (C1RL), complement component C6 (C6), complement component C8 gamma chain (C8G), and vitamin K-dependent protein S (PROS) were significantly different between the CRPS and CR groups. These proteins are involved in inflammation, the immune system, and coagulation responses. Moreover, blood low-density lipoprotein cholesterol levels were significantly and positively correlated with C6 plasma levels in both groups. **CONCLUSIONS:** These findings suggest that CRPS improves inflammatory responses in middle-aged women with MetS. Specific plasma protein expression (i.e., A2M, C4BPA, C1RL, C6, C8G, and PROS) associated with the complement system was highly correlated with fasting blood glucose (FBG), blood lipids (BLs), and body fat.

[27] *Chan JCM, Ng MH, Wong RSM, Tomlinson B. A case of simvastatin-induced myopathy with SLCO1B1 genetic predisposition and co-ingestion of linagliptin and Stevia rebaudiana. Journal of clinical pharmacy and therapeutics* 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30714173>

ABSTRACT

WHAT IS KNOWN AND OBJECTIVE: SLCO1B1 T521>C variant carriers are susceptible to simvastatin-induced myopathy. We report a patient who developed rhabdomyolysis possibly triggered by a drug-drug and/or herb-drug interaction. **CASE DESCRIPTION:** A 69-year-old man presented with myalgia and weakness progressing to severe rhabdomyolysis. He had been taking 40 mg simvastatin daily for 10 years and recently consumed supplements, including Stevia rebaudiana and linagliptin. Genotyping revealed he carried one copy of SLCO1B1 T521>C and two copies of ABCG2 C421>A. **WHAT IS NEW AND CONCLUSION:** Despite apparent long-term safe administration, co-ingestion of simvastatin and other CYP3A4 inhibitors may result in severe myopathy in those at increased genetic risk.

[28] *Butler AA, Price CA, Graham JL et al. Fructose-induced hypertriglyceridemia in rhesus macaques is attenuated with fish oil or apoC3 RNA interference. Journal of lipid research* 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30723097>

ABSTRACT

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Dyslipidemia and insulin resistance are significant adverse outcomes of consuming high-sugar diets. Conversely, dietary fish oil reduces plasma lipids. Diet-induced dyslipidemia in a rhesus model better approximates the pathophysiology of human metabolic syndrome than rodent models. Here we investigated relationships between metabolic parameters and hypertriglyceridemia in rhesus macaques consuming a high fructose diet (n=59) and determined effects of fish oil supplementation or RNA interference (RNAi) on plasma apoC3 and TG concentrations. Fructose supplementation increased body weight, fasting insulin, leptin, TGs, and large VLDL particles and reduced adiponectin concentrations (all $p < 0.001$). In multiple regression analyses, increased plasma apoC3 was the most consistent and significant variable related to diet-induced hypertriglyceridemia. Fish oil supplementation, which attenuated increases of plasma TG and apoC3 concentrations, reversed fructose-induced shifts of lipoprotein particle size toward IDL and VLDL, a likely mechanism contributing to beneficial metabolic effects, and reduced hepatic expression of genes regulated by the SREBP pathway, particularly acetyl-CoA carboxylase. Furthermore, RNAi-mediated apoC3 inhibition lowered plasma TG concentrations in animals with diet-induced hypertriglyceridemia. In summary, apoC3 is an important independent correlate of TG-rich lipoprotein concentrations in rhesus macaques consuming a high-fructose diet. ApoC3 is a promising therapeutic target for hypertriglyceridemia in patients with metabolic syndrome and diabetes.

[29] *Huynh T, Lecca P, Montigny M et al. Ten-Year Statin Adherence in Survivors of ST-Segment Elevation Myocardial Infarction. Journal of population therapeutics and clinical pharmacology = Journal de la therapeutique des populations et de la pharamcologie clinique* 2018; 25:e63-e77.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30725543>

ABSTRACT

Background Adherence to statins is often sub-optimal and declines over time. Direct costs incurred by patients are frequently cited as responsible for inadequate statin adherence. To determine whether survivors of ST-segment elevation myocardial infarction (STEMI), who benefit from low or no cost drug dispensation, have optimal long-term adherence to statins, we aimed to evaluate the ten-year adherence to statin of these patients. Methods The AMI-QUEBEC Study follows a cohort of STEMI survivors hospitalized at 17 hospitals in Quebec, Canada during the year 2003. We obtained their 10-year data on lipid lowering therapy (LLT) consumption. Optimal adherence was defined as the proportion of days covered of $\geq 80\%$. We used multivariate logistic regression to determine factors independently associated with optimal adherence to statins. Results Complete 10-year data on statin dispensation was available for 524 patients. Optimal adherence remained stable over time at 80% and more during the 10-year follow-up period. During the last five years, 12% of patients did not use any LLT. Older age, living in less socially deprived areas, concomitant use of angiotensin-converting-enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB), and admission to hospitals with percutaneous coronary interventions facilities (PCI-hospitals) were associated with improved statin adherence. Conclusion Future studies are needed to explore the potential factors associated with concomitant use of ACEI/ARB, and admission to PCI-hospitals that may have optimized statin adherence. Socially deprived patients may benefit from more support and encouragement to enhance their long-term statin adherence.

