Literature update week 34 (2018)

[1] *Zhang C, Wang K, Yang L et al.* **Lipid metabolism in inflammation-related diseases**. Analyst 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30128447
ABSTRACT
There are thousands of lipid species existing in cells, which belong to eight different categories. Lipids are the essential building blocks of cells. Recent studies have started to unveil the important functions of lipids in regulating cell metabolism. However, we are still at a very early stage in fully understanding the physiological and pathological functions of lipids. The application of lipidomics for studying lipid metabolism can provide a direct readout of the cellular status and broadens our understanding of the mechanisms that underpin metabolic disease states. This review provides an introduction to lipid metabolism and its role in modulating homeostasis and immunity. We also describe representative applications of lipidomics for studying lipid metabolism in inflammation-related diseases.

[2] *Veronese N, Koyanagi A, Stubbs B et al.* **Statin use and knee osteoarthritis outcomes: A longitudinal cohort study**. Arthritis care & research 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30144308
ABSTRACT
OBJECTIVE: Statins have several pleiotropic effects, but the literature regarding the possible relationship between statins use and outcomes in knee osteoarthritis (OA) is limited. We investigated whether statins use is associated with lower risk of radiographic (ROA), radiographic symptomatic knee OA (SxOA) and pain in North American people. METHODS: A total of 4,448 community-dwelling adults from the Osteoarthritis Initiative were followed-up for 4 years. Statins use (including the time from baseline and the type) was defined through self-report information and confirmed by a trained interviewer. Knee OA outcomes included incident (1) ROA, (2) SxOA, as the new onset of a combination of a painful knee and ROA, (3) knee pain worsening, i.e. a Western Ontario and McMaster Universities Osteoarthritis Index difference between baseline and each annual exam >/=14%. RESULTS: At baseline, 1,127 participants (=25.3%) used statins. Based on a multivariable Poisson regression analysis with robust variance estimators, any statins use was not associated with lower risk of pain worsening (relative risk, RR=0.97; 95%CI, confidence intervals: 0.93-1.02), incident ROA or SxOA. However, statins use > 5 years (RR=0.91; 95%CI: 0.83-0.997) and atorvastatin use (RR=0.95; 95%CI: 0.91-0.996) were associated with a reduced risk of developing pain, whilst rosuvastatin to a higher risk (RR=1.18; 95%CI: 1.12-1.24). The adjustment for the propensity score confirmed these findings. CONCLUSION: The effect of statins use on knee OA outcomes remains unclear, although in our study those using statins for over five years and those using atorvastatin reported a significant lower risk of developing knee pain. This article is protected by copyright. All rights reserved.

[3] *Zhu Y, Xian X, Wang Z et al.* **Research Progress on the Relationship between Atherosclerosis and Inflammation**. Biomolecules 2018; 8.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30142970
ABSTRACT

Literature update week 34 (2018)

Atherosclerosis is a chronic inflammatory disease; unstable atherosclerotic plaque rupture, vascular stenosis, or occlusion caused by platelet aggregation and thrombosis lead to acute cardiovascular disease. Atherosclerosis-related inflammation is mediated by proinflammatory cytokines, inflammatory signaling pathways, bioactive lipids, and adhesion molecules. This review discusses the effects of inflammation and the systemic inflammatory signaling pathway on atherosclerosis, the role of related signaling pathways in inflammation, the formation of atherosclerosis plaques, and the prospects of treating atherosclerosis by inhibiting inflammation.

[4] *Evdokimenko AN, Gulevskaya TS, Druina LD et al.* **Neovascularization of Carotid Atherosclerotic Plaque and Quantitative Methods of Its Dynamic Assessment in Vivo**. Bulletin of experimental biology and medicine 2018; 165:521-525.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30121924
ABSTRACT
The study demonstrates significant variety of neovascularization degree and vessel diameter in the carotid atherosclerotic plaque. It is suggested that the increase in the number of vessels with a diameter <20 mu can be indicative of increased atherosclerosis activity, while the increase in the number of vessels with a diameter >/=40 mu indicates "reparative potential" of plaques. Duplex contrast-enhanced ultrasound scanning allows characterization of the localization and number of vessels with a diameter of >/=30 mu in the plaque, while even slight elevation of plasma concentration of basic fibroblast growth factor attests, first of all, to increased content of small vessels <30 mu in the plaque. The level of fibroblast growth factor >1.5 pg/ml is a reliable marker of increased number of both small and large vessels in the plaque.

[5] *Sulciner ML, Gartung A, Gilligan MM et al.* **Targeting lipid mediators in cancer biology**. Cancer metastasis reviews 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30136088
ABSTRACT
Bioactive lipids are essential components of human cells and tissues. As discussed in this review, the cancer lipidome is diverse and malleable, with the ability to promote or inhibit cancer pathogenesis. Targeting lipids within the tumor and surrounding microenvironment may be a novel therapeutic approach for treating cancer patients. Additionally, the emergence of a novel super-family of lipid mediators termed specialized pro-resolving mediators (SPMs) has revealed a new role for bioactive lipid mediators in the resolution of inflammation in cancer biology. The role of SPMs in cancer holds great promise in our understanding of cancer pathogenesis and can ultimately be used in future cancer diagnostics and therapy.

[6] *Zhang HW, Zhao X, Xu RX et al.* **Relationship between Plasma Proprotein Convertase Subtilisin/Kexin Type 9 and Estimated Glomerular Filtration Rate in the General Chinese Population**. Cardiorenal Med 2018; 8:311-320.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30121647
ABSTRACT

BACKGROUND: Elevated levels of proprotein convertase subtilisin/kexin type 9 (PCSK9) have been reported to be related to dyslipidemia, including patients with kidney dysfunction. However, its association with estimated glomerular filtration rate (eGFR) in individuals with normal serum creatinine (SCr) has not been determined. METHODS: A total of 2,089 subjects with normal SCr and without lipid-lowering treatment were consecutively enrolled in this study. Plasma PCSK9 levels were measured by ELISA kit and eGFR was evaluated by the Chronic Kidney Disease Epidemiology Collaboration equation. Subjects were divided into a normal eGFR group (n = 1,205, >/=90 mL/min/1.73 m2) and a decreased eGFR group (n = 884, < 90 mL/min/1.73 m2). Baseline characteristics and laboratory findings were compared between the two groups. Spearman's correlation and linear regression were performed to determine the association between PCSK9 and eGFR. RESULTS: No significant difference in PCSK9 levels was found between the normal eGFR group and the decreased eGFR group (236.84 +/- 67.87 vs. 239.98 +/- 68.72 ng/mL, p = 0.303). In Spearman's correlation and multivariable linear regression analysis, no association of PCSK9 levels with eGFR was detected in the total cohort (r = -0.039, p = 0.079; adjusted beta = -0.013, p = 0.630). This result remained the same in the subgroups of normal eGFR (r = -0.038, p = 0.190; adjusted beta = -0.031, p = 0.367) and decreased eGFR (r = -0.054, p = 0.109; adjusted beta = -0.034, p = 0.319). CONCLUSION: In this single-center study with moderate sample size, the data showed no relationship of PCSK9 levels with normal or decreased eGFR in untreated patients with normal SCr, suggesting that further studies may be needed to understand the relationship between PCSK9 and lipid disorder in different stage of kidney dysfunction.

[7] *Ferrieres J, Gorcyca K, Iorga SR et al.* **Lipid-lowering Therapy and Goal Achievement in High-risk Patients From French General Practice**. Clinical therapeutics 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30126705

ABSTRACT

PURPOSE: The goal of this study was to summarize patterns of lipid-lowering therapy (LLT) usage and achievement of guideline-identified lipid goals in a 2015 general practice cohort of French patients with atherosclerotic cardiovascular disease (ASCVD) and/or diabetes mellitus (DM). METHODS: From the IMS Health Real-World Data database, patients aged >/=18 years were classified hierarchically into mutually exclusive categories of ASCVD subgroups and DM. LLT use and lipid goal achievement were assessed on the date of lipid measurement. The data were compared with previously published results of LLT use and lipid goal achievement in a 2014 UK population. FINDINGS: Of 32,924 patients meeting the inclusion criteria, only 47.5% were prescribed a statin as of the index date. Hierarchically, the highest rates of use of any statin (73.3%) and high-intensity statins (43.3%) were among patients with recent acute coronary syndrome; rates in DM without ASCVD were 38.7% and 2.3%, respectively. Overall, achievement of LDL-C levels <1.8 mmol/L (<70 mg/dL) was only 13.9% for patients with ASCVD and 10.7% with DM. Relative to a 2014 UK population, the 2015 French cohort (data reanalyzed according to the UK statin categorization) were prescribed "high-dose statins" less frequently (31.4% vs 20.9%, and 18.7% vs 7.2%, for ASCVD and DM). Similarly, the proportion of patients with high-dose statins achieving LDL-C levels <1.8 mmol/L was higher in the 2014 UK population than in the 2015 French population (37.3% vs 22.2%, and 36.8% vs 20.3%, for ASCVD and DM). IMPLICATIONS: In a large cohort of French patients with ASCVD and/or DM, LLT usage and LDL-

C goal achievement were suboptimal, relative to current guidelines. (Clin Ther. 2018;40:XXX-XXX) (c) 2018 Elsevier HS Journals, Inc.

[8] *Cuadrado-Godia E, Maniruzzaman M, Araki T et al.* **Morphologic TPA (mTPA) and composite risk score for moderate carotid atherosclerotic plaque is strongly associated with HbA1c in diabetes cohort**. Computers in biology and medicine 2018; 101:128-145.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30138774
ABSTRACT
BACKGROUND: This study examines the association between six types of carotid artery disease image-based phenotypes and HbA1c in diabetes patients. Six phenotypes (intima-media thickness measurements (cIMT (ave.), cIMT (max.), cIMT (min.)), bidirectional wall variability (cIMTV), morphology-based total plaque area (mTPA), and composite risk score (CRS)) were measured in an automated setting using AtheroEdge (AtheroPoint, CA, USA). METHOD: Consecutive 199 patients (157M, age: 68.96+/-10.98 years), L/R common carotid artery (CCA; 398 US scans) who underwent a carotid ultrasound (L/R) were retrospectively analyzed using AtheroEdge system. Two operators (novice and experienced) manually calibrated all the US scans using AtheroEdge. Logistic regression (LR) and Odds ratio (OR) was computed and phenotypes were ranked. RESULTS: The baseline results showed 150 low-risk patients (HbA1c<6.50mg/dl) and 49 high-risk patients (HbA1c>/=6.50mg/dl). The fasting blood sugar (FBS) was highly associated with HbA1c (P<0.001). Except for cIMTV, all phenotypes showed an OR > 1.0 (P<0.001) for left common carotid artery (LCCA), right carotid artery (RCCA), and mean of left and right common carotid artery (MCCA). After adjusting the FBS, the OR for mTPA showed a higher risk for LCCA, RCCA, and MCCA. The coefficient of correlation (CC) between phenotypes and HbA1c were strong and inter-CC between cIMT and mTPA/CRS was above 0.9 (P<0.001). The statistical tests showed that phenotypes were significantly associated with diabetes (P-value<0.0001). CONCLUSIONS: All phenotypes using AtheroEdge, except cIMTV, showed a strong association with HbA1c. mTPA and CRS were equally strong phenotypes as cIMT. The CRS phenotype showed the strongest relationship to HbA1c.

[9] *Ohukainen P, Ruskoaho H, Rysa J*. **Cellular mechanisms of valvular thickening in early and intermediate calcific aortic valve disease**. Current cardiology reviews 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30124158
ABSTRACT
BACKGROUND: Calcific aortic valve disease is common in an aging population. It is an active atheroinflammatory process that has an initial pathophysiology and similar risk factors as atherosclerosis. However, the ultimate disease phenotypes are markedly different. While coronary heart disease results in rupture-prone plaques, calcific aortic valve disease leads to heavily calcified and ossified valves. Both are initiated by retention of low-density lipoprotein particles in the subendothelial matrix leading to sterile inflammation. In calcific aortic valve disease, the process towards calcification and ossification is preceded by valvular thickening, which can cause the first clinical symptoms. This is attributable to the accumulation of lipids, inflammatory cells and subsequently disturbances in the valvular extracellular matrix. Fibrosis is also increased but the innermost extracellular matrix layer is simultaneously loosened. Ultimately, the pathological changes in the valve cause massive calcification and bone

formation - the main reasons for the loss of valvular function and the subsequent myocardial pathology. CONCLUSION: Calcification may be irreversible, and no drug treatments have been found to be effective, thus it is imperative to emphasize lifestyle prevention of the disease. Here we review the mechanisms underpinning the early stages of the disease.

[10] *Ahmadvand A, Yazdanfar A, Yasrebifar F et al.* **Evaluation the effects of oral and topical simvastatin as adjunct therapy in the treatment of acne vulgaris**. Current clinical pharmacology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30129417
ABSTRACT
OBJECTIVES: Acne vulgaris is a common dermatologic disorder which results in psychological consequences. Inflammation plays an important role in the formation of acne lesions. Recently, many studies demonstrated anti-inflammatory effects of statins; thus, the aim of this study was to evaluate the efficacy of oral and topical Simvastatin as adjunct treatment in acne vulgaris. MATERIAL AND METHOD: In 76 patients with moderate to very severe acne vulgaris, beside antibiotic treatment including oral azithromycin (250 mg, 3 times a week, orally) and topical benzoyl peroxide gel (5%, once daily), oral group received 20mg/day of oral simvastatin and blank solution, topical group received simvastatin 1% topical solution and oral placebo, and placebo group received oral placebo and blank solution. Acne severity of each patient was determined by global acne grading system (GAGS) at baseline and after 8 weeks treatment. RESULT: Comparing the three groups' differences of acne severity scores at baseline and 8 weeks of treatment showed that topical simvastatin was associated with greater decrease in acne severity as compared with those of oral and placebo groups, while the oral simvastatin appeared to be more efficacious as compared with placebo group (P value<0.001). Also oral and topical simvastatin were well tolerated in all patients. CONCLUSION: Although preliminary, the results of this study showed that oral and topical statins, agents with anti-inflammatory properties, can be considered as effective treatment for acne vulgaris adjunct to standard treatment. However, further studies with larger sample size and longer follow-up are needed to confirm these results.

[11] *Bergstrom U, Jovinge S, Persson J et al.* **Effects of Treatment with Adalimumab on Blood Lipid Levels and Atherosclerosis in Patients with Rheumatoid Arthritis**. Current therapeutic research, clinical and experimental 2018; 89:1-6.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30128057
ABSTRACT
Background: Treatment with tumor necrosis factor inhibitors for rheumatoid arthritis has been associated with a decreased risk of cardiovascular disease in observational studies. There are conflicting data on the influence of tumor necrosis factor inhibitors on lipid levels. Objectives: To evaluate the effect of treatment with adalimumab on blood lipid levels, lipoproteins, and atherosclerosis of the carotid artery. Methods: Fourteen patients with active rheumatoid arthritis (11 women and 3 men; mean age 63.7 years; median disease duration 9.0 years; and 78% rheumatoid factor positive) were treated with adalimumab 40 mg subcutaneously every 2 weeks and followed for 3 months. The patients had not been treated with adalimumab previously and had not received other tumor necrosis factor inhibitors within the past 3 months

or moderate/high dose corticosteroids within the past 2 weeks. The intima-media thickness of the common carotid artery was assessed using B mode ultrasonography. Triglycerides, total cholesterol, LDL cholesterol, and HDL cholesterol levels were analyzed in fresh fasting blood samples, whereas apolipoprotein B and apolipoprotein A1 (apoA1) levels were determined in thawed plasma samples using standard turbidimetric immunoassays. Results: Total cholesterol (mean=5.36 vs 5.96 mmol/L; P=0.005), LDL cholesterol (mean=3.33 vs 3.77 mmol/L; P=.005), HDL cholesterol (mean=1.43 vs 1.55 mmol/L; P=0.048), apolipoprotein B (mean=1.04 vs 1.13 g/L; P=.012), and apoA1 (mean=1.42 vs 1.58 g/L; P=0.005) all increased, but there were no major changes in the LDL to HDL cholesterol ratio (median=2.56 vs 2.35; P=0.27) or the apolipoprotein B to apoA1 ratio (mean=0.76 vs 0.74; P=0.46). There was no change in triglyceride levels (P=0.55). Disease activity decreased significantly from baseline to the 3-month evaluation (disease activity score based on 28 joints mean=5.6 vs 4.1; P=0.007). An increase in apoA1 correlated with decreases in the patient global assessment of disease severity (r=0.79; P=0.001) and C-reactive protein level (r=0.74; P=0.003). Changes in the apoliprotein B to apoA1 ratio correlated with changes in erythrocyte sedimentation rate (r=0.54; P=0.046). There was no major change in the common carotid artery intima-media thickness (mean=0.78 vs 0.80 mm; P=0.48). Conclusions: Although these results suggest that control of inflammation could have a beneficial effect on the lipid profile through an increase in HDL cholesterol levels, the observed protective effect on cardiovascular disease events by tumor necrosis factor blockers is likely to be explained by other mechanisms than changes in lipid levels or short-term effects on atherosclerosis of the carotid artery.

[12] *Liao JK, Oesterle A*. **The Pleiotropic Effects of Statins - From Coronary Artery Disease and Stroke to Atrial Fibrillation and Ventricular Tachyarrhythmia**. Current vascular pharmacology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30124154
ABSTRACT
Statins, 3-hydroxy-methylglutaryl coenzyme A reductase inhibitors, have been used for decades for the prevention of coronary artery disease and stroke. They act primarily by lowering serum cholesterol through the inhibition of cholesterol synthesis in the liver, which results in the upregulation of low-density lipoprotein receptors in the liver. This results in the removal of low-density lipoprotein-cholesterol. Studies have suggested that statins may demonstrate additional effects that are independent of their effects on low-density lipoprotein-cholesterol. These have been termed "pleiotropic" effects. Pleiotropic effects may be due to the inhibition of isoprenoid intermediates by statins. Isoprenoid inhibition has effects on the small guanosine triphosphate binding proteins Rac and Rho which in turn effects nicotinamide adenine dinucleotide phosphate oxidases. Therefore, there are changes in endothelial nitric oxide synthase expression, atherosclerotic plaque stability, pro-inflammatory cytokines and reactive oxygen species production, platelet reactivity, and cardiac fibrosis and hypetrophy development. Recently, statins have been compared to the ezetimibe and the recently published outcomes data on the proprotein convertase subtilisin kexin type 9 inhibitors has allowed for a reexamination of statin pleiotropy. As a result of these diverse effects, it has been suggested that statins also have anti-arrhythmic effects. This review focuses on the mechanisms of statin pleiotropy and discusses evidence from the statin clinical trials as well as

examining the possible anti-arrhythmic effects atrial fibrillation and ventricular tachyarrhythmias.

[13] *Bjerg L, Hulman A, Carstensen B et al.* **Development of Microvascular Complications and Effect of Concurrent Risk Factors in Type 1 Diabetes: A Multistate Model From an Observational Clinical Cohort Study**. Diabetes Care 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30131399
ABSTRACT
OBJECTIVE: Type 1 diabetes is a complex disease, and development of multiple complications over time can be analyzed only with advanced statistical methods. This study describes the development of microvascular complications and explores the effect of complication burden and important concurrent risk factors by applying a multistate model. RESEARCH DESIGN AND METHODS: We used a clinical cohort at the Steno Diabetes Center Copenhagen to study the development of diabetic kidney disease, retinopathy, and neuropathy. We extracted information from electronic patient records and estimated incidence rates of complications by concurrent complication burden. We explored the extent to which concurrent complications modify the effect of selected risk factors on the development of microvascular complications. RESULTS: We included 3,586 individuals. Incidence rate ratios in individuals with two previous complications were 3.2 (95% CI 2.3-4.5) for diabetic kidney disease, 2.1 (1.5-3.1) for retinopathy, and 1.7 (1.2-2.4) for neuropathy compared with individuals without complications. The models included diabetes duration; calendar time and age as timescales; and sex, HbA1c, lipid-lowering and antihypertensive treatment, systolic blood pressure, BMI, estimated glomerular filtration rate (eGFR), cardiovascular disease (CVD), LDL cholesterol, insulin dose (units/kg/day), and smoking status as covariates. Effects of HbA1c, diabetes duration, systolic blood pressure, BMI, eGFR, and LDL cholesterol where not modified by concurrent complication burden, whereas the effect of sex and CVD were. CONCLUSIONS: The risk of microvascular complications highly depends on the concurrent complication burden and risk factor profile in individuals with type 1 diabetes. The results emphasize attention to risk factors, regardless of existing number of complications, to prevent development of further microvascular complications.

[14] *Kim JH*. **Letter: Serum Levels of PCSK9 Are Associated with Coronary Angiographic Severity in Patients with Acute Coronary Syndrome (Diabetes Metab J 2018;42:207-14)**. Diabetes Metab J 2018; 42:348-349.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30136453
ABSTRACT

[15] *Kim SW, Park KG*. **Response: Serum Levels of PCSK9 Are Associated with Coronary Angiographic Severity in Patients with Acute Coronary Syndrome (Diabetes Metab J 2018;42:207-14)**. Diabetes Metab J 2018; 42:350-352.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30136454
ABSTRACT

[16] *Aldalaen S, El-Gogary RI, Nasr M*. **Fabrication of rosuvastatin-loaded polymeric nanocapsules: A promising modality for treating hepatic cancer delineated by apoptotic and cell cycle arrest assessment**. Drug development and industrial pharmacy 2018:1-29.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30139281

ABSTRACT

Nanotechnology has provided several advantages for the treatment of cancer. Polymeric nanocapsules (PNCs) were proven promising in the treatment of different cancer types, such as hepatic cancer. Meanwhile, the exploration of novel indications of old molecules with the purpose of cancer treatment has been widely reported. Among the promising therapeutic moieties, rosuvastatin (RV) was delineated as a potential anticancer drug. Hence, the target of the presented manuscript was to develop PNCs loaded with RV to overcome its delivery challenges and augment its anticancer activity. RV PNCs were fabricated by the nanoprecipitation method using poly-lactide-co-glycolide PLGA polymer, and were characterized for the size, polydispersity index (PDI), charge, entrapment efficiency EE%, in-vitro release, stability, and morphology. Furthermore, their anticancer activity was tested on HepG2 cells using MTT assay, followed by elucidating the cytotoxic activity using flow cytometry. Results showed that RV PNCs displayed particle size ranging from 186-239 nm, average PDI, and negative zeta potential with sufficient stability for 3 months. PNCs were able to load RV at high EE% reaching 82.6% and sustain its release for 8 hours. RV PNCs were superior in their anticancer activity on HepG2 cells, as delineated from the viability study and further elucidated by enhanced apoptosis in addition to cell cycle arrest at G2/M phase, suggesting their promise in treatment of hepatic cancer.

[17] *Junior VC, Fuchs FD, Schaan BD et al.* **Effect of metformin on blood pressure in patients with hypertension: a randomized clinical trial**. Endocrine 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30132262

ABSTRACT

OBJECTIVE: Part of the beneficial effects of metformin on the prevention of cardiovascular events in diabetes can be attributed to pleiotropic effects, including a blood pressure (BP)-lowering effect. In a double-blind parallel clinical trial (NCT02072382), the effect of metformin on BP evaluated by ambulatory blood pressure monitoring (ABPM) was measured. METHODS: Ninety-seven patients with hypertension, but without diabetes mellitus, were randomized to receive 850-1700 mg of metformin (n = 48) or placebo (n = 49). Clinical, laboratory, and ABPM data were collected at the baseline and after 8 weeks of follow-up. RESULTS: The sample consisted mainly of White overweight women. There was no difference in BP reduction measured by ABPM between both groups. There was no effect in BP measured in the different periods of ABP monitoring and office BP. Additionally, fasting plasma glucose, lipids, and C-reactive protein remained unchanged during the trial. There was a significant reduction in waist circumference with metformin (95.1 +/- 10.4 to 89.3 +/- 27.4 cm; p = 0.02). CONCLUSION: In the present trial, metformin did not reduce BP, measured by ABP monitoring, in hypertensive patients without diabetes.

Literature update week 34 (2018)

[18] *Decano JL, Aikawa M*. **Dynamic Macrophages: Understanding Mechanisms of Activation as Guide to Therapy for Atherosclerotic Vascular Disease**. Frontiers in cardiovascular medicine 2018; 5:97.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30123798
ABSTRACT
An emerging theory is that macrophages are heterogenous; an attribute that allows them to change behavior and execute specific functions in disease processes. This review aims to describe the current understanding on factors that govern their phenotypic changes, and provide insights for intervention beyond managing classical risk factors. Evidence suggests that metabolic reprogramming of macrophages triggers either a pro-inflammatory, anti-inflammatory or pro-resolving behavior. Dynamic changes in bioenergetics, metabolome or influence from bioactive lipids may promote resolution or aggravation of inflammation. Direct cell-to-cell interactions with other immune cells can also influence macrophage activation. Both paracrine signaling and intercellular molecular interactions either co-stimulate or co-inhibit activation of macrophages as well as their paired immune cell collaborator. More pathways of activation can even be uncovered by inspecting macrophages in the single cell level, since differential expression in key gene regulators can be screened in higher resolution compared to conventional averaged gene expression readouts. All these emerging macrophage activation mechanisms may be further explored and consolidated by using approaches in network biology. Integrating these insights can unravel novel and safer drug targets through better understanding of the pro-inflammatory activation circuitry.

[19] *Hosseinkhani B, Kuypers S, van den Akker NMS et al.* **Extracellular Vesicles Work as a Functional Inflammatory Mediator Between Vascular Endothelial Cells and Immune Cells**. Frontiers in immunology 2018; 9:1789.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30131806
ABSTRACT
Extracellular vesicles (EV) mediated intercellular communication between monocytes and endothelial cells (EC) might play a major role in vascular inflammation and atherosclerotic plaque formation during cardiovascular diseases (CVD). While critical involvement of small (exosomes) and large EV (microvesicles) in CVD has recently been appreciated, the pro- and/or anti-inflammatory impact of a bulk EV (exosomes + microvesicles) on vascular cell function as well as their inflammatory capacity are poorly defined. This study aims to unravel the immunomodulatory content of EV bulk derived from control (uEV) and TNF-alpha induced inflamed endothelial cells (tEV) and to define their capacity to affect the inflammatory status of recipients monocytes (THP-1) and endothelial cells (HUVEC) in vitro. Here, we show that EV derived from inflamed vascular EC were readily taken up by THP-1 and HUVEC. Human inflammation antibody array together with ELISA revealed that tEV contain a pro-inflammatory profile with chemotactic mediators, including intercellular adhesion molecule (ICAM)-1, CCL-2, IL-6, IL-8, CXCL-10, CCL-5, and TNF-alpha as compared to uEV. In addition, EV may mediate a selective transfer of functional inflammatory mediators to their target cells and modulate them toward either pro-inflammatory (HUVEC) or anti/pro-inflammatory (THP-1) mode. Accordingly, the expression of pro-inflammatory markers (IL-6, IL-8, and ICAM-1) in tEV-treated HUVEC was increased. In the case of THP-1, EC-EV do induce a mixed of pro- and anti-inflammatory

response as indicated by the elevated expression of ICAM-1, CCL-4, CCL-5, and CXCL-10 proteins. At the functional level, EC-EV mediated inflammation and promoted the adhesion and migration of THP-1. Taken together, our findings proved that the EV released from inflamed EC were enriched with a cocktail of inflammatory markers, chemokines, and cytokines which are able to establish a targeted cross-talk between EC and monocytes and reprogramming them toward a pro- or anti-inflammatory phenotypes.

[20] *Liu Y, Carmona-Rivera C, Moore E et al.* **Myeloid-Specific Deletion of Peptidylarginine Deiminase 4 Mitigates Atherosclerosis**. Frontiers in immunology 2018; 9:1680.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30140264
ABSTRACT
Increasing evidence suggests that neutrophil extracellular traps (NETs) may play a role in promoting atherosclerotic plaque lesions in humans and in murine models. The exact pathways involved in NET-driven atherogenesis remain to be systematically characterized. To assess the extent to which myeloid-specific peptidylarginine deiminase 4 (PAD4) and PAD4-dependent NET formation contribute to atherosclerosis, mice with myeloid-specific deletion of PAD4 were generated and backcrossed to Apoe(-/-) mice. The kinetics of atherosclerosis development were determined. NETs, but not macrophage extracellular traps, were present in atherosclerotic lesions as early as 3 weeks after initiating high-fat chow. The presence of NETs was associated with the development of atherosclerosis and with inflammatory responses in the aorta. Specific deletion of PAD4 in the myeloid lineage significantly reduced atherosclerosis burden in association with diminished NET formation and reduced inflammatory responses in the aorta. NETs stimulated macrophages to synthesize inflammatory mediators, including IL-1beta, CCL2, CXCL1, and CXCL2. Our data support the notion that NETs promote atherosclerosis and that the use of specific PAD4 inhibitors may have therapeutic benefits in this potentially devastating condition.

[21] *Gabryelska A, Lukasik ZM, Makowska JS, Bialasiewicz P*. **Obstructive Sleep Apnea: From Intermittent Hypoxia to Cardiovascular Complications via Blood Platelets**. Frontiers in neurology 2018; 9:635.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30123179
ABSTRACT
Obstructive sleep apnea is a chronic condition characterized by recurrent episodes of apneas or hypopneas during sleep leading to intermittent hypoxemia and arousals. The prevalence of the sleep disordered breathing is estimated that almost 50% of men and 24% of women suffer from moderate to severe form of the disorder. Snoring, collapse of upper airways and intermittent hypoxia are main causes of smoldering systemic inflammation in patients suffering from obstructive sleep apnea. The systematic inflammation is considered one of the key mechanisms leading to significant cardiovascular complications. Blood platelets, formerly not even recognized as cells, are currently gaining attention as crucial players in the immune continuum. Platelet surface is endowed with receptors characteristic for cells classically belonging to the immune system, which enables them to recognize pathogens, immune complexes, and interact in a homo- and heterotypic aggregates. Platelets participate in the process of transcellular production of bioactive lipids by delivering both specific enzymes and substrate molecules.

Despite their lack of nucleus, platelets synthetize proteins in a stimuli-dependent manner. Atherosclerosis and consequent cardiovascular complications result from disruption in homeostasis of both of the platelet roles: blood coagulation and inflammatory processes modulation. Platelet parameters, routinely evaluated as a part of complete blood count test, were proposed as markers of cardiovascular comorbidity in patients with obstructive sleep apnea. Platelets were found to be excessively activated in this group of patients, especially in obese subjects. Persistent activation results in enhanced spontaneous aggregability and change in cytokine production. Platelet-lymphocyte ratio was suggested as an independent marker for cardiovascular disease in obstructive sleep apnea syndrome and continuous positive air pressure therapy was found to have an impact on platelet parameters and phenotype. In this literature review we summarize the current knowledge on the subject of platelets involvement in obstructive sleep apnea syndrome and consider the possible pathways in which they contribute to cardiovascular comorbidity.

[22] *Mahajan R*. **Novel Lipid-Lowering Agents Proprotein Convertase Subtilisin-Kexin Type 9 Inhibitors: Do They Show Mortality Benefits?** International journal of applied & basic medical research 2018; 8:135-136.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30123740
ABSTRACT

[23] *Grames MS, Dayton RD, Lu X et al.* **Gene Transfer Induced Hypercholesterolemia in Amyloid Mice**. Journal of Alzheimer's disease : JAD 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30124449
ABSTRACT
A risk factor for cardiovascular disease (CVD), mutant PCSK9, was expressed in APP/PS1 mice to study the CVD-Alzheimer's disease inter-relationship. Cholesterol levels were elevated by 5-6-fold from 3 to 13 weeks after PCSK9 gene transfer. We tested whether hypercholesterolemia would increase amyloid-beta plaques at a relatively early stage of plaque deposition. Plaque burden was increased in the hippocampus of PCSK9 treated mice though the increase was modest compared to the large elevation in cholesterol. Elevating cholesterol via gene transfer could be valuable in a variety of disease models compared to making crosses with germ-line transgenic mouse models of CVD.

[24] *Lundkvist P, Pereira MJ, Kamble PG et al.* **Glucagon Levels during Short-term SGLT2 Inhibition are Largely Regulated by Glucose Changes in Type 2 Diabetes Patients**. The Journal of clinical endocrinology and metabolism 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30137410
ABSTRACT
Context: Sodium glucose cotransporter-2 (SGLT2) inhibitors can raise glucagon levels, but whether this is mediated via direct effects on islet cells or indirectly via blood glucose lowering is unknown. Objective: To assess short-term effects on glucagon and other hormones as well as energy substrates following SGLT2 inhibition and whether such effects are secondary to glucose lowering. Moreover, the impact of adding a dipeptidyl peptidase-4 inhibitor was addressed. Design and Setting: A phase IV, single-center, randomized 3-treatment crossover, open-label

study. Patients: 15 metformin-treated type 2 diabetes patients. Interventions: At the three visits patients received a single-dose of dapagliflozin 10mg accompanied by either of the following in randomized order: isoglycemic clamp (experiment DG); saline infusion (experiment D); or saxagliptin 5mg plus saline infusion (experiment DS). Directly after 5-h infusion periods, a 2-h oral glucose tolerance test (OGTT) was performed. Results: Glucose and insulin levels were stable in experiment DG and decreased in experiment D (Pdiff <0.001). Glucagon (Pdiff <0.01), glucagon/insulin ratio (Pdiff <0.001), non-esterified fatty acids (Pdiff <0.01), glycerol (Pdiff <0.01) and beta-OH-butyrate (Pdiff <0.05) were all lower in DG vs D. In multivariate analysis, change in glucose level was the main predictor of change in glucagon level. In DS, glucagon and active GLP-1 were higher vs D but glucose and insulin did not differ. During OGTT, DS had less glucose rise and greater glucagon fall vs D. Conclusion: The degree of glucose lowering markedly contributes to regulation of glucagon and insulin secretion as well as lipid mobilization during short-term SGLT2 inhibition.

[25] *Leung J, Brady JL, Crook MA*. **The clinical importance of recognizing capecitabine-induced hypertriglyceridemia: A case report and review of the literature**. Journal of clinical lipidology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30126762
ABSTRACT
This case report describes a patient who developed a mixed hyperlipidemia and severe hypertriglyceridemia (>20 mmol/L or 1772 mg/dL) while receiving capecitabine chemotherapy. After lipid-lowering treatment (statin and omega-3 acid ethyl esters) and completion of chemotherapy, her lipid levels had been significantly reduced. Other secondary causes of hyperlipidemia were also investigated. In view of the abnormal lipid results worsened by capecitabine, we suggest that careful lipid monitoring and thorough lipid management are important in such patients to avoid acute pancreatitis.

[26] *Probstfield JL, Boden WE, Anderson T et al.* **Cardiovascular outcomes during extended follow-up of the AIM-HIGH trial cohort**. Journal of clinical lipidology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30131256
ABSTRACT
BACKGROUND: Epidemiologic studies have shown that low levels of high-density lipoprotein-cholesterol (HDL-C) and elevated triglycerides are independent predictors of cardiovascular (CV) events, though randomized trials of HDL-C-raising therapies to reduce clinical events have been largely disappointing. The Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides and Impact on Global Health Outcomes (AIM-HIGH) trial failed to show that extended release niacin (ERN) reduced CV events in patients with atherogenic dyslipidemia who were on statin-based therapy. OBJECTIVE: We sought to determine whether extended follow-up of AIM-HIGH participants changed these null results. METHODS: AIM-HIGH was a placebo-controlled trial of 3414 patients with established CV disease, low baseline HDL-C, and elevated triglycerides levels randomized to ERN 1500-2000 mg/d vs placebo. Participants also received simvastatin with or without ezetimibe to attain on-treatment low-density lipoprotein cholesterol levels of 40-80 mg/dL. The trial was halted after a mean 3-year follow-up because of futility. RESULTS: Among 3236 participants alive at the end of blinded study,

2613 (81%; ERN = 1,312, placebo = 1301) were followed a mean 1.1 additional years. Ninety-five percent of subjects remained on statin, but only 4% on ERN. At a mean total follow-up of 4.1 years, there were 343 primary CV endpoints in the ERN arm and 305 CV endpoints in placebo participants (HR 1.11, 95% CI 0.96, 1.30). Ischemic stroke was also not significantly different after extended follow-up in the two groups (2.2% vs 1.5%, P = .13). CONCLUSIONS: In patients with CV disease and atherogenic dyslipidemia on statin-based therapy, 3 years of ERN treatment did not lower CV event rates. An additional year of follow-up off assigned treatment did not alter these findings.

[27] *Krysiak R, Szkrobka W, Okopien B*. **Different Effects of Atorvastatin on Cardiometabolic Risk Factors in Young Women With and Without Hyperprolactinemia**. Journal of clinical pharmacology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30129670
ABSTRACT
Long-term prolactin excess is often accompanied by numerous metabolic complications. No previous study has compared the effect of statin therapy on circulating levels of cardiometabolic risk factors in patients with elevated and normal prolactin levels. The study population consisted of 3 age-, weight-, and lipid-matched groups of young women: 19 women with untreated hyperprolactinemia (group A), 20 normoprolactinemic women receiving bromocriptine treatment (because of previous hyperprolactinemia) (group B), and 20 untreated women with prolactin levels within the reference range (group C). Because of elevated total and low-density lipoprotein cholesterol levels, all women were then treated with atorvastatin (40 mg daily). Apart from measuring plasma lipids, glucose homeostasis markers, and hormone levels at the beginning of the study and 12 weeks later, we measured circulating levels of uric acid, high-sensitivity C-reactive protein, homocysteine, and fibrinogen. Despite similar baseline levels of plasma lipids, levels of uric acid, high-sensitivity C-reactive protein, homocysteine, and fibrinogen as well as the degree of insulin resistance were higher in group A than in the remaining 2 groups. Atorvastatin reduced total and low-density lipoprotein cholesterol levels in all study groups. However, only in normoprolactinemic women (groups B and C) did atorvastatin reduce circulating levels of nonlipid cardiometabolic risk factors, whereas only in group A did the drug slightly impair insulin sensitivity. The results of the study suggest that cardiometabolic effects of atorvastatin depend on the prolactin status of patients.

[28] *Kullo IJ, Bailey KR*. **Design of a Controlled Trial of Cascade Screening for Hypercholesterolemia: The (CASH) Study**. Journal of personalized medicine 2018; 8.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30142941
ABSTRACT
To inform guidelines for screening family members of patients with familial hypercholesterolemia (FH), we designed a clinical trial to compare the yield of cascade screening in FH patients with and without an identifiable pathogenic variant. Participants with hypercholesterolemia (Low-density lipoprotein cholesterol (LDL-C) > 155 mg/dL) underwent sequencing of LDLR, APOB, and PCSK9 and genotyping of six single nucleotide polymorphisms associated with LDL-C followed by calculation of a polygenic score for LDL-C. We identified 24 patients with definite FH (pathogenic variant in one of the three FH genes), 76 patients with

probable FH (Dutch lipid clinic network (DLCN) score >/= 6, no pathogenic variant), and 262 patients with possible FH (DLCN score 3(-)5, no pathogenic variant). We will enroll 50 patients with definite FH by recruiting an additional 26 from the FH Clinic at Mayo and 50 patients each with probable and possible FH, matching on age and sex. Family members of patients with definite FH will undergo testing for the relevant pathogenic variant using saliva kits and family members of those with probable/possible FH will have a lipid profile checked. We will assess the number of new cases detected (defined as presence of a pathogenic variant in the family member of definite FH patient or LDL-C > 155 mg/dL (>130 mg/dL in children) in family members of probable/possible FH patients, and the cost of detecting a new case. The proposed clinical trial will compare the yield and cost of cascade screening for FH patients with/without an identifiable pathogenic variant, and thereby inform guidelines for cascade screening for FH.

[29] *Xia B, Li Y, Zhang Y et al.* **UHPLC-MS/MS method for determination of atorvastatin calcium in human plasma: Application to a pharmacokinetic study based on healthy volunteers with specific genotype**. Journal of pharmaceutical and biomedical analysis 2018; 160:428-435.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30130726
ABSTRACT
A rapid, selective and sensitive ultra high performance liquid chromatography coupled with tandem triple quaternary mass spectrometry (UHPLC-MS/MS) method was developed and validated for the quantitative determination of atorvastatin calcium (AC) in human plasma. Separation of AC and rosuvastatin calcium (internal standard, IS) were achieved on a Dikma Leapsil C18 reversed phase column (100 x 2.1 mm, 2.7 mum) with gradient elution using 0.2% (v/v) formic acid in water and acetonitrile as mobile phases, at the flow rate of 0.3 mL/min. AC and IS were detected using MS/MS with turbo ion pray source in negative mode by monitoring the precursor-to-product ion transitions m/z 557.0-->453.0 for AC and m/z 480.0-->418.0 for IS. The calibration curves were linear from 0.05 to 50 ng/mL with a correlation coefficient (r(2)) of 0.9992 or better. Thereafter, 187 healthy candidates were checked to the genetic polymorphism analysis of SLCO1B1 521TC(rs4149056), SLCO1B1 388AG(rs2306283), CYP3A4 1*B(rs2740574), CYP3A4 1*G(rs2242480) and CYP3A5*3(rs776746) using fluorescence in situ hybridization technology. The genotype frequencies of wild-type homozygote, mutant heterozygote and mutant homozygote were 62.57%(TT), 34.22%(TC) and 3.21%(CC) for SLCO1B1 521TC, and 8.56%(AA), 33.69%(AG) and 57.75%(GG) for SLCO1B1 388AG, and 62.57%(CC), 34.22%(CT) and 3.21%(TT) for CYP3A4 1 G, and 58.29%(GG), 34.76%(GA) and 6.95%(AA) for CYP3A5*3, respectively. Furthermore, each tested genotype of CYP3A4 1B was wild type. Finally, 5 candidates with specific genotype described above were recruited to carry out the clinical pharmacokinetics of AC (n = 5). The validated UHPLC-MS/MS method was implemented in a high-throughput setting, capable of analyzing up to 288 samples per day, and was successfully applied to the pharmacokinetic study of AC based on healthy volunteers with specific genotype. The Cmax of AC in human volunteers with the specific genotype was nearly 10 times higher than that previous reported, indicating that genetic polymorphisms of these specific genotypes have significant influence on pharmacokinetics of atorvastatin.

Literature update week 34 (2018)

[30] *Sadeghi-Ardekani K, Haghighi M, Zarrin R*. **Effects of omega-3 fatty acid supplementation on cigarette craving and oxidative stress index in heavy-smoker males: A double-blind, randomized, placebo-controlled clinical trial**. Journal of psychopharmacology (Oxford, England) 2018; 32:995-1002.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30136619
ABSTRACT
BACKGROUND: Smoking-induced oxidative stress is thought to contribute to lower levels of omega-3 fatty acids in plasma and brain tissue. This lower level leads to impaired function in a dopaminergic system related to dependence and craving. AIMS: The aim of this study was to evaluate the effects of omega-3 fatty acid supplementation on cigarette craving and oxidative stress index in heavy-smoker males. METHODS: In this double-blind, randomized clinical trial, 54 heavy-smoker males (smoke 20 cigarettes per day) were randomly selected to receive either five capsules of fish-oil-derived omega-3 fatty acid supplements (n = 27, each 1 g capsule containing 180 mg of eicosapentaenoic acid and 120 mg of docosahexanoic acid) or a placebo (n = 27) for 3 months. The psychometric evaluations (nicotine dependence and cigarette craving), biochemical markers (urinary cotinine, serum total antioxidant capacity and total oxidant status) and self-reported smoking status were used to assess the cigarette craving and oxidative stress index (oxidative stress index = total oxidant status/total antioxidant capacity). RESULTS: There was a greater reduction in levels of nicotine dependence, cigarette craving and cigarettes smoked per day in the omega-3 fatty acid group compared to the placebo group, and the difference between the two groups increased from baseline to 3-month follow up. The model estimated that these differences were statistically significant ($p < 0.001$, $p < 0.001$ and $p < 0.001$, respectively). Also, a significant decrease was observed in levels of total oxidant status ($p = 0.008$) and oxidative stress index ($p = 0.011$) in the omega-3 fatty acid group after intervention. CONCLUSIONS: This study showed that high-dose omega-3 fatty acid supplementation appears to be useful in reducing cigarette craving and oxidative stress index in heavy-smoker males.

[31] *Kulik A, Abreu AM, Boronat V, Ruel M*. **Intensive versus moderate statin therapy and early graft occlusion after coronary bypass surgery: The Aggressive Cholesterol Therapy to Inhibit Vein Graft Events randomized clinical trial**. The Journal of thoracic and cardiovascular surgery 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30122341
ABSTRACT
OBJECTIVE: Statins prevent saphenous vein graft (SVG) disease and improve outcomes after coronary artery bypass graft surgery. However, the optimal postoperative statin dose remains unclear. The Aggressive Cholesterol Therapy to Inhibit Vein Graft Events trial was undertaken to evaluate whether early postoperative high-dose statin therapy reduces SVG occlusion compared with conventional moderate-dose therapy. METHODS: In this pilot, multicenter, double-blind randomized trial, 173 patients who had coronary artery bypass graft surgery with SVG were randomized to receive 10 mg or 80 mg atorvastatin daily for 1 year. The primary outcome was SVG occlusion at 1 year. Secondary outcomes were SVG stenosis and major adverse cardiovascular events. RESULTS: During trial enrollment, patients randomized to 80 mg atorvastatin achieved significantly lower low-density lipoprotein cholesterol levels ($P < .00001$).

One-year graft assessment was performed in 145 patients (83.8%). The primary outcome, SVG occlusion at 1 year, did not significantly differ between the 2 groups (12.9% vs 11.4% for 10 mg atorvastatin vs 80 mg atorvastatin; P = .85). The incidence of vein graft stenosis also did not significantly differ between the groups (P = .54). However, there was a trend toward fewer patients developing vein graft disease (either occlusion or stenosis) in the 80 mg atorvastatin group (29.2% vs 19.2%, 10 mg atorvastatin vs 80 mg atorvastatin; P = .18). Freedom from major adverse cardiovascular events at 1 year was similar between the groups (P = .27). CONCLUSIONS: Compared with 10 mg atorvastatin, 80 mg atorvastatin did not significantly reduce vein graft occlusion 1 year after coronary artery bypass graft surgery in this pilot trial.

[32] *Yoon YE, Kim KM, Han JS et al.* **Prediction of Subclinical Coronary Artery Disease With Breast Arterial Calcification and Low Bone Mass in Asymptomatic Women: Registry for the Women Health Cohort for Breast, Bone, and Coronary Artery Disease Study**. JACC. Cardiovascular imaging 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30121271

ABSTRACT

OBJECTIVES: This study sought to determine whether evaluations of breast arterial calcification (BAC) and low bone mass (LBM) could improve the ability to predict subclinical coronary artery disease (CAD) in asymptomatic women. BACKGROUND: An improved risk stratification strategy beyond the measurement of conventional risk factors is needed to identify women at high risk of CAD. METHODS: The BBC (Women Health Registry Study for Bone, Breast, and Coronary Artery Disease) enrolled 2,100 asymptomatic women who underwent dual-energy X-ray absorptiometry, digital mammography, and coronary computed tomography angiography. We assessed the predicted 10-year atherosclerotic cardiovascular disease (ASCVD) risk and evaluated the presence and severity of BAC, LBM, coronary artery calcification (CAC), and coronary atherosclerotic plaque (CAP). RESULTS: CAC and CAP were found in 11.2% and 15.6% of participants, respectively. In women with CAC or CAP, increasing trends in the presence and severity of both BAC and LBM were observed. Both BAC and LBM were found to be associated with the presence of CAC (unadjusted odds ratios [OR]: 3.54 and 2.22, respectively) and CAP (unadjusted OR: 3.02 and 1.91, respectively). However, in multivariate analysis, only the presence of BAC and BAC score remained as independent predictors. For the prediction of CAC and CAP, addition of the BAC presence to the 10-year ASCVD risk significantly increased the areas under the curve (area under the curve: 0.71 to 0.72; p = 0.016; and area under the curve: 0.66 to 0.68; p = 0.010; respectively) and resulted in net reclassification index improvements (area under the curve: 0.304; p <0.001; and area under the curve: 0.245; p <0.001; respectively). CONCLUSIONS: The presence and severity of BAC and LBM were significantly associated with the risk of subclinical CAD in asymptomatic women. BAC evaluation especially provides an independent and incremental value over conventional risk algorithms. (Women Health Cohort for Breast, Bone and Coronary Artery Disease [BBC]; NCT03235622.).

[33] *Oleynikov VE, Dushina EV, Barmenkova YA et al.* **[The Impact of Effective Therapy With Atorvastatin on the Dynamics of Parameters of Electrical Instability in Patients with ST-Elevation Myocardial Infarction]**. Kardiologiia 2018:18-24.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30131038

ABSTRACT

AIM: To assess the dynamics of parameters of myocardial electrical instability in patients with ST-elevation (STE) myocardial infarction (MI) treated with various doses of atorvastatin. MATERIALS AND METHODS: Patients with STEMI (n=70), who received atorvastatin 20 or 80 mg/day for 48 weeks, were divided into two groups: group "capital IE, Cyrillic" - 38 patients (54.3 %) in whom by 48th week target values of low density lipoprotein cholesterol (LDLC) were achieved, and group "NE" - 32 patients (45.7 %) in whom these levels were not achieved. On days 7-9, at 24th and 48th weeks after onset of MI the patients underwent 24hour 12leads ECG monitoring with subsequent analysis of parameters of myocardial electrical inhomogeneity: late ventricular potentials (LVP), dispersion of QT-interval duration, heart rate variability (HRV) and turbulence. RESULTS: After of treatment with atorvastatin target value of LDLC was achieved in 73.5 and 36.1 % of patients receiving 80 and 20 mg/day, respectively. In the group "E" we observed positive dynamics of LVP parameters (QRSf - p.

[34] *Feng C, Zhang P, Han B et al.* **Optical coherence tomographic analysis of drug-eluting in-stent restenosis at different times: A STROBE compliant study**. Medicine (Baltimore) 2018; 97:e12117.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30142870

ABSTRACT

The imaging characteristics of drug-eluting in-stent restenosis (ISR) at different times varied; however, the mechanism had not yet been elucidated.To analyze the imaging characteristics of drug-eluting ISR at different time points by optical coherence tomography (OCT) and investigate the cause of the stent treatment failure.A total of 70 patients with drug-eluting ISR undergoing OCT were enrolled (intimal hyperplasia >/=50% of stent area) and implanted with drug-eluting stents. According to stent implantation time, the patients were divided into 2 groups: early in-stent restenosis group (E-ISR group) (group A, n = 35, stent age </=12 months) and late in-stent restenosis group (L-ISR group) (group B, n = 35, stent age >/=24 months). A qualitative analysis of the restenosis tissue included the nature of restenosis tissue (homogeneous and heterogeneous), neoatherosclerosis, thin-cap fibroatheroma (TCFA), and microvessels.The ratio of >/=75% cross-sectional area stenosis between the L-ISR and E-ISR groups was (60.00% vs 34.28%, P < .05). The heterogeneous intima, neoatherosclerosis, TCFA, and microvessels were more prevalent in the L-ISR group as compared to the E-ISR group (71.43% vs 45.71%, P < .05; 48.57% vs 22.86%, P < .05; 25.71% vs 5.71%, P < .05; 22.86% vs 2.86%, P < .05, respectively).The morphological characteristics of L-ISR were significantly different from those in the E-ISR; the former was closer to the atherosclerotic plaque, which provided a new approach for the treatment of drug-eluting ISR.

[35] *Hui L, Shijun H, Tao L et al.* **Bilateral thalamic and mesencephalic infarctions with hypopituitarism as long-term complications postradiotherapy: A case report**. Medicine (Baltimore) 2018; 97:e11917.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30142801

ABSTRACT

BACKGROUND: Radiation is widely used as the first-line treatment for nasopharyngeal carcinoma (NPC) and improves survival. Nevertheless, radiation also places the patients at risk

of radiation-induced adverse effects, such as transient ischemic attack, ischemic stroke, hypopituitarism, and cranial nerve and temporal lobe dysfunction. CASE REPORT: A 54-year-old woman who had undergone radiation treatment for NPC 14 years earlier and had no cerebrovascular risk factors, visited our department 4 days after sudden onset of consciousness disturbance. Brain magnetic resonance imaging (MRI) revealed bilateral thalamic and left mesencephalic infarctions with empty sella. Meanwhile, MR angiography showed narrowing in the bilateral posterior cerebral artery. Furthermore, laboratory tests showed low total triiodothyronine (T3), thyroxine (T4), free T3, free T4, luteinizing hormone, estradiol, follicle-stimulating hormone, and serum natrium and normal thyroid-stimulating hormone, which indicated radiation-related hypopituitarism. Serologically, she had low hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, ferritin, and serum iron levels and elevated transferrin, manifesting microcytic anemia. The treatment, including aspirin, atorvastatin, levothyroxine, prednisone, saline infusion, and chalybeate, promoted the patient's recovery. CONCLUSION: To our knowledge, this is the first report of bilateral thalamic and mesencephalic infarction together with hypopituitarism following radiotherapy for NPC.

[36] *Millar CL, Duclos Q, Garcia C et al.* **Effects of Freeze-Dried Grape Powder on High-Density Lipoprotein Function in Adults with Metabolic Syndrome: A Randomized Controlled Pilot Study**. Metab Syndr Relat Disord 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30129815
ABSTRACT
BACKGROUND: High-density lipoprotein (HDL) particles are protective against atherosclerosis. However, HDL function is impaired in metabolic syndrome (MetS) due to low-grade inflammation and dyslipidemia. Foods containing polyphenols, such as grapes, may prevent HDL dysfunction via antioxidant or anti-inflammatory effects. We evaluated the effects of grape powder ingestion on measures of HDL function in adults with MetS. METHODS: Twenty adults (age: 32-70 years; body mass index: 25.3-45.4 kg/m(2)) consumed either 60 grams/day of freeze-dried grape powder (GRAPE) or a placebo for 4 weeks, separated by a 3-week washout period, in a randomized, double-blind crossover study. The primary outcome was serum paraoxonase-1 (PON1) arylesterase activity, a measure of HDL antioxidant function. Secondary outcomes included PON1 lactonase activity, plasma lipids, metabolic markers, cholesterol efflux capacity, and other HDL functional markers. RESULTS: After 4 weeks, GRAPE did not alter the serum PON1 activity or other markers of HDL function compared with placebo. Measures of HDL function were positively correlated with each other and inversely with measures of insulin resistance and inflammation. GRAPE intake led to a significant reduction in fasting plasma triglycerides compared with placebo (P = 0.032). No other significant effects of GRAPE were observed for other plasma lipids, anthropometrics, or metabolic measures. CONCLUSIONS: Grape powder consumption did not impact HDL function in this cohort of adults with MetS. However, it was shown to improve fasting triglycerides, a risk factor for cardiovascular disease.

[37] *Rasmussen LD, Bottcher M, Ivarsen P et al.* **Association between circulating proprotein convertase subtilisin/kexin type 9 levels and prognosis in patients with severe chronic kidney**

disease. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30137516
ABSTRACT
Background: Chronic kidney disease is a risk factor for premature development of coronary atherosclerosis and mortality. A high level of proprotein convertase subtilisin/kexin type 9 (PCSK9) is a recently recognized cardiovascular risk factor and has become the target of effective inhibitory treatment. In 167 kidney transplantation candidates, we aimed to: (i) compare levels of PCSK9 with those of healthy controls, (ii) examine the association between levels of PCSK9 and low-density lipoprotein cholesterol (LDL-c) and the degree of coronary artery disease (CAD) and (iii) evaluate if levels of PCSK9 predict major adverse cardiac events (MACE) and mortality. Methods: Kidney transplant candidates (n = 167) underwent coronary computed tomography angiography (CCTA) and invasive coronary angiography (ICA) before transplantation. MACE and mortality data were extracted from the Western Denmark Heart Registry, a review of patient records and patient interviews. A group of 79 healthy subjects were used as controls. Results: Mean PCSK9 levels did not differ between healthy controls and kidney transplant candidates. In patients not receiving lipid-lowering therapy, PCSK9 correlated positively with LDL-c (rho = 0.24, P < 0.05). Mean PCSK9 was similar in patients with and without obstructive CAD at both CCTA and ICA. In a multiple regression analysis, PCSK9 was associated with neither LDL-c (beta=-6.45, P = 0.44) nor coronary artery calcium score (beta=2.17, P = 0.84). During a follow-up of 3.7 years, PCSK9 levels were not associated with either MACE or mortality. Conclusions: The ability of PCSK9 levels to predict cardiovascular disease and prognosis does not seem to apply to a cohort of kidney transplant candidates.

[38] *Ciric D, Martinovic T, Petricevic S et al.* **Metformin exacerbates and simvastatin attenuates myelin damage in high fat diet-fed C57BL/6 J mice**. Neuropathology : official journal of the Japanese Society of Neuropathology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30123961
ABSTRACT
Diabetic neuropathy is one of the most deleterious complications of diabetes mellitus in humans. High fat diet (HFD)-fed C57BL/6 J mice are a widely used animal model for type 2 diabetes mellitus and metabolic syndrome. We investigated the effects of metformin and simvastatin on the ultrastructural characteristics of sciatic nerve fibers in these mice. Metformin treatment increased the number of structural defects of the myelin sheet surrounding these fibers in already affected nerves of HFD fed mice, and simvastatin treatment reduced these numbers to the levels seen in control mice. These results warrant further research on the effects of metformin and statins in patients developing diabetic neuropathy and advise caution when deciding about optimal treatment modalities in these patients.

[39] *Bloomer RJ, Schriefer JHM, Gunnels TA et al.* **Nutrient Intake and Physical Exercise Significantly Impact Physical Performance, Body Composition, Blood Lipids, Oxidative Stress, and Inflammation in Male Rats**. Nutrients 2018; 10.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30126091
ABSTRACT

BACKGROUND: Humans consuming a purified vegan diet known as the "Daniel Fast" realize favorable changes in blood lipids, oxidative stress, and inflammatory biomarkers, with subjective reports of improved physical capacity. OBJECTIVE: We sought to determine if this purified vegan diet was synergistic with exercise in male rats. METHODS: Long(-)Evans rats (n = 56) were assigned to be exercise trained (+E) by running on a treadmill three days per week at a moderate intensity or to act as sedentary controls with normal activity. After the baseline physical performance was evaluated by recording run time to exhaustion, half of the animals in each group were fed ad libitum for three months a purified diet formulated to mimic the Daniel Fast (DF) or a Western Diet (WD). Physical performance was evaluated again at the end of month 3, and body composition was assessed using dual-energy x-ray absorptiometry. Blood was collected for measurements of lipids, oxidative stress, and inflammatory biomarkers. RESULTS: Physical performance at the end of month 3 was higher compared to baseline for both exercise groups ($p < 0.05$), with a greater percent increase in the DF + E group (99%) than in the WD + E group (51%). Body fat was lower in DF than in WD groups at the end of month 3 ($p < 0.05$). Blood triglycerides, cholesterol, malondialdehyde, and advanced oxidation protein products were significantly lower in the DF groups than in the WD groups ($p < 0.05$). No significant differences were noted in cytokines levels between the groups ($p > 0.05$), although IL-1beta and IL-10 were elevated three-fold and two-fold in the rats fed the WD compared to the DF rats, respectively. CONCLUSIONS: Compared to a WD, a purified diet that mimics the vegan Daniel Fast provides significant anthropometric and metabolic benefits to rats, while possibly acting synergistically with exercise training to improve physical performance. These findings highlight the importance of macronutrient composition and quality in the presence of ad libitum food intake.

[40] *Picou F, Debeissat C, Bourgeais J et al.* **n-3 Polyunsaturated fatty acids induce acute myeloid leukemia cell death associated with mitochondrial glycolytic switch and Nrf2 pathway activation**. Pharmacological research : the official journal of the Italian Pharmacological Society 2018; 136:45-55.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30142422

ABSTRACT

Acute Myeloid Leukemia (AML) remains a therapeutic challenge and improvements in chemotherapy are needed. n-3 polyunsaturated fatty acids (PUFAs), present in fish oil (FO) at high concentrations, have antitumoral properties in various cancer models. We investigated the effects of two n-3 PUFAs, docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), in AML cell lines and primary AML blasts. EPA and DHA induced a dose-dependent decrease in cell viability in five AML cell lines, which was also observed with FO, but not SO (devoid of n-3 PUFAs) in cell lines and primary leucoblasts. Mitochondrial energy metabolism shifted from oxidative respiration to glycolytic metabolism in the U937, MOLM-13, and HL-60 cell lines. This phenomenon was associated with major disorganization of the mitochondrial network and mitochondrial swelling. Transcriptomic analysis after 6 h and 24 h of exposure to FO revealed a Nrf2 activation signature, which was confirmed by evidence of Nrf2 nuclear translocation in response to oxidative stress, but insufficient to prevent cell death following prolonged exposure. Apoptosis studies showed consistent phosphatidylserine exposition among the AML cell lines tested and a reduced mitochondrial membrane potential. The cell-killing effect of FO

was additive with that of cytarabine (AraC), by the Chou and Talalay method, and this combination effect could be reproduced in primary AML blasts. Altogether, our results show deleterious effects of n-3 PUFAs on mitochondrial metabolism of AML cells, associated with oxidative stress and Nrf2 response, leading to cell death. These observations support further investigation of n-3 PUFA addition to standard chemotherapy in AML.

[41] *Gummesson A, Stromberg U, Schmidt C et al.* **Non-alcoholic fatty liver disease is a strong predictor of coronary artery calcification in metabolically healthy subjects: A cross-sectional, population-based study in middle-aged subjects**. PloS one 2018; 13:e0202666.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30133541

ABSTRACT

OBJECTIVES: This study aims to estimate the relationship between non-alcoholic fatty liver disease (NAFLD) and measures of atherosclerotic cardiovascular disease (ASCVD), and to determine to what extent such relationships are modified by metabolic risk factors. METHODS: The study was conducted in the population-based Swedish CArdioPulmonary bioImage Study (SCAPIS) pilot cohort (n = 1015, age 50-64 years, 51.2% women). NAFLD was defined as computed tomography liver attenuation </=40 Hounsfield Units, excluding other causes of liver fat. Coronary artery calcification score (CACS) was assessed using the Agatston method. Carotid plaques and intima media thickness (IMT) were measured by ultrasound. Metabolic status was based on assessments of glucose homeostasis, serum lipids, blood pressure and inflammation. A propensity score model was used to balance NAFLD and non NAFLD groups with regards to potential confounders and associations between NAFLD status and ASCVD variables in relation to metabolic status were examined by logistic and generalized linear regression models. RESULTS: NAFLD was present in 106 (10.4%) of the subjects and strongly associated with obesity-related traits. NAFLD was significantly associated with CACS after adjustment for confounders and metabolic risk factors (OR 1.77, 95% CI 1.07-2.94), but not with carotid plaques and IMT. The strongest association between NAFLD and CACS was observed in subjects with few metabolic risk factors (n = 612 [60% of all] subjects with 0-1 out of 7 predefined metabolic risk factors; OR 5.94, 95% CI 2.13-16.6). CONCLUSIONS: NAFLD was independently associated with coronary artery calcification but not with measures of carotid atherosclerosis in this cohort. The association between NAFLD and CACS was most prominent in the metabolically healthy subjects.

[42] *Oda Y, Sasaki H, Miura T et al.* **Bone marrow stromal cells from low-turnover osteoporotic mouse model are less sensitive to the osteogenic effects of fluvastatin**. PloS one 2018; 13:e0202857.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30142209

ABSTRACT

This study aimed to investigate the effects of fluvastatin on the differentiation of bone marrow stromal cells (BMSCs) into osteoblasts in senescence-accelerated mouse prone 6 (SAMP6) compared with that in the normal senescence-accelerated-resistant mouse (SAMR1) model. SAMP strains arose spontaneously from the AKR/J background and display shortened life span and an array of signs of accelerated aging, compared with control SAMR strains. The dose effects of fluvastatin were also evaluated. BMSCs were cultured with/without fluvastatin (0

muM, 0.1 muM, 0.5 muM, and 1.0 muM). WST-1-based colorimetry was performed to evaluate cell proliferation. To evaluate cell differentiation, gene expression levels of bmp2 and runx2 were determined by quantitative reverse transcription polymerase chain reaction (qRT-PCR), and protein expression levels were determined using enzyme-linked immunosorbent assay (BMP2) and immunofluorescence staining (BMP2 and Runx2). Alkaline phosphatase (ALP) activity assay and histochemical detection were determined; the effect of noggin, a BMP-specific antagonist, was examined using ALP histochemical detection. To assess for mature osteogenic marker, gene expression levels of bglap2 were determined by qRT-PCR and mineralization was determined by alizarin red staining. RhoA activity was also examined by Western blotting. In SAMP6, BMP2, Runx2 and Bglap2 mRNA and protein expressions were significantly increased by fluvastatin, and ALP activity was increased by BMP2 action. RhoA activity was also inhibited by fluvastatin. The concentration of fluvastatin sufficient to increase BMP2 and Runx2 expression and ALP activity was 0.5 muM in SAMP6 and 0.1 muM in SAMR1. In conclusion, the present study revealed that fluvastatin promoted BMSC differentiation into osteoblasts by RhoA-BMP2 pathway in SAMP6. BMSCs of SAMP6 are less sensitive to the osteogenic effects of fluvastatin than SAMR1.

[43] *Rauca VF, Licarete E, Luput L et al.* **Combination therapy of simvastatin and 5, 6-dimethylxanthenone-4-acetic acid synergistically suppresses the aggressiveness of B16.F10 melanoma cells**. PloS one 2018; 13:e0202827.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30138430
ABSTRACT
The major drawback of current anti-angiogenic therapies is drug resistance, mainly caused by overexpression of the transcription factor, hypoxia-inducible factor 1alpha (HIF-1alpha) as a result of treatment-induced hypoxia, which stimulates cancer cells to develop aggressive and immunosuppressive phenotypes. Moreover, the cancer cell resistance to anti-angiogenic therapies is deeply mediated by the communication between tumor cells and tumor-associated macrophages (TAMs)-the most important microenvironmental cells for the coordination of all supportive processes in tumor development. Thus, simultaneous targeting of TAMs and cancer cells could improve the outcome of the anti-angiogenic therapies. Since our previous studies proved that simvastatin (SIM) exerts strong antiproliferative actions on B16.F10 murine melanoma cells via reduction of TAMs-mediated oxidative stress and inhibition of intratumor production of HIF-1alpha, we investigated whether the antitumor efficacy of the anti-angiogenic agent-5,6-dimethylxanthenone-4-acetic acid (DMXAA) could be improved by its co-administration with the lipophilic statin. Our results provide confirmatory evidence for the ability of the combined treatment to suppress the aggressive phenotype of the B16.F10 melanoma cells co-cultured with TAMs under hypoxia-mimicking conditions in vitro. Thus, proliferation and migration capacity of the melanoma cells were strongly decelerated after the co-administration of SIM and DMXAA. Moreover, our data suggested that the anti-oxidant action of the combined treatment, as a result of melanogenesis stimulation, might be the principal cause for the simultaneous suppression of key molecules involved in melanoma cell aggressiveness, present in melanoma cells (HIF-1alpha) as well as in TAMs (arginase-1). Finally, the concomitant suppression of these proteins might have contributed to a very strong inhibition of the angiogenic capacity of the cell co-culture microenvironment.

[44] *Gunduz C, Basoglu OK, Hedner J et al.* **Obstructive sleep apnoea independently predicts lipid levels: Data from the European Sleep Apnea Database**. Respirology (Carlton, Vic.) 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30133061

ABSTRACT

BACKGROUND AND OBJECTIVE: Obstructive sleep apnoea (OSA) and dyslipidaemia are independent risk factors for cardiovascular disease. This study investigates the association between OSA and plasma lipid concentrations in patients enrolled in the European Sleep Apnea Database (ESADA) cohort. METHODS: The cross-sectional analysis included 8592 patients without physician-diagnosed hyperlipidaemia or reported intake of a lipid-lowering drug (age 50.1 +/- 12.7 years, 69.1% male, BMI: 30.8 +/- 6.6 kg/m(2) , mean apnoea-hypopnoea index (AHI): 25.7 +/- 25.9 events/h). The independent relationship between measures of OSA (AHI, oxygen desaturation index (ODI), mean and lowest oxygen saturation) and lipid profile (total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) and fasting triglycerides (TG)) was determined by means of general linear model analysis. RESULTS: There was a dose response relationship between TC and ODI (mean +/- SE (mg/dL): 180.33 +/- 2.46, 184.59 +/- 2.42, 185.44 +/- 2.42 and 185.73 +/- 2.44; P < 0.001 across ODI quartiles I-IV). TG and LDL concentrations were better predicted by AHI than by ODI. HDL-C was significantly reduced in the highest AHI quartile (mean +/- SE (mg/dL): 48.8 +/- 1.49 vs 46.50 +/- 1.48; P = 0.002, AHI quartile I vs IV). Morbid obesity was associated with lower TC and higher HDL-C values. Lipid status was influenced by geographical location with the highest TC concentration recorded in Northern Europe. CONCLUSION: OSA severity was independently associated with cholesterol and TG concentrations.

[45] *Roughead EE, Kim DS, Ong B, Kemp-Casey A*. **Pricing policies for generic medicines in Australia, New Zealand, the Republic of Korea and Singapore: patent expiry and influence on atorvastatin price**. WHO South-East Asia journal of public health 2018; 7:99-106.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30136668

ABSTRACT

Background: Little is known about how the different policies available to promote use of generic medicines affect the price per unit supplied or sold. This study compares the influence of pricing policies for generic medicines on atorvastatin prices in Australia, New Zealand, the Republic of Korea and Singapore, after market entry of generic atorvastatin. Methods: The annual price of atorvastatin per defined daily dose supplied (price/DDD) was examined for each country from 2006 to 2015 (>/=2 years before and >/=4 years after generic market entry). Prices were converted to international dollars and cumulative percentage price reductions were calculated for the first 4 years following generic entry. Results: Prior to market entry of generic atorvastatin, New Zealand had the lowest price ($0.10/DDD), and the Republic of Korea the highest ($2.89/DDD). The price/DDD fell immediately after generic entry in all countries except New Zealand, which already had low prices. The largest immediate decrease was observed in Singapore (46%, year 1). By the fourth year after generic entry, the price had fallen by 46-80% in all countries; however, large price differences between countries remained. Conclusion: New Zealand's tendering system and use of preferred medicines resulted in very low atorvastatin prices well before patent expiry. Pricing policies in the other three countries were effective in

reducing atorvastatin prices, with reductions of between 46% and 80% within 4 years of generic entry. Where tendering and use of preferred medicines were the mechanisms for atorvastatin procurement (New Zealand), prices were lowest before and after generic entry. Mandatory price cuts, combined with price-disclosure policies (Australia), produced similar relative price reductions to tendering systems (New Zealand, Singapore) at 4 years. By comparison, mandatory price cuts upon generic entry as the sole measure, while initially effective, were associated with the smallest relative reduction in price after 4 years (Republic of Korea).