Literature update week 11 (2018)

[1] *Kowalska K, Habrowska-Gorczynska DE, Neumayer C et al.* **Lower levels of Caveolin-1 and higher levels of endothelial nitric oxide synthase are observed in abdominal aortic aneurysm patients treated with simvastatin**. Acta biochimica Polonica 2018; 65:111-118.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29549671
ABSTRACT
This study was undertaken to verify whether simvastatin modulates Cav-1/eNOS expression, and if this modulation is associated with changes in pro- and anti-inflammatory cytokine and Toll-like receptor 4 (TLR4) level in abdominal aortic aneurysm (AAA). It is a 1:2 case-control study of non-statin (n=12) and simvastatin-treated patients (n=24) who underwent open AAA repair. Simvastatin treatment decreased Cav-1 ($p<0.05$) and increased eNOS expression ($p<0.01$) in the AAA wall. These changes might be dose dependent. The changes in Cav-1 and eNOS were associated with a trend towards decreased IL-6 and IL-17 concentration ($p>0.05$) and increased IL-10 concentration ($p=0.055$); however, TLR4 expression was unaffected, suggesting that simvastatin influences Cav-1 and eNOS in the AAA wall by other mechanisms. Simvastatin may modulate Cav-1 and eNOS expression in the aneurysmal wall, indicating a potentially beneficial role for statins in AAA patients.

[2] *Karalis DG, Mallya UG, Ghannam AF et al.* **Prescribing Patterns of Proprotein Convertase Subtilisin-Kexin Type 9 Inhibitors in Eligible Patients With Clinical Atherosclerotic Cardiovascular Disease or Heterozygous Familial Hypercholesterolemia**. The American journal of cardiology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29548678
ABSTRACT
Two proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors are approved for patients with atherosclerotic cardiovascular disease or heterozygous familial hypercholesterolemia who require additional low-density lipoprotein cholesterol (LDL-C) lowering. This retrospective study sought to determine differences between eligible patients who were prescribed and those who were not prescribed a PCSK9 inhibitor. Patients from an electronic medical record database were included in the analysis, and their demographic, clinical, and treatment characteristics were evaluated. Of 368,624 PCSK9 inhibitor-eligible patients, 1,752 (<0.5%) received a PCSK9 inhibitor prescription. Patients who received a PCSK9 inhibitor were more frequently associated with a higher cardiovascular disease risk category and a higher baseline LDL-C level (139.4 vs 103.5 mg/dl; $p <0.0001$) compared with those who did not. Patients with a PCSK9 inhibitor prescription were significantly more likely to be on ezetimibe, alone or in combination with a statin, at baseline compared with those without (29% vs 5%; $p <0.0001$). The use of a PCSK9 inhibitor was very low in the 2 groups of patients identified as PCSK9 inhibitor-eligible based on the American College of Cardiology Expert Consensus Decision Pathway. In conclusion, this study demonstrates that most PCSK9 inhibitor-eligible patients do not receive a PCSK9 inhibitor prescription, highlighting that many high-risk patients could benefit from additional LDL-C lowering with a PCSK9 inhibitor.

[3] *Olkkonen VM, Sinisalo J, Jauhiainen M*. **New medications targeting triglyceride-rich lipoproteins: Can inhibition of ANGPTL3 or apoC-III reduce the residual cardiovascular risk?** Atherosclerosis 2018; 272:27-32.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29544086

ABSTRACT

Remarkably good results have been achieved in the treatment of atherosclerotic cardiovascular diseases (CVD) by using statin, ezetimibe, antihypertensive, antithrombotic, and PCSK9 inhibitor therapies and their proper combinations. However, despite this success, the remaining CVD risk is still high. To target this residual risk and to treat patients who are statin-intolerant or have an exceptionally high CVD risk for instance due to familial hypercholesterolemia (FH), new therapies are intensively sought. One pathway of drug development is targeting the circulating triglyceride-rich lipoproteins (TRL) and their lipolytic remnants, which, according to the current view, confer a major CVD risk. Angiopoietin-like protein 3 (ANGPTL3) and apolipoprotein C-III (apoC-III) are at present the central molecular targets for therapies designed to reduce TRL, and there are new drugs emerging that suppress their expression or inhibit the function of these two key proteins. The medications targeting these components are biological, either human monoclonal antibodies or antisense oligonucleotides. In this article, we briefly review the mechanisms of action of ANGPTL3 and apoC-III, the reasons why they have been considered promising targets of novel therapies for CVD, as well as the current status and the most important results of their clinical trials.

[4] *Sheikh-Hasani V, Babaei M, Azadbakht A et al.* **Atorvastatin treatment softens human red blood cells: an optical tweezers study**. Biomedical optics express 2018; 9:1256-1261.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29541518

ABSTRACT

Optical tweezers are proven indispensable single-cell micro-manipulation and mechanical phenotyping tools. In this study, we have used optical tweezers for measuring the viscoelastic properties of human red blood cells (RBCs). Comparison of the viscoelastic features of the healthy fresh and atorvastatin treated cells revealed that the drug softens the cells. Using a simple modeling approach, we proposed a molecular model that explains the drug-induced softening of the RBC membrane. Our results suggest that direct interactions between the drug and cytoskeletal components underlie the drug-induced softening of the cells.