[30] *Garcia-So J, Zhang X, Yang X et al. Omega-3 fatty acids suppress Fusobacterium nucleatum-induced placental inflammation originating from maternal endothelial cells. JCI insight* 2019; 4.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30728337>

ABSTRACT

Fusobacterium nucleatum is an oral anaerobe prevalent in intrauterine infection associated with a wide spectrum of adverse pregnancy outcomes. We demonstrate here that *F. nucleatum* triggers placental inflammation through maternal, rather than paternal, TLR4-mediated signaling. Elimination of TLR4 from maternal endothelial cells alleviated placental inflammation and reduced fetal and neonatal death, while elimination of TLR4 in the hematopoietic cells had no effect. The placental inflammatory response followed a spatiotemporal pattern, with NF- κ B activation observed first in the maternal endothelial cells and then in the decidual cells surrounding the endothelium, followed by induction of inflammatory cytokines and chemokines. Supplementation of pregnant mice with fish oil as a source of omega-3 fatty acids suppressed placental inflammation, reduced *F. nucleatum* proliferation in the placenta, and increased fetal and neonatal survival. In vitro analysis illustrates that omega-3 fatty acids inhibit bacterial-induced inflammatory responses from human umbilical cord endothelial cells. Our study therefore reveals a mechanism by which microbial infections affect pregnancy and identifies a prophylactic therapy to protect against intrauterine infections.

[31] *Tournadre A. Statins, myalgia, and rhabdomyolysis. Joint Bone Spine* 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30735805>

ABSTRACT

Statin-associated muscle symptoms (SAMSs) vary considerably in frequency and severity, with a spectrum extending from myalgia with normal creatine kinase (CK) levels or asymptomatic hyperCKemia to potentially life-threatening rhabdomyolysis and necrotizing autoimmune myopathy. Myalgia with CK elevation is the most common presentation. Onset is usually within 1 month after statin initiation or dosage intensification, and the symptoms can be expected to resolve within a few weeks after treatment discontinuation. The mechanism of muscle injury combines statin accumulation within muscles, which varies with the type and dosage of the drug; muscle fragility; abnormalities in statin transport or liver metabolism; drug-drug interactions; and genetic susceptibility. HMG-CoA reductase inhibition in muscles by statins exerts pleiotropic effects that can affect energy metabolism, induce mitochondrial dysfunction, modify lipid oxidation, promote apoptosis and cell membrane lysis, alter muscle protein synthesis, or trigger an autoimmune process. Statins are used to treat several chronic conditions and comorbidities, including inflammatory rheumatic diseases, which are associated with an increased cardiovascular risk. When the cardiovascular risk is high or very high, statin therapy is indispensable and has a very favorable risk/benefit ratio. Otherwise, the risks should be weighed against the benefits before reinitiating statin therapy, and a different statin or lower dosage should be used. If statin therapy cannot be successfully reintroduced, other classes of lipid-lowering drugs should be considered. Severe SAMSs with major weakness and marked CK elevation should suggest the rare eventuality of necrotizing autoimmune myopathy.

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and prompt an anti-HMGCR antibody assay and muscle biopsy to ensure that immunosuppressant therapy is started rapidly if needed.

[32] *Todorov SS. Kardiologija* 2019; 59:57-61.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30710990>

ABSTRACT

PURPOSE: to conduct morphohistochemical and immunohistochemical study of arterial unstable atherosclerotic plaques for assessment of the state of smooth muscle cells (SMC) and macrophages. MATERIALS AND METHODS: The surgical material of the peripheral arteries (femoral, popliteal, external carotid) was obtained from 50 patients aged over 60 years, followed by morphohistochemical, immunohistochemical studies. RESULTS: Hyperplasia of secretory smooth muscle cells (SMC), and new formation of thin-walled capillary vessels was noted in unstable atherosclerotic plaques. Macrophagic infiltration was detected in the intima of arteries, in places of accumulation of foam cells. CONCLUSION: Unstable atherosclerotic plaque is a cellular-intercellular process with the participation of lipids, macrophages, and with predominance of SMC and newly formed vessels.

[33] *Bruder-Nascimento T, Callera GE, Montezano AC et al. Atorvastatin inhibits pro-inflammatory actions of aldosterone in vascular smooth muscle cells by reducing oxidative stress. Life sciences* 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30721707>

ABSTRACT

Vascular inflammatory responses play an important role in several cardiovascular diseases. Of the many pro-inflammatory vasoactive factors implicated in this process, is aldosterone, an important mediator of vascular oxidative stress. Statins, such as atorvastatin, are cholesterol-lowering drugs that have pleiotropic actions, including anti-oxidant properties independently of their cholesterol-lowering effect. This study investigated whether atorvastatin prevents aldosterone-induced VSMC inflammation by reducing reactive oxygen species (ROS) production. Vascular smooth muscle cells (VSMC) from WKY rats were treated with 1µM atorvastatin for 60min or for 72h prior to aldosterone (100nM) stimulation. Atorvastatin inhibited Rac1/2 and p47phox translocation from the cytosol to the membrane, as well as reduced aldosterone-induced ROS production. Atorvastatin also attenuated aldosterone-induced vascular inflammation and macrophage adhesion to VSMC. Similarly EHT1864, a Rac1/2 inhibitor, and tiron, ROS scavenger, reduced macrophage adhesion. Through its inhibitory effects on Rac1/2 activation and ROS production, atorvastatin reduces vascular ROS generation and inhibits VSMC inflammation. Our data suggest that in conditions associated with aldosterone-induced vascular damage, statins may have vasoprotective effects by inhibiting oxidative stress and inflammation.

[34] *Diaz-Gerevini GT, Dain A, Pasqualini ME et al. Diabetic encephalopathy: beneficial effects of supplementation with fatty acids omega3 and nordihydroguaiaretic acid in a spontaneous diabetes rat model. Lipids in health and disease* 2019; 18:43.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30736810>

ABSTRACT

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BACKGROUND: Diabetic encephalopathy is a chronic complications of diabetes mellitus that affects the central nervous system. We evaluated the effect of omega3 and omega6 polyunsaturated fatty acids (PUFAs) supplementation plus the antioxidant agent nordihydroguaiaretic acid (NDGA) on the etiopathology of diabetic encephalopathy in eSS rats, a spontaneous model of type 2 diabetes. **METHODS:** One hundred twenty spontaneous diabetic eSS male rats and 38 non-diabetic Wistar, used as healthy control, received monthly by intraperitoneal route, omega3 or omega6 PUFA (6.25 mg/kg) alone or plus NDGA (1.19 mg/kg) for 12 months. Diabetic rats had a worse performance in behavioural Hole-Board test. Histopathological analysis confirmed lesions in diabetic rats brain tissues. We also detected low expression of synaptophysin, a protein linked to release of neurotransmitters, by immunohistochemically techniques in eSS rats brain. Biochemical and histopathological studies of brain were performed at 12th month. Biochemical analysis showed altered parameters related to metabolism. High levels of markers of oxidative stress and inflammation were detected in plasma and brain tissues. Data were analysed by ANOVA test and paired t test was used by comparison of measurements of the same parameter at different times. **RESULTS:** The data obtained in this work showed that behavioural, biochemical and morphological alterations observed in eSS rats are compatible with previously reported indices in diabetic encephalopathy and are associated with increased glucolipotoxicity, chronic low-grade inflammation and oxidative stress burden. Experimental treatments assayed modulated the values of studied parameters. **CONCLUSIONS:** The treatments tested with omega3 or omega6 plus NDGA showed improvement in the values of the studied parameters in eSS diabetic rats. These observations may form the basis to help in prevent and manage the diabetic encephalopathy.

[35] *Cardoso R, Blumenthal RS, Kopecky S et al. How Low to Go With Lipid-Lowering Therapies in a Cost-effective and Prudent Manner. Mayo Clinic proceedings 2019.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30737057>

ABSTRACT

The 2013 American College of Cardiology/American Heart Association guideline on the treatment of blood cholesterol was a landmark document guiding health care professionals around the globe on how to administer lipid-lowering therapies. Those guidelines were primarily focused on statin therapy benefit groups. The writing committee found insufficient evidence for specific low-density lipoprotein cholesterol (LDL-C) treatment targets. There have been many important updates in the lipid literature since the publication of that document. Most importantly, clinical trials have provided definitive evidence for the pivotal role of LDL-C in atherogenesis and the improvement in clinical outcomes by means of aggressive LDL-C reduction. Ezetimibe, evolocumab, and alirocumab treatment resulted in substantial reductions in major adverse cardiovascular outcomes. These data encourage a discussion on whether LDL-C targets are warranted in primary and/or secondary prevention, and if so, how low should those targets be. In order to answer such questions, the costs and safety of such therapies, as well as the safety of very low levels of LDL-C need to be addressed. This review discusses the relationship between LDL-C lowering and cardiovascular risk reduction, the efficacy, safety, and cost-effectiveness of high-intensity lipid-lowering therapies, and the recommendations from the most recent lipid guidelines.

[36] *Brieger D, D'Souza M, Huyn K et al. Intensive lipid-lowering therapy in the 12 months after an acute coronary syndrome in Australia: an observational analysis. The Medical journal of Australia* 2019; 210:80-85.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30712304>

ABSTRACT

OBJECTIVE: To determine the prevalence and identify predictors of people hospitalised with acute coronary syndrome (ACS) receiving intensive lipid-lowering therapy during the 12 months after their discharge from hospital. DESIGN: Retrospective observational analysis. SETTING: Data were extracted from CONCORDANCE, a prospective, Australian investigator-initiated ACS registry. PARTICIPANTS: Patients enrolled in CONCORDANCE during January 2015 - May 2016 who survived to hospital discharge, for whom information on lipid-lowering therapy 6 or 12 months after discharge from hospital were available. MAIN OUTCOME MEASURES: Not receiving intensive lipid-lowering therapy (with or without ezetimibe) at the most recent follow-up (6 or 12 months); predictors of not receiving intensive lipid-lowering therapy. RESULTS: 1876 of 3441 patients (55%) were receiving intensive lipid-lowering therapy 6 or 12 months after their hospitalisation with an ACS. Predictors of not receiving intensive lipid-lowering therapy included not been prescribed this treatment prior to their hospital admission (odds ratio [OR], 1.53; 95% CI, 1.26-1.85) or at hospital discharge (aOR, 7.24; 95% CI, 4.37-12.0), being a woman (aOR, 1.20; 95% CI, 1.02-1.41), and not being referred for cardiac rehabilitation (aOR 1.39; 95% CI, 1.09-1.78). Patients who were managed medically in hospital (not revascularised; aOR, 1.54; 95% CI, 1.25-1.91) or underwent coronary artery bypass grafting (aOR 1.55; 95% CI, 1.26-1.92) were less likely to be receiving intensive lipid-lowering therapy at follow-up than those with a percutaneous coronary intervention. Unmeasured hospital factors accounted for 17% of the variation in the likelihood of intensive lipid-lowering therapy. CONCLUSIONS: 45% of patients in Australia are not receiving intensive lipid-lowering therapy in the 12 months after their ACS. Optimising oral lipid-lowering therapy would reduce the recurrence of coronary events in this high risk group.

[37] *Kostner K. High intensity lipid-lowering therapy after acute coronary syndromes: room for improvement. The Medical journal of Australia* 2019; 210:73-74.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30712297>

ABSTRACT

[38] *Ma X, Jiao Z, Liu Y et al. Probucol Protects Against Contrast-Induced Acute Kidney Injury via the Extracellular Signal-Regulated Kinases 1 and 2 (ERK1/2)/JNK-Caspase 3 Pathway in Diabetic Rats. Medical science monitor : international medical journal of experimental and clinical research* 2019; 25:1038-1045.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30728344>

ABSTRACT

BACKGROUND Contrast-induced acute kidney injury is an important clinical problem, yet its pathogenic mechanisms are incompletely understood. In this study we explored the potential beneficial effects of probucol as treatment of contrast-induced acute kidney injury in diabetic rats. MATERIAL AND METHODS Rats were divided into 3 groups: i) diabetic control, ii) diabetic

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with contrast, and iii) probucol treatment groups. Probucol was administered by gavage and the contrast diatrizoate (60%) was injected via femoral vein. After 24 h, the rats were sacrificed and samples were taken to measure biochemical indicators. Pathological damage of renal tubules was evaluated by HE staining. Expression of Bcl-2, Bax, p-ERKs, and p-JNK proteins in the kidneys was examined by Western blotting, whereas expression level of caspase-3 in kidneys was detected by immunohistochemistry. **RESULTS** Compared to the probucol treatment group, the diabetes with contrast group showed higher serum creatinine and lower creatinine clearance. The pathological changes of kidneys in the probucol treatment group were improved compared with the contrast group. Moreover, Western blot analyses revealed that use of contrast agent led to lower p-ERK1/2, higher p-JNK, lower Bcl-2, and higher Bax levels, which were reversed by probucol. Finally, immunohistochemical findings revealed higher caspase-3 after contrast use, which was partially reversed by probucol. **CONCLUSIONS** Probucol exerts protective effects on contrast-induced acute kidney injury in diabetic rats by inhibition of renal cell apoptosis. This is achieved by reducing mitochondrial caspase-3 expression through increasing and decreasing the expression of the upstream mediators p-ERK1/2 and p-JNK, respectively.

[39] Yan X, Xie B, Wu G *et al.* **Interleukin-37: The Effect of Anti-Inflammatory Response in Human Coronary Artery Endothelial Cells.** *Mediators of inflammation* 2019; 2019:2650590.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30728750>

ABSTRACT

Interleukin-37 (IL-37) is unique in the IL-1 family since it broadly suppresses innate immunity and elevates in humans with inflammatory and autoimmune diseases. IL-37 shows definite groups and transcripts for human IL37 gene, but it is still not completely understood the effect and mechanisms of inflammatory response in endothelial cells. It is well accepted that endothelial dysfunction caused by inflammation is a key initiating event in atherosclerotic plaque formation, which leads to the occurrence and development of the cardiovascular adverse events in clinical since the inflammatory responses of endothelial cells could induce and enhance the deposition of extensive lipid and the formation of atherosclerotic plaque in the intima. Thus, it is essential to investigate the role and potential mechanisms in endothelial inflammatory response to prevent the formation and development of many cardiovascular diseases including atherosclerosis. So far, the recent studies have revealed that IL-37 is able to inhibit inflammatory response by suppressing the TLR2-NF-kappaB-ICAM-1 pathway intracellularly in human coronary artery endothelial cells (HCAECs). Further, the role of IL-37 may be related to the IL-18 pathway extracellularly and involved in the adhesion and transmigration of neutrophils in HCAECs.

[40] Zhao Z, Du S, Shen S *et al.* **Comparative efficacy and safety of lipid-lowering agents in patients with hypercholesterolemia: A frequentist network meta-analysis.** *Medicine (Baltimore)* 2019; 98:e14400.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30732185>

ABSTRACT

BACKGROUND: The comparative efficacy and safety of PCSK9 inhibitors, statins, and ezetimibe to lower lipid levels in patients with hypercholesterolemia remain unknown. We aimed to

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investigate the benefits and harms of the lipid-lowering agents in these patients. **METHODS:** PubMed, Embase, and the Cochrane Library were searched from January 1, 2000 to June 1, 2018 for relevant randomized controlled trials (RCTs). Frequentist network meta-analysis was used to pool all estimates. Ranking probabilities were used to rank the comparative effects of all drugs against placebo. **RESULTS:** Eighty-four RCTs enrolled 246,706 patients were included. Most of the included were assessed as low risk of bias. The probabilities of PCSK9 inhibitors that ranked first in improving lipid outcomes were all 100%. The probability of statins that ranked first in reducing the risk of cardiovascular (CV) events was 60.6%, and the probability of PCSK9 inhibitor was 37.1%, while no significant difference of efficacy in reducing CV events was observed between the 2 agents (odds ratios [OR] 0.98, 95% CI 0.87-1.11). Statin ranked first in reducing all-cause and CV death. Compared with placebo, statins were associated with reduced risks of all-cause (OR 0.90, 95% CI 0.85-0.96) and CV death (OR 0.83, 95% CI 0.75-0.91) while PCSK9 inhibitors and ezetimibe were not. No agents caused adverse events (including neurocognitive events), except that statins therapy significantly increases the levels of alanine aminotransferase (ALT) (OR 1.89, 95% CI 1.42-2.51) and creatine kinase (CK) (OR 1.45, 95% CI 1.09-1.93) and the incidence of diabetes (OR 1.13, 95% CI 1.02-1.26). **CONCLUSIONS:** PCSK9 inhibitors were the most effective lipid-lowering agents in improving lipid levels. Furthermore, PCSK9 inhibitors achieved similar CV benefits like statins, while PCSK9 inhibitors were not associated with any increased risk of statin-related side-effects. Thus, PCSK9 inhibitors may also be recommended as promisingly first-line lipid-lowering treatment for patients with hypercholesterolemia, especially for these with statins intolerance or resistance.

[41] *Sekine A, Fukuwatari T. Acute liver failure increases kynurenic acid production in rat brain via changes in tryptophan metabolism in the periphery. Neurosci Lett 2019.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30738081>

ABSTRACT

The tryptophan metabolite, kynurenic acid (KYNA), is a preferential antagonist of the $\alpha 7$ nicotinic acetylcholine receptor and N-methyl-D-aspartic acid receptor at endogenous brain concentrations. Recent studies have suggested that increased brain KYNA levels are involved in psychiatric disorders such as schizophrenia and depression. Most of the brain kynurenine (KYN), the KYNA precursor, comes from the periphery, and the liver has a central role in the peripheral tryptophan metabolism. In this study, the effect of acute liver failure (ALF) on brain KYNA production and on the peripheral tryptophan metabolism was investigated in rats. ALF was induced by administration of the hepatotoxin, thioacetamide (TAA). Brain KYNA levels were increased by TAA-induced ALF, and these increases were consistent with KYN levels in the brain, serum and liver. These results suggest that the ALF-induced increase in serum KYN contributes to the increase in brain KYNA via elevated KYN uptake within the brain. This increase in serum KYN level can be caused by the changes in tryptophan-2,3-dioxygenase activity in the liver and the immune-related activation of indoleamine-2,3-dioxygenase in extrahepatic tissues. These findings suggest that hepatic dysfunction may contribute to neurological and psychiatric diseases associated with increased KYNA levels.

[42] *Ross LJ, Barnes KA, Ball LE et al. Effectiveness of dietetic consultation for lowering blood lipid levels in the management of cardiovascular disease risk: A systematic review and meta-*

analysis of randomised controlled trials. Nutrition & dietetics: the journal of the Dietitians Association of Australia 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30714668>

ABSTRACT

AIM: Evidence of the effectiveness of dietetic consultation for the management of cardiovascular disease (CVD) risk factors has not been previously synthesised. A systematic review and four meta-analyses evaluated the effectiveness of dietetic consultation for lowering blood lipid levels in high-risk individuals in primary health-care settings. METHODS: Of the 4860 records identified, 10 eligible randomised controlled trials (RCTs, n = 1530) were evaluated for reporting blood lipid outcomes following dietetic consultation (DN)-defined as at least one exclusive individual face-to-face consultation with a dietitian and comparators (C)-defined as no nutrition intervention or usual or minimal care provided by physicians and/or nurses. RESULTS: DN groups were effective for lowering blood lipid levels across nine studies reporting total cholesterol (TC) and LDL; and across five of six studies reporting triglycerides (TG). Between-group differences were not consistently assessed, with significance levels reported in four studies all in favour of DN, $P < 0.05$. Meta-analyses for TC and LDL (seven studies) confirmed DN and C groups were equally effective, $P > 0.05$; and for TG (six studies) DN groups were significantly more effective than C groups, $P < 0.05$. CONCLUSIONS: This review provides RCT evidence that dietetic counselling is effective for lowering TG levels and at least as effective as usual and minimal care for improving cholesterol levels in high-risk individuals in primary health care. However, more adequate reporting of methods and greater consistency in timing interventions and data collection will enhance the quality of the evidence and increase confidence in the health benefits of dietetic counselling for the management of CVD risk.

[43] *Chang CM, Chiu THT, Chang CC et al. Plant-Based Diet, Cholesterol, and Risk of Gallstone Disease: A Prospective Study.* Nutrients 2019; 11.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30720747>

ABSTRACT

Vegetarian diets may lower symptomatic gallstone disease via cholesterol lowering. This study aimed to examine the risk of symptomatic gallstone disease (GSD) in Taiwanese vegetarians vs. nonvegetarians in a prospective cohort and to explore if this association is related to cholesterol concentration. We prospectively followed 4839 participants, and in the 29,295 person-years of follow-up, 104 new incident GSD cases were confirmed. Diet was assessed through a validated food frequency questionnaire. Symptomatic GSD was ascertained through linkage to the Taiwan National Health Insurance Research Database. Blood cholesterol profiles were measured at recruitment. Cox regression was applied to assess the effect of diet on symptomatic GSD, adjusting for age, education, smoking, alcohol, physical activities, diabetes, kidney diseases, body mass index, lipid-lowering medication, and hypercholesterolemia. Vegetarian diet was associated with a decreased risk of symptomatic GSD compared with nonvegetarian diet in women (hazard ratio [HR], 0.52; 95% confidence interval [CI], 0.28(-)0.96) but not in men. In women, nonvegetarians with hypercholesterolemia had 3.8 times the risk of GSD compared with vegetarians with normal cholesterol (HR, 3.81, 95% CI, 1.61(-)9.01). A vegetarian diet may therefore protect against GSD independent of baseline

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hypercholesterolemia. A nonvegetarian diet and hypercholesterolemia may have an additive effect in increasing GSD risk in women.

[44] *Tsur A, Kalish F, Burgess J et al. Pravastatin improves fetal survival in mice with a partial deficiency of heme oxygenase-1. Placenta* 2019; 75:1-8.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30712660>

ABSTRACT

INTRODUCTION: Statins induce heme oxygenase-1 (HO-1) expression in vitro and in vivo. Low HO-1 expression is associated with pregnancy complications, e.g. preeclampsia and recurrent miscarriages. Here, we investigated the effects of pravastatin on HO-1 expression, placental development, and fetal survival in mice with a partial HO-1 deficiency. METHODS: At E14.5, untreated pregnant wild-type (WT, n=13-18), untreated HO-1(+/-) (Het, n=6-9), and Het mice treated with pravastatin (Het+Pravastatin, n=12-14) were sacrificed. Numbers of viable fetuses/resorbed concepti were recorded. Maternal livers and placentas were harvested for HO activity. Hematoxylin and eosin (H&E) and CD31 immunohistochemical staining were performed on whole placentas. RESULTS: Compared with WT, HO activity in Het livers (65+/-18%, P<0.001) and placentas (74+/-7%, P<0.001) were significantly decreased. Number of viable fetuses per dam was significantly lower in Untreated Het dams (6.0+/-2.2) compared with WT (9.1+/-1.4, P<0.01), accompanied by a higher relative risk (RR) for concepti resorption (17.1, 95% CI 4.0-73.2). In Hets treated with pravastatin, maternal liver and placental HO activity increased, approaching levels of WT controls (to 83+/-7% and 87+/-14%, respectively). The number of viable fetuses per dam increased to 7.7+/-2.5 with a decreased RR for concepti resorption (2.7, 95% CI 1.2-5.9). In some surviving Untreated Het placentas, there were focal losses of cellular architecture and changes suggestive of reduced blood flow in the labyrinth. These findings were absent in Het+Pravastatin placentas. DISCUSSION: Pravastatin induces maternal liver and placental HO activity, may affect placental function and improve fetal survival in the context of a partial deficiency of HO-1.

[45] *Gonzalez-Cantero A, Gonzalez-Cantero J, Sanchez-Moya AI et al. Subclinical atherosclerosis in psoriasis. Usefulness of femoral artery ultrasound for the diagnosis, and analysis of its relationship with insulin resistance. PloS one* 2019; 14:e0211808.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30735527>

ABSTRACT

BACKGROUND: Psoriasis is associated with an increased risk of cardiovascular disease (CVD) at younger ages that is not identifiable by traditional risk factors. Screening for subclinical atherosclerosis with ultrasound has only been investigated in carotid arteries. Femoral artery ultrasound has never been considered for this purpose. The link between psoriasis and accelerated atherosclerosis has not yet been established. OBJECTIVE: To study the usefulness of femoral artery ultrasound for the detection of subclinical atherosclerosis in psoriasis. We also investigated its possible relationship with changes in insulin resistance. METHODS: We conducted a cross-sectional study in 140 participants, 70 patients with moderate-to-severe psoriasis and 70 healthy controls, matched 1:1 for age, sex, and BMI. Femoral and carotid atherosclerotic plaques were evaluated by ultrasonography. Insulin resistance was assessed by the homeostasis model assessment method (HOMA-IR). RESULTS: Femoral atherosclerotic

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plaque prevalence was significantly higher in patients with psoriasis (44.64%) than in controls (19.07%) ($p < 0.005$), but no significant difference was found in carotid plaque prevalence ($p < 0.3$). Femoral plaques were significantly more prevalent than carotid plaques (21.42%) among patients with psoriasis ($p < 0.001$). In the regression analysis, insulin resistance was the most influential determinant of atherosclerosis in psoriasis and C-reactive protein the most significant predictor of insulin resistance. **CONCLUSIONS:** Ultrasound screening for femoral atherosclerotic plaques improves the detection of subclinical atherosclerosis in patients with psoriasis, whereas the study of carotid arteries is not sufficiently accurate. Insulin resistance appears to play a greater role in the development of atherosclerosis in these patients in comparison to other classical CVD risk factors.

[46] Mitchell KA, Moore JX, Rosenson RS et al. **PCSK9 loss-of-function variants and risk of infection and sepsis in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) cohort.** *PLoS one* 2019; 14:e0210808.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30726226>

ABSTRACT

BACKGROUND: Elevated proprotein convertase subtilisin/kexin type 9 (PCSK9) levels have been associated with adverse outcomes in patients hospitalized for sepsis. PCSK9 loss-of-function (LOF) variants are associated with lower low-density lipoprotein cholesterol (LDL-C) levels. Decreased LDL-C is a biomarker of acute and chronic infection and sepsis risk. We examined the association between presence of two genetic PCSK9 LOF variants and risk of infection and sepsis in community-dwelling adults. **METHODS:** We analyzed data from 10,924 Black participants tested for PCSK9 LOF variants in the REasons for Geographic and Racial Differences in Stroke (REGARDS) cohort. The primary endpoint was hospitalization for a serious infection. Within serious infection hospitalizations, we defined sepsis as ≥ 2 system inflammatory response syndrome criteria. Using multivariable Cox and logistic regression, we investigated the association between LOF variants and hospitalization for infection and sepsis events, adjusting for sociodemographics, health behaviors, chronic medical conditions and select biomarkers. **RESULTS:** Among 10,924 Black participants, PCSK9 LOF variants were present in 244 (2.2%). Serious infection hospitalizations occurred in 779 participants (14 with PCSK9 variants and 765 without). The presence of PCSK9 variants was not associated with infection risk (adjusted HR 0.68; 95% CI: 0.38-1.25). Among participants hospitalized for a serious infection, the presence of PCSK9 variants was not associated with sepsis (adjusted OR 7.31; 95% CI = 0.91-58.7). **CONCLUSIONS:** PCSK9 LOF variants are not associated with increased risk of hospitalization for a serious infection. Among those hospitalized for a serious infection, PCSK9 LOF variants were not associated with odds of sepsis.

[47] **Statins: increased risk of type 2 diabetes.** *Prescrire international* 2017; 26:18-19.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30730639>

ABSTRACT

Five meta-analyses of double-blind randomised comparative clinical trials have shown a small but statistically significant increase in the risk of type 2 diabetes in statin users. The relative risk was about 1.1. One additional case of diabetes occurred for approximately every 255 patients treated with a statin for 4 years. The risk is dose-dependent. It was observed with all the statins

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studied, including pravastatin, simvastatin, atorvastatin and rosuvastatin. In practice, the risk of diabetes is not a reason for choosing one statin rather than another. When statin therapy is justified, pravastatin and simvastatin remain the statins of choice.

[48] *Linder K, Willmann C, Kantartzis K et al. Dietary Niacin Intake Predicts the Decrease of Liver Fat Content During a Lifestyle Intervention. Scientific reports 2019; 9:1303.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30718741>

ABSTRACT

Niacin inhibits fatty acid flux from adipose tissue to liver, reduces hepatic triglyceride synthesis and increases hepatic lipid oxidation. Thus, niacin may have a role in the regulation of liver fat content in humans. We tested if dietary intake of niacin predicts change of liver fat content during a lifestyle intervention. To this end, we estimated the composition of diet from diaries of 202 healthy subjects at risk of type 2 diabetes undergoing lifestyle intervention comprising physical activity and diet counselling. Total-, subcutaneous- and visceral adipose tissue mass were measured by magnetic resonance (MR) tomography and liver fat content by (1)H-MR spectroscopy at baseline and after 9 months of follow-up. Among fat compartments, liver fat content showed the largest decrease (-32%, $p < 0.0001$). High baseline niacin intake predicted a larger decrease of liver fat ($p = 0.004$). Subjects in the highest quartile of niacin intake at baseline also had the largest decrease of liver fat (1(st):-10%; 2(nd):-27%; 3(rd):-35%; 4(th):-37%). Among 58 subjects with nonalcoholic fatty liver disease (NAFLD) at baseline, NAFLD resolved in 23 subjects during the lifestyle intervention. For one standard deviation increase in niacin intake, the odds ratio for resolution of NAFLD was 1.77 (95% CI, 1.00-3.43). High dietary niacin intake may have a favorable effect on the reduction of liver fat during lifestyle intervention.

[49] *Zhu FL, Zhang N, Ma XJ et al. Circulating Hematopoietic Stem/Progenitor Cells are Associated with Coronary Stenoses in Patients with Coronary Heart Disease. Scientific reports 2019; 9:1680.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30737465>

ABSTRACT

Inflammatory cells in atherosclerotic plaque exclusively originate from hematopoietic stem/progenitor cells (HSPCs). In this study, we investigated whether circulating HSPCs frequency related to coronary stenosis in patients with coronary heart disease (CHD). Coronary angiography was performed in 468 participants who were recruited at Cardiology Centre in LuHe Hospital from March 2016 to May 2017. Among these subjects, 344 underwent echocardiography. Mononuclear cells isolated from peripheral blood were stained with an antibody cocktail containing anti-human CD34, anti-human lineage, anti-human CD38, and anti-human CD45RA. Lineage(-)CD38(-)CD45RA(dim)CD34(+)HSPCs were quantified by flow cytometry. CHD was defined as coronary stenosis $\geq 50\%$ and the extent of CHD was further categorised by coronary stenosis $\geq 70\%$. A $p < 0.0031$ was regarded statistically significant by the Bonferroni correction. Circulating HSPCs frequency was 1.8-fold higher in CHD patients than non-CHD participants ($p = 0.047$). Multivariate-adjusted logistic analysis demonstrated that HSPCs was the only marker that was associated with the odds ratio of having mild vs. severe coronary stenosis (2.08 (95% CI, 1.35-3.21), $p = 0.0009$). Left ventricular ejection fraction was

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inversely correlated with HSPCs frequency and CRP in CHD patients ($p < 0.05$ for both). In conclusion, HSPCs frequency in circulation is intimately related to coronary stenoses in CHD patients.

[50] Schulz J, Vollmer C, Truse R et al. **Effect of Pravastatin Pretreatment and Hypercapnia on Intestinal Microvascular Oxygenation and Blood Flow During Sepsis.** *Shock* 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30724816>

ABSTRACT

INTRODUCTION: In septic patients, adequate microvascular oxygenation (μHBO_2) of the intestine is vital for their outcome. Recent studies suggest that statins can ameliorate septic microcirculation in a variety of tissues. However, the effect on intestinal microvascular oxygenation and blood flow is largely unknown. Furthermore, there are indications that statin therapy might not be beneficial in the presence of hypercapnia, as observed in septic ARDS patients. Therefore, the present study explores the effect of pravastatin with and without additional moderate acute hypercapnia on intestinal microvascular oxygenation and blood flow in experimental sepsis. **METHODS:** 40 male Wistar rats were randomized into 4 groups. Half of the animals received 0.2 mg * kg pravastatin s.c., the other half received the same volume as vehicle (NaCl 0.9%). After 18 h, colon ascendens stent peritonitis (CASP)-surgery was conducted in all animals to induce sepsis. 24 hours after surgery, baseline was established and the animals were subjected to either 120 minutes of normocapnic ($p\text{CO}_2$ 40 +/- 6 mmHg) or moderate hypercapnic ($p\text{CO}_2$ 72 +/- 10 mmHg) ventilation. Microcirculatory oxygenation (μHBO_2) and perfusion (μflow) of the colon were continuously recorded using tissue reflectance spectrophotometry and laser doppler, respectively. **RESULTS:** In normocapnic septic animals μHBO_2 decreased over time (- 8.4 +/- 8.7%; $p < 0.05$ vs. baseline), whereas after pravastatin pretreatment μHBO_2 remained constant (- 1.9 +/- 5.7% vs. baseline). However, in hypercapnic septic animals pretreated with pravastatin μHBO_2 declined significantly over time (- 8.9 +/- 11.8%; $p < 0.05$ vs. baseline) and was significantly lower compared to normocapnic pravastatin-pretreated animals. μflow did not change over time in any group. **CONCLUSION:** Pravastatin pretreatment ameliorates the intestinal microvascular oxygenation in sepsis and thus seems to prevent intestinal hypoxia. Furthermore, we demonstrated that additional hypercapnia abolishes this effect, indicating why septic ARDS patients might not benefit from pravastatin therapy.

[51] Pirahanchi Y, Sharma S. Biochemistry, Lipoprotein Lipase. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2018.

[52] Rattanachotphanit T, Limwattananon C, Waleekhachonloet O. **Trends and variations in outpatient coprescribing of simvastatin or atorvastatin with potentially interacting drugs in Thailand.** *Therapeutic advances in drug safety* 2019; 10:2042098618820502.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30728944>

ABSTRACT

Background: The aim of this study was to assess trends and variations in coprescribing of simvastatin or atorvastatin with interacting drugs in Thailand. **Methods:** Outpatient prescriptions between 2013 and 2015 in 26 tertiary care hospitals were analyzed for statin

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coprescribing. The proportion of patients exposed to coprescribing was estimated for semi-annual changes, using a time-series analysis and for hospital variations, using an interquartile range (IQR). Results: The coprescribing of simvastatin with all contraindicated drugs in 10 university and 16 general hospitals, respectively, was 3.6 and 3.1% in 2013, then decreased to 3.2 and 2.6% in 2014 and to 2.6 and 2.0% in 2015. The drug most frequently coprescribed with simvastatin, on a decreasing trend (by 0.19 percentage points) was gemfibrozil (in 2013, 2014 and 2015, respectively; 2.9, 2.3 and 2.0% in university hospitals, and 2.5, 2.0 and 1.6% in general hospitals). A similar trend was found in atorvastatin-gemfibrozil coprescribing. Patients coprescribed simvastatin with the rest of the contraindicated drugs were relatively stable at 0.6-0.8%. No protease inhibitors were coprescribed with simvastatin and atorvastatin. The IQR of simvastatin coprescribing in the university hospitals was smaller than that in the general hospitals and decreased over time. Conclusions: Coprescriptions potentially leading to drug interactions with simvastatin in Thailand were observed although the contraindicated drugs were acknowledged. Mutual awareness among health professionals and the implementation of electronic prescribing should be strengthened as zero drug interaction was possible as in the case of protease inhibitors in the present study.

[53] *Mooranian A, Zamani N, Mikov M et al. Stability and biological testing of taurine-conjugated bile acid antioxidant microcapsules for diabetes treatment. Therapeutic delivery* 2019; 10:99-106.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30729887>

ABSTRACT

AIM: Taurine-conjugated bile acids possess positive formulation-stabilization effects, which are desirable in diabetes treatments. The taurine-conjugated bile acid, taurocholic acid (TCA), has shown promising formulation-stabilizing effects on the delivery of the antioxidant drug, probucol (PB), but success is limited due to its poor release profile. This study aimed to design new PB-TCA formulations using new polymers, and examine antioxidant and antidiabetic effects using beta-cells for PB with or without TCA. MATERIALS AND METHODS: Different formulations using alginate-insoluble esters of polymethylacrylate polymers encapsulating PB and TCA were developed, microencapsulated and examined for stability and biological activity. RESULTS: TCA addition to new PB matrices improved osmotic and mechanical properties, and this effect was dependent on polymethylacrylate composition and concentration.

CONCLUSION: TCA can optimize the oral delivery of anti-diabetic compounds.

[54] *El-Ganainy SO, El-Mallah A, Abdallah D et al. A novel investigation of statins myotoxic mechanism: Effect of atorvastatin on respiratory muscles in hypoxic environment. Toxicology letters* 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30735765>

ABSTRACT

Myopathy is a well-known adverse effect of statins, affecting a large sector of statins users. The reported experimental data emphasized on mechanistic study of statin myopathy on large muscles. Clinically, both large muscles and respiratory muscles are reported to be involved in the myotoxic profile of statins. However, the experimental data investigating the myopathic mechanism on respiratory muscles are still lacking. The present work aimed to study the effect

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of atorvastatin treatment on respiratory muscles using rat isolated hemidiaphragm in normoxic & hypoxic conditions. The contractile activity of isolated hemidiaphragm in rats treated with atorvastatin for 21 days was investigated using nerve stimulated technique. Muscle twitches, train of four and tetanic stimulation was measured in normoxic, hypoxic and reoxygenation conditions. Atorvastatin significantly increased the tetanic fade, a measure of muscle fatigability, in hypoxic conditions. Upon reoxygenation, rat hemidiaphragm regains its normal contractile profile. Co-treatment with coenzyme Q10 showed significant improvement in defective diaphragmatic contractility in hypoxic conditions. This work showed that atorvastatin treatment rapidly deteriorates diaphragmatic activity in low oxygen environment. The mitochondrial respiratory dysfunction is probably the mechanism behind such finding. This was supported by the improvement of muscle contractile activity following CoQ10 co-treatment.

[55] *Shah PK. Inflammation, infection and atherosclerosis. Trends in cardiovascular medicine* 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30733074>

ABSTRACT

Atherosclerotic cardiovascular disease is a leading cause of death in much of the world. Adoption of a healthy lifestyle and cholesterol lowering are the key measures used to prevent major complications of atherosclerosis. Recent data have identified a critical role for inflammation mediated through activation of both innate and adaptive immune pathways in the pathophysiology of atherosclerosis opening up opportunities for development of anti-inflammatory interventions that could supplement risk factor modification and lipid lowering as an approach to further reducing the burden of atherosclerotic cardiovascular disease.