[5] *Tauriainen MM, Mannisto V, Kaminska D et al.* **Serum, liver and bile sitosterol and sitostanol in obese patients with and without NAFLD**. Bioscience reports 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29540533

ABSTRACT

Background & aims : Non-alcoholic fatty liver disease (NAFLD) associates with low levels of serum plant sterols in cross-sectional studies. However, parenterally given plant sterols may lead to liver injury. In addition, it has been suggested that the hepatic sterol transport mechanisms are altered in NAFLD. Therefore, we investigated the association between serum, liver and bile plant sterols and sitostanol with NAFLD. Methods : Out of the 138 individuals (age: 46.3+/-8.9, BMI: 43.3+/-6.9 kg/m(2), 28% men and 72% women), 44 could be histologically categorized to have normal liver, and 94 to have NAFLD. Within the NAFLD group, 28 had simple steatosis and 27 had non-alcoholic steatohepatitis (NASH). Plant sterols and sitostanol were measured from serum (n=138), liver (n=38) and bile (n=41). The mRNA expression of genes regulating liver sterol metabolism and inflammation was measured (n=102). Results :

Liver and bile sitostanol ratios to cholesterol were higher in those with NAFLD compared to those with histologically normal liver (all P<0.022). Furthermore, liver sitostanol to cholesterol ratio correlated positively with histological steatosis and lobular inflammation (rs>0.407, Ps=-0.392, P=0.015) and lobular inflammation (rs=-0.395, P=0.014). Transcriptomics analysis revealed suggestive correlations between serum plant sterol levels and mRNA expression. Conclusion : Our study showed that high liver and bile sitostanol ratios to cholesterol and low liver sitosterol ratio to cholesterol associate with liver steatosis and inflammation in obese individuals with NAFLD.

[6] *Palmer M, Jennings L, Silberg DG et al.* **A randomised, double-blind, placebo-controlled phase 1 study of the safety, tolerability and pharmacodynamics of volixibat in overweight and obese but otherwise healthy adults: implications for treatment of non-alcoholic steatohepatitis**. BMC pharmacology & toxicology 2018; 19:10.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29548345

ABSTRACT

BACKGROUND: Accumulation of toxic free cholesterol in hepatocytes may cause hepatic inflammation and fibrosis. Volixibat inhibits bile acid reuptake via the apical sodium bile acid transporter located on the luminal surface of the ileum. The resulting increase in bile acid synthesis from cholesterol could be beneficial in patients with non-alcoholic steatohepatitis. This adaptive dose-finding study investigated the safety, tolerability, pharmacodynamics, and pharmacokinetics of volixibat. METHODS: Overweight and obese adults were randomised 3:1 to double-blind volixibat or placebo, respectively, for 12 days. Volixibat was initiated at a once-daily dose of 20 mg, 40 mg or 80 mg. Based on the assessment of predefined safety events, volixibat dosing was either escalated or reduced. Other dose regimens (titrations and twice-daily dosing) were also evaluated. Assessments included safety, tolerability, stool hardness, faecal bile acid (FBA) excretion, and serum levels of 7alpha-hydroxy-4-cholesten-3-one (C4) and lipids. RESULTS: All 84 randomised participants (volixibat, 63; placebo, 21) completed the study, with no serious adverse events at doses of up to 80 mg per day (maximum assessed dose). The median number of daily bowel evacuations increased from 1 (range 0-4) to 2 (0-8) during volixibat treatment, and stool was looser with volixibat than placebo. Volixibat was minimally absorbed; serum levels were rarely quantifiable at any dose or sampling time point, thereby precluding pharmacokinetic analyses. Mean daily FBA excretion was 930.61 mumol (standard deviation [SD] 468.965) with volixibat and 224.75 mumol (195.403) with placebo; effects were maximal at volixibat doses >/=20 mg/day. Mean serum C4 concentrations at day 12 were 98.767 ng/mL (standard deviation, 61.5841) with volixibat and 16.497 ng/mL (12.9150) with placebo. Total and low-density lipoprotein cholesterol levels decreased in the volixibat group, with median changes of - 0.70 mmol/L (range - 2.8 to 0.4) and - 0.6990 mmol/L (- 3.341 to 0.570), respectively. CONCLUSIONS: This study indicates that maximal inhibition of bile acid reabsorption, as assessed by FBA excretion, occurs at volixibat doses of >/=20 mg/day in obese and overweight adults, without appreciable change in gastrointestinal tolerability. These findings guided dose selection for an ongoing phase 2 study in patients with non-alcoholic steatohepatitis. TRIAL REGISTRATION: ClinicalTrials.gov identifier: NCT02287779 (registration first received 6 November 2014).

[7] *Zahr RS, Chappa P, Yin H et al.* **Renal protection by atorvastatin in a murine model of sickle cell nephropathy**. British journal of haematology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29527679
ABSTRACT
Recent studies have demonstrated pleiotropic effects of statins in various mouse models of kidney disease. In this study, Townes humanized sickle cell mice were treated for 8 weeks with atorvastatin at a dose of 10 mg/kg/day starting at 10 weeks of age. Treatment with atorvastatin significantly reduced albuminuria, and improved both urine concentrating ability and glomerular filtration rate. Atorvastatin also decreased markers of kidney injury and endothelial activation, and ameliorated oxidant stress in renal tissues and peripheral macrophages. Atorvastatin downregulated the expression of mRNA levels of the NADPH oxidases, Cybb (also termed Nox2) and Nox4, which are major sources of oxidant stress in the kidney. These findings highlight the pleiotropic effects of atorvastatin and suggest that it may provide beneficial effects in sickle cell nephropathy.

[8] *Yasar M, Erdi I, Kaya B*. **The preventive effects of atorvastatin and N-acetyl cysteine in experimentally induced ischemia-reperfusion injury in rats**. Bratislavske lekarske listy 2018; 119:167-174.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29536746
ABSTRACT
AIM: We investigated the effects of atorvastatin and N-acetyl cysteine in decreasing ischemia-reperfusion damage after detorsion of a volvulus of the cecum and ascending colon. METHODS: Wistar albino rats (250-300 g) were divided into four groups. A cecal-ascending colon volvulus was created by the intestinal clockwise 720 degrees rotation. At the end of one hour, the bowel was detorsioned. Group I (n = 7) was the sham (laparotomy) group, Group II (n = 7) the control (no treatment, volvulus or detorsion), Group III (n = 7) (N-acetyl cysteine administered) , and Group IV (n = 7) (atorvastatin administered) group. Blood samples were collected from each group via peripheral veins and centrifuged one hour after detorsion. The parameters of ischemia including malondialdehyde, glutathione peroxidase, catalase, and superoxide dismutase were then observed in the serous fluid. RESULTS: Malondialdehyde and superoxide dismutase increased in the control group, whereas they were reduced in the Group III and Group IV ($p = 0.005$; $p = 0.008$, respectively). The glutathione peroxidase levels revealed no significant differences ($p > 0.05$), whereas the catalase levels of the group III was higher than in each of the other three groups ($p < 0.001$). Histopathological evaluation detected reduced lesioning of the organ in the groups which were given atorvastatin and N-acetyl cysteine. CONCLUSION: Atorvastatin and of N-acetyl cysteine have a similar preventive effect in experimental ischemia-reperfusion injury (Tab. 8, Fig. 6, Ref. 24).

[9] *Wang JC, Li XX, Sun X et al.* **Activation of AMPK by simvastatin inhibited breast tumor angiogenesis via impeding HIF-1alpha-induced pro-angiogenic factor**. Cancer science 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29532562
ABSTRACT
Substantial data from preclinical studies have revealed the biphasic effects of statins on cardiovascular angiogenesis. Although some have reported the anti-angiogenic potential of

statins in malignant tumors, however, the underlying mechanism remains poorly understood. The aim of this study is to elucidate the mechanism by which simvastatin, a member of the statin family, inhibits tumor angiogenesis. Simvastatin significantly suppressed tumor cells-conditioned medium (TCM)-induced angiogenic promotion in vitro, and resulted in a dose-dependent anti-angiogenesis in vivo. Further genetic silencing of HIF-1alpha reduced VEGF and FGF-2 expressions in 4T1 cells and correspondingly ameliorated HUVECs proliferation facilitated by TCM. Additionally, simvastatin induced angiogenic inhibition via a mechanism of post-transcriptional down-regulation of HIF-1alpha by increasing phosphorylation level of AMP kinase (AMPK). These results were further validated by the fact that AICAR reduced HIF-1alpha protein level and ameliorated the angiogenic ability of endothelial cells in vitro and in vivo. Critically, inhibition of AMPK phosphorylation by compound C almost completely abrogated simvastatin-induced anti-angiogenesis, which was accompanied by the reduction of protein levels of HIF-1alpha and its downstream pro-angiogenic factors. These findings demonstrate the mechanism in which simvastatin induces tumor anti-angiogenesis, and therefore identify the target that explains the beneficial effects of statins on malignant tumors.

[10] *Demir V, Dogru MT, Ede H et al.* **The effects of treatment with atorvastatin versus rosuvastatin on endothelial dysfunction in patients with hyperlipidaemia**. Cardiovasc J Afr 2018; 29:1-5.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29528361

ABSTRACT

INTRODUCTION: Statins can reduce cardiovascular events and improve endothelial function. However, differences in the effect of statins on endothelial dysfunction have not been researched sufficiently. Here, we aimed to compare the effects of atorvastatin versus rosuvastatin on endothelial function via flow-mediated and endothelial-independent dilation. METHODS: Hyperlipidaemic subjects on treatment with statins for one year (either 20 mg/day atorvastatin or 10 mg/day rosuvastatin) were enrolled in the study. In accordance with the literature, flow-mediated dilation (FMD) and nitrate-mediated endothelium-independent dilation (EID) were measured by ultrasonography on the right brachial artery of each subject. Baseline and final measurements were compared in each group and between the groups. RESULTS: One hundred and four subjects (50 atorvastatin and 54 rosuvastatin users) were enrolled in the study. Fifty-eight subjects were female. The groups were statistically similar in terms of age and body mass index, and haemoglobin, creatinine, total cholesterol, triglyceride, high-density lipoprotein and low-density lipoprotein cholesterol levels. In each group, the mean final FMD and EID values were higher compared to their respective baseline values, but the mean changes in FMD and EID were statistically similar in both groups ($p = 0.958$ for FMD and 0.827 for EID). There was no statistically significant difference between the atorvastatin and rosuvastatin groups in terms of final FMD and EID values ($p = 0.122$ and 0.115, respectively). CONCLUSIONS: This study demonstrated that both one-year atorvastatin and rosuvastatin treatments significantly improved endothelial function, when assessed with FMD and EID and measured by ultrasonography. However, the amount of improvement in endothelial dysfunction was similar in the two treatments.

Literature update week 11 (2018)

[11] *Lestiani L, Chandra DN, Laitinen K et al.* **Double-Blind Randomized Placebo Controlled Trial Demonstrating Serum Cholesterol Lowering Efficacy of a Smoothie Drink with Added Plant Stanol Esters in an Indonesian Population**. Cholesterol 2018; 2018:4857473.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29535869
ABSTRACT
Indonesians have a high intake of saturated fats, a key contributing dietary factor to elevated blood cholesterol concentrations. We investigated the cholesterol lowering efficacy of a smoothie drink with 2 grams of plant stanols as esters to lower serum total and LDL-cholesterol concentrations in hypercholesterolemic Indonesian adults. The double-blind randomized placebo controlled parallel design study involved 99 subjects. Fifty subjects received control drink and dietary advice, and 49 subjects received intervention drink (Nutrive Benecol(R)) and dietary advice. Baseline, midline (week 2), and endline (week 4) assessments were undertaken for clinical, anthropometric, and biochemical variables. Compared to control, the smoothie drink with plant stanols reduced serum LDL-cholesterol concentration by 7.6% ($p < 0.05$) and 9.0% ($p < 0.05$) in two and four weeks, respectively. Serum total cholesterol was reduced by 5.7% ($p < 0.05$ compared to control) in two weeks, and no further reduction was detected after four weeks (5.6%). Compared to baseline habitual diet, LDL-cholesterol was reduced by 9.3% ($p < 0.05$) and 9.8% ($p < 0.05$) in the plant stanol ester group in two and four weeks, respectively. We conclude that consumption of smoothie drink with added plant stanol esters effectively reduces serum total and LDL-cholesterol of hypercholesterolemic Indonesian subjects already in two weeks. Trial is registered as NCT02316808.

[12] *Kataoka Y*. **Obstacles to Optimal Lipid-Lowering Therapy- Any Solution?** Circulation journal : official journal of the Japanese Circulation Society 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29526987
ABSTRACT

[13] *Menni C, Gudelj I, MacDonald-Dunlop E et al.* **Glycosylation Profile of Immunoglobulin G Is Cross-Sectionally Associated with Cardiovascular Disease Risk Score and Subclinical Atherosclerosis in Two Independent Cohorts**. Circulation research 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29535164
ABSTRACT
Rationale: One measure of protein glycosylation (GlycA) has been reported to predict higher cardiovascular risk by reflecting inflammatory pathways Objective: To assess the role of a comprehensive panel of immunoglobulin (IgG) glycosylation traits on traditional risk factors for cardiovascular disease and on presence of subclinical atherosclerosis in addition to GlycA. Methods and Results: We measured 76 IgG glycosylation traits in 2970 women (age range 40-79 years) from the TwinsUK cohort and correlated it to their estimated 10-year atherosclerotic cardiovascular disease (ASCVD) risk score and their carotid and femoral plaque measured by ultrasound imaging. Eight IgG glycan traits are associated with the 10-year ASCVD risk score after adjusting for multiple tests and for individual risk factors - 5 with increased risk and 3 with decreased risk. These glycans replicated in 967 women from ORCADES cohort, six of them were also associated in 845 men. A linear combination of IgG glycans and GlycA is also associated with presence of carotid (OR[95%CI]=1.55 [1.25;1.93], P=7.5X10-5) and femoral

(OR[95%CI]==1.32[1.06;1.64], P=0.01) plaque in a subset of women with atherosclerosis data after adjustment for traditional risk factors. One specific glycosylation trait, GP18 was negatively correlated with VLDL and triglyceride levels in serum and with presence of carotid plaque (OR[95%CI] = 0.60[0.50;0.71], P = 5x10(-4)). Conclusions: We find molecular pathways linking IgG to arterial lesion formation. Glycosylation traits are independently associated with subclinical atherosclerosis. One specific trait related to the sialylated N-glycan is negatively correlated with CVD risk, VLDL and triglyceride serum levels and presence of carotid plaque.

[14] *Bohula EA, Giugliano RP, Leiter LA et al.* **Inflammatory and Cholesterol Risk in the FOURIER Trial (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Patients With Elevated Risk)**. Circulation 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29530884
ABSTRACT
BACKGROUND : In the FOURIER trial (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Patients With Elevated Risk), the PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitor evolocumab reduced low-density lipoprotein cholesterol (LDL-C) and cardiovascular risk. It is not known whether the efficacy of evolocumab is modified by baseline inflammatory risk. We explored the efficacy of evolocumab stratified by baseline high-sensitivity C-reactive protein (hsCRP). We also assessed the importance of inflammatory and residual cholesterol risk across the range of on-treatment LDL-C concentrations. METHODS : Patients (n=27564) with stable atherosclerotic cardiovascular disease and LDL-C >/=70 mg/dL on a statin were randomly assigned to evolocumab versus placebo and followed for a median of 2.2 years (1.8-2.5). The effects of evolocumab on the primary end point of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina or coronary revascularization, and the key secondary end point of cardiovascular death, myocardial infarction, or stroke were compared across strata of baseline hsCRP (<1, 1-3, and >3 mg/dL). Outcomes were also assessed across values for baseline hsCRP and 1-month LDL-C in the entire trial population. Multivariable models adjusted for variables associated with hsCRP and 1-month LDL-C were evaluated. RESULTS : A total of 7981 (29%) patients had a baseline hsCRP<1 mg/L, 11177 (41%) had a hsCRP 1 to 3 mg/L, and 8337 (30%) had a hsCRP >3 mg/L. Median (interquartile range) baseline hsCRP was 1.8 (0.9-3.6) mg/L and levels were not altered by evolocumab (change at 48 weeks of -0.2 mg/dL [-1.0 to 0.4] in both treatment arms). In the placebo arm, patients in higher baseline hsCRP categories experienced significantly higher 3-year Kaplan-Meier rates of the primary and key secondary end points: 12.0%, 13.7%, and 18.1% for the primary end point (Ptrend<0.0001) and 7.4%, 9.1%, and 13.2% for the key secondary end point (Ptrend<0.0001) for categories of <1, 1 to 3, and >3 mg/dL, respectively. The relative risk reductions for the primary end point and key secondary end point with evolocumab were consistent across hsCRP strata (P-interactions>0.15 for both). In contrast, the absolute risk reductions with evolocumab tended to be greater in patients with higher hsCRP: 1.6%, 1.8%, and 2.6% and 0.8%, 2.0%, and 3.0%, respectively, for the primary and key secondary end points across hsCRP strata. In adjusted analyses of the association between LDL-C and hsCRP levels and cardiovascular risk, both LDL-C and hsCRP were independently associated with the primary outcome (P<0.0001 for each). CONCLUSIONS : LDL-C reduction with evolocumab reduces cardiovascular events across hsCRP strata with greater absolute risk reductions in patients with higher-baseline hsCRP. Event

rates were lowest in patients with the lowest hsCRP and LDL-C. CLINICAL TRIAL REGISTRATION : URL: https://www.clinicaltrials.gov. Unique identifier: NCT01764633.

[15] *Okereke OI, Reynolds CF, 3rd, Mischoulon D et al.* **The VITamin D and OmegA-3 TriaL-Depression Endpoint Prevention (VITAL-DEP): Rationale and design of a large-scale ancillary study evaluating vitamin D and marine omega-3 fatty acid supplements for prevention of late-life depression**. Contemporary clinical trials 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29526608
ABSTRACT
RATIONALE: Depression is a leading cause of disease burden and disability for older adults; thus, prevention is a priority. Biologic and observational data support potential mental health benefits of vitamin D and omega-3 fatty acids; however, it is unclear whether these supplements can prevent late-life depression. DESIGN: We describe the novel methodology of a large-scale prevention study: VITAL-DEP (VITamin D and OmegA-3 TriaL-Depression Endpoint Prevention), an ancillary to the VITAL trial. Using long-term (mean=5years) supplementation with vitamin D (vitamin D3 [cholecalciferol], 2000IU/day) and marine omega-3 fatty-acids (eicosapentaenoic acid+docosahexaenoic acid, 1g/day) in a 2x2 factorial design among 25,874 older adults, VITAL-DEP will determine these agents' effects on prevention of depression and on trajectory of mood symptoms. Furthermore, using pre-randomization blood samples collected in ~17,000 participants VITAL-DEP will address whether baseline blood levels of the nutrients and other biomarkers influence depression risk and/or modify treatment effects. Finally, VITAL-DEP will test impacts of vitamin D on depression risk among African-Americans (an at-risk group for vitamin D deficiency), and of both agents among those with high-risk factors or sub-syndromal symptoms in a sub-set of ~1000 participants with detailed in-person examinations at baseline and 2-year follow-up. CONCLUSION: VITAL-DEP applies all modalities of state-of-the-art prevention research - universal, selective and indicated. VITAL-DEP will clarify the effect of supplemental vitamin D and/or omega-3 FAs on mood outcomes, and inform clinical care and public health guidelines on the use of these agents for the prevention of depression in mid-life and older adults.

[16] *Khan S, Khan I, Novak M et al.* **The Concomitant Use of Atorvastatin and Amlodipine Leading to Rhabdomyolysis**. Cureus 2018; 10:e2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29531873
ABSTRACT
A 65-year-old man, with a history of hypertension and hyperlipidemia, presented with intractable lower back pain, shortness of breath, and decreasing urine output at the emergency room and was admitted after he was found to have elevated creatinine kinase levels of greater than 160,000 U/L. We discontinued all his home medications, which included atorvastatin and amlodipine. We trended his creatine phosphokinase (CPK) level daily and noticed it decreasing significantly off these meds. We hydrated him with normal saline and monitored his kidney functions. By the time he was ready for discharge, his CPK levels were back to normal. This case report summarizes the drug-drug interactions of atorvastatin and amlodipine.

Literature update week 11 (2018)

[17] *Karagiannis AD, Liu M, Toth PP et al.* **Pleiotropic Anti-atherosclerotic Effects of PCSK9 InhibitorsFrom Molecular Biology to Clinical Translation**. Current atherosclerosis reports 2018; 20:20.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29525934
ABSTRACT
PURPOSE OF REVIEW: Clinical trials with PCSK9 inhibitors have shown a robust decrease in plasma LDL levels and a significant reduction in the incidence of cardiovascular atherosclerotic events. However, the role of PCSK9 in atherosclerosis is not well investigated and it remains unclear whether PCSK9 inhibition has direct, LDL-independent, anti-atherosclerotic effects. This review outlines the molecular pathways and targets of PCSK9 in atherosclerosis and summarizes the experimental and clinical data supporting the anti-atherosclerotic (pleiotropic) actions of PCSK9 inhibitors. RECENT FINDINGS: PCSK9 is expressed by various cell types that are involved in atherosclerosis (e.g., endothelial cell, smooth muscle cell, and macrophage) and is detected inside human atherosclerotic plaque. Preclinical studies have shown that inhibition of PCSK9 can attenuate atherogenesis and plaque inflammation. Besides increasing plasma LDL, PCSK9 appears to promote the initiation and progression of atherosclerosis. Inhibition of PCSK9 may confer atheroprotection that extends beyond its lipid-lowering effects.

[18] *Nascimento RD, Guerra Jnr AA, Alvares J et al.* **Statin use in Brazil: findings and implications**. Current medical research and opinion 2018:1-21.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29528246
ABSTRACT
INTRODUCTION AND OBJECTIVES: Stains have become an integral part of treatment to reduce cardiac events in patients with cardiovascular disease. However, their use within the public healthcare system in Brazil is unknown. Consequently, we sought to determine and characterize statin use in primary healthcare delivered by the public health system (SUS) in Brazil and evaluate associated patient factors to improve future use. METHODS: Cross-sectional study with a national representative sample from five Brazilian regions, derived from the National Survey on Access, Use and Promotion of Rational Use of Medicines using a multi-stage complex sampling plan. Patients over 18 years old were interviewed from July/2014 to May/2015. Prevalence of statin use and statins' self-reported adherence were determined amongst medicine users. The association between statin use and sociodemographic/health condition variables were assessed using logistic regression. RESULTS: 8,803 patients were interviewed; of which, 6,511 were medicines users. The prevalence of statins use was 9.4% with simvastatin (90.3%), atorvastatin (4.7%) and rosuvastatin (1.9%) the most used statins. Poor adherence was described by 6.5% of patients. Statins use was significantly associated with age >/=65 years old, higher educational level, residence in the South, metabolic and heart diseases, alcohol consumption and polypharmacy. CONCLUSIONS: This is the first population based study in Brazil to assess statin use in SUS primary healthcare patients. Addressing inequalities in access and use of medicines including statins is an important step in achieving the full benefit of statins in Brazil, with the findings guiding future research and policies.

[19] *Ramms B, Gordts P*. **Apolipoprotein C-III in triglyceride-rich lipoprotein metabolism**. Current opinion in lipidology 2018.

Literature update week 11 (2018)

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29547399

ABSTRACT

PURPOSE OF REVIEW: Apolipoprotein (apo) C-III is a key player in triglyceride-rich lipoprotein metabolism and strongly associated with elevated plasma triglyceride levels. Several new studies added important insights on apoC-III and its physiological function confirming its promise as a valid therapeutic target. RECENT FINDINGS: APOC3 is expressed in liver and intestine and regulates triglyceride-rich lipoprotein (TRL) catabolism and anabolism. The transcriptional regulation in both organs requires different regulatory elements. Clinical and preclinical studies established that apoC-III raises plasma triglyceride levels predominantly by inhibiting hepatic TRL clearance. Mechanistic insights into missense variants indicate accelerated renal clearance of apoC-III variants resulting in enhanced TRL catabolism. In contrast, an APOC3 gain-of-function variant enhances de novo lipogenesis and hepatic TRL production. Multiple studies confirmed the correlation between increased apoC-III levels and cardiovascular disease. This has opened up new therapeutic avenues allowing targeting of specific apoC-III properties in triglyceride metabolism. SUMMARY: Novel in vivo models and APOC3 missense variants revealed unique mechanisms by which apoC-III inhibits TRL catabolism. Clinical trials with Volanesorsen, an APOC3 antisense oligonucleotide, report very promising lipid-lowering outcomes. However, future studies will need to address if acute apoC-III lowering will have the same clinical benefits as a life-long reduction.

[20] *Fernandez ML, Thomas MS, Lemos BS et al.* **TA-65, A Telomerase Activator, Improves Cardiovascular Markers in Patients with Metabolic Syndrome**. Current pharmaceutical design 2018.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29546832

ABSTRACT

BACKGROUND: Telomerase Activator 65 (TA-65), a compound extracted from Astragalus membranaceus has been used in Chinese traditional medicine for extending life span. Scarce information exists on the effects of TA-65 on parameters of metabolic syndrome (MetS). METHODS: We recruited 40 patients with MetS to determine the effects of TA-65 on dyslipidemias, hypertension, and oxidative stress in this at-risk population. The study was a double-blind, randomized crossover design in which patients were allocated to consume either 16 mg daily of a TA-65 supplement or a placebo for 12 weeks. Following a 3-week washout, participants were allocated to the alternate treatment for an additional 12 weeks. Anthropometric and biological markers were measured at the end of each treatment. Plasma lipids, glucose, C-reactive protein (CRP), liver enzymes, and glycosylated hemoglobin were measured using a Cobas c-111. Inflammatory cytokines were measured by Luminex technology and markers of oxidative stress by use of spectroscopy. RESULTS: Compared to the placebo period, HDL cholesterol (HDL-C) was higher while body mass index, waist circumference, and the LDL/HDL ratio were lower ($p < 0.05$) during TA-65 treatment. In addition, plasma tumor necrosis factor-alpha (TNF-alpha) was lower during the TA-65 period ($p< 0.05$). Positive correlations were observed in changes between the placebo and the TA-65 periods in HDL-C and CRP ($r = -0.511$, $p < 0.01$), alanine aminotransferase ($r = -0.61$, $p < 0.001$) and TNF-alpha ($r = -0.550$, $p < 0.001$) suggesting that the favorable changes observed in HDL were associated with

decreases in inflammation. CONCLUSION: TA-65 improved key markers of cardiovascular disease risk, which were also associated with reductions in inflammation.

[21] *Posadas-Sanchez R, Angeles-Martinez J, Perez-Hernandez N et al.* **The IL-10-1082 (rs1800896) G allele is associated with a decreased risk of developing premature coronary artery disease and some IL-10 polymorphisms were associated with clinical and metabolic parameters. The GEA study**. Cytokine 2018; 106:12-18.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29525679
ABSTRACT
Interleukin 10 (IL-10) is an anti-inflammatory cytokine with a protective role in the formation and the development of the atherosclerotic plaque. The aim of the present study was to establish if IL-10 gene polymorphisms are associated with the development of premature coronary artery disease (pCAD) and cardiovascular risk factors in Mexican individuals. Three IL-10 gene polymorphisms [-592C/A (rs1800872), -819C/T (rs1800871), and -1082 A/G (rs1800896)] and IL-10 plasma levels were analyzed in 2266 individuals (1160 pCAD patients and 1106 healthy controls). Under recessive and co-dominant2 models, the -1082 A/G (rs1800896) G allele was associated with decreased risk of developing pCAD (OR=0.572, Prec=0.022 and OR=0.567, Pcod2=0.023). In pCAD patients, the polymorphisms were associated with hyperinsulinemia, small and dense LDLs, hypertension, and diabetes mellitus. In the control group, the polymorphisms were associated with hypertension, hyperuricemia, and small and dense LDLs. pCAD patients have significantly higher IL-10 plasma levels than healthy controls [0.91 (0.55-1.67) pg/mL vs 0.45 (0.24-0.98) pg/mL, respectively, P<0.0001]. Nevertheless, these levels were not associated with the genotypes analyzed in the present study. The results suggest that the IL-10-1082 A/G (rs1800896) G allele is associated with a decreased risk of developing pCAD. In patients and controls, the polymorphisms analyzed were associated with some cardiovascular risk factors. Although, in pCAD patients the IL-10 plasma levels were higher, they were not associated with the genotypes of the polymorphisms examined.

[22] *Saber-Ayad M, Manzoor S, El-Serafy A et al.* **Statin-induced myopathy SLCO1B1 521T>C is associated with Prediabetes, high Body mass index and normal lipid profile in Emirati Population**. Diabetes Res Clin Pract 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29534995
ABSTRACT
BACKGROUND: Statin-induced myopathy has been linked to the C allele of a single nucleotide polymorphism (SNP) (rs4149056) of SLCO1B1 gene. This effect is more significant, but not restricted to simvastatin. Many studies have included European, American, African and Southeast Asian ancestries, but few were carried out on Middle Eastern population. AIM: To detect the prevalence of SLCO1B1 rs4149056 (521T>C) in Emirati population. METHOD: We recruited 282 Emiratis through the UAE National Diabetes and Lifestyle Project. Ethical approval was obtained before the study starts. Besides basic data collection, venous samples were collected. Fasting blood glucose, Lipid profile, and insulin levels were measured. Genotyping for rs4149056 (521T>C) in triplicates through Real Time-PCR using TaqMan(R) Drug Metabolism Genotyping Assay. rs2306283 (388A>G) was analyzed for comparison. In addition, both SNP's

define more association with statin-induced myopathy. RESULTS: The study included 282 individuals, 52.8% were males with median age of 39.5 years., 10% had Diabetes Mellitus and 23% were hypertensive. Median of Body mass index (BMI) was 27.68 kg/m(2) in males and 28.38 kg/m(2) in females. One-hundred ninety- seven (69.9%) showed abnormal lipid profile (either increased LDL-cholesterol or triglycerides or both). For rs4149056, C allele was present in 21.3% (2.8% homozygous C and 18.4% heterozygous CT). Although homozygous C genotype prevalence was low, compared with Caucasians (4%) and Africans (0%), C allele was associated with a trend of having higher BMI and abnormal lipid profile. C allele subjects were all pre-diabetics with mean glycated Hemoglobin above 6%. Mean BMI in CC, CT, and TT genotypes was 30.91+/-4.4, 29.48+/-4.2, 27.96+/-5.5 kg/m(2) respectively, with lack of such a trend observed with the different genotypes of the rs2306283 (used for comparison). Abnormal lipid profile was observed in 7/8(87.5%), 38/52(73.1%) and 152/222(70%) of the CC, CT, and TT genotypes respectively. CONCLUSION: There is lower prevalence of statin-induced myopathy-linked C allele of rs4149056 in SLCO1B1 gene in Emirati population, compared to Caucasians and Africans. However, there is a trend of higher glycosylated hemoglobin and BMI associated with normal lipid profile in patients having this allele.

[23] *Liu LY, Liu Y, Wu MY et al.* **Efficacy of atorvastatin on the prevention of contrast-induced acute kidney injury: a meta-analysis**. Drug design, development and therapy 2018; 12:437-444.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29535505

ABSTRACT

Background: Results of studies on the efficacy of atorvastatin pretreatment on reducing the prevalence of contrast-induced acute kidney injury (CIAKI) in patients undergoing coronary angiography (CAG) or percutaneous coronary intervention (PCI) have been controversial. Objective: We undertook a meta-analysis to evaluate the efficacy of atorvastatin on contrast-induced nephropathy (CIN) after CAG or PCI. Materials and methods: We undertook a systematic search of electronic databases (PubMed, Embase, and the Cochrane Library) up to June 2017. A meta-analysis was carried out including randomized controlled trials (RCTs) that compared atorvastatin pretreatment with pretreatment with a low-dose statin or placebo for CIAKI prevention in patients undergoing CAG. The main endpoint was CIN prevalence. Results: Nine RCTs were included in our meta-analysis. Atorvastatin pretreatment reduced the prevalence of CIN significantly (odds ratio [OR] 0.46; 95% confidence interval [95% CI] 0.27-0.79; p=0.004). The benefit of high-dose atorvastatin pretreatment was consistent when compared with the control group (OR 0.45; 95% CI 0.21-0.95; p=0.04). Conclusion: At high doses, atorvastatin pretreatment was associated with a significant reduction in the prevalence of CIAKI in patients undergoing CAG. Pretreatment with high-dose atorvastatin could be employed to prevent CIAKI.

[24] *Miyazawa I, Kadota A, Miura K et al.* **Twelve-year trends of increasing overweight and obesity in patients with diabetes: the Shiga Diabetes Clinical Survey**. Endocrine journal 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29526989

ABSTRACT

The prevalence of obesity is increasing globally in patients with diabetes. This study aimed to examine 12-year trends of increasing obesity in Japanese patients with diabetes, and their

clinical features. The study used results of the Shiga Diabetes Clinical Survey, which recorded medical performance in diabetic patients in 2000, 2006 and 2012. Data were analyzed from 14,205, 14,407 and 21,449 adult patients in these three years, respectively. Overweight and obesity prevalence and the clinical features of diabetes patients were examined, stratified by body mass index (BMI) and age. The prevalence of overweight (BMI 25-30 kg/m(2)) and obesity (BMI >/=30 kg/m(2)) were 27.0% and 5.1% in 2000, 28.9% and 7.3% in 2006 and 30.9% and 10.0% in 2012. Glycemic control, blood pressure and serum lipid profile improved over 12 years in all BMI categories. However, glycemic and triglyceride control were insufficient in obese patients aged <65 years (hemoglobin A1c 7.5 +/- 1.4%, triglyceride 197.7 +/- 178.4 mg/dL in 2012). The percentage of patients who used antihypertensive and lipid-lowering drugs increased and patients with higher BMI had increased frequency of using these drugs, both in young and old age groups. Higher BMI was significantly and positively associated with albuminuria. In summary, overweight and obesity have increased in Japanese diabetic patients, particularly for younger generations. Findings suggest that obesity may lead to poorer glycemic control, blood pressure and lipid profiles. Overweight and obesity are important modifiable risk factors for diabetes, suggesting that more active weight-control interventions are warranted.

[25] *Clifton P, Keogh J*. **Cholesterol-Lowering Effects of Plant Sterols in One Serve of Wholegrain Wheat Breakfast Cereal Biscuits-a Randomised Crossover Clinical Trial**. Foods (Basel, Switzerland) 2018; 7.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29547511
ABSTRACT
The meta-analysis of plant sterol supplement studies suggests an 8% lowering of low density lipoprotein (LDL) cholesterol for 2 to 2.5 g/day of plant sterols. Cereal foods have been rarely tested, and one study showed a lower LDL lowering of 5.4% with 1.6 g of plant sterol in breakfast cereal. We aimed to test a breakfast wheat biscuit with 2 g of plant sterols in a single serve of two wholegrain wheat breakfast cereal biscuits. Fifty volunteers with a total cholesterol of >5.5 mmol/L were recruited for a randomised crossover study with two 4-week periods with no washout, of which 45 successfully completed the study. After exclusion of four outliers, the difference in LDL cholesterol between standard wholegrain wheat breakfast cereal biscuit and plant sterol-enriched wholegrain wheat breakfast cereal biscuit was 0.23 mmol/L or 5.6% ($p = 0.001$) with a 95% confidence interval of 2.4-8.9%. Men and daily cereal consumers had greater responses 9.8% vs. 3.6% and 7.2% vs. 3.8% respectively ($p < 0.05$). The LDL lowering effect of 2 g of plant sterol enriched from one serve of wholegrain wheat breakfast cereal biscuit was not significantly different from other food products delivering 2-2.5 g of plant sterols daily. Regular cereal consumers have a better response.

[26] **[Consensus document and recommendations for the prevention of cardiovascular disease in Italy - 2018]**. Giornale italiano di cardiologia (2006) 2018; 19:1-95.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29531376
ABSTRACT
Cardiovascular prevention represents a cornerstone of modern strategies to reduce the burden of cardiovascular disease. It is of key importance to prevent cardiovascular diseases and associated events, not only to reduce morbidity and mortality, but also to increase the years of

wellness in the aging population and to make the growing socio-economic burden imposed by cardiovascular events more sustainable.The current approach to prevention is based on an integrated use of effective lifestyle measures and, whenever appropriate, of antihypertensive and antidiabetic drugs, lipid-lowering agents and antiplatelet drugs.Given that population characteristics, in terms of ethnicity, demography and lifestyle habits, and healthcare system organizations differ among countries, international guidelines are not always applicable to specific countries and, often, are difficult to translate into daily clinical practice.In order to afford the specific features of Italy, 10 Scientific Societies and Research Institutions, mostly involved in preventive strategies, contributed to the present Italian consensus document, which includes brief, practical recommendations to support the preventive actions within the physician community and the general practice setting.

[27] *Cortese B, Di Palma G, Lettieri C, Musumeci G*. **[PCSK9 inhibitors: how to bridge the gap between scientific evidence and regulatory barriers?]**. Giornale italiano di cardiologia (2006) 2018; 19:77-80.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29531379
ABSTRACT

[28] *Covolo E, Bilato C*. **[Nutraceuticals: a useful tool for cardiologists to improve lipid profile?]**. Giornale italiano di cardiologia (2006) 2018; 19:81-90.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29531380
ABSTRACT
Hyperlipidemia is a major risk factor for cardiovascular morbidity and mortality. Treatment strategies include both lifestyle modification and pharmacological therapy. Statins are among the most effective agents to achieve optimal LDL-cholesterol levels, but, not infrequently, patients suffer from myalgia or other side effects. The proven or perceived intolerance to statins requires, therefore, alternative lipid-lowering strategies. In recent years, nutraceuticals have become extensively accepted, and a growing number of molecules with hypothetical cholesterol-lowering activity have been proposed, sometimes with no scientific evidence and/or no methodological accuracy, based only on the belief that these agents are "natural" and do not show side effects. Here, nutraceuticals with potential evidence-based hypolipidemic effect will be reviewed (red yeast rice, berberine, phytosterols) in order to discuss their role in lipid control, their potential risks and their future prospective in clinical cardiology.

[29] *van der Tuin SJL, Li Z, Berbee JFP et al.* **Lipopolysaccharide Lowers Cholesteryl Ester Transfer Protein by Activating F4/80(+)Clec4f(+)Vsig4(+)Ly6C(-) Kupffer Cell Subsets**. Journal of the American Heart Association 2018; 7.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29525783
ABSTRACT
BACKGROUND: Lipopolysaccharide (LPS) decreases hepatic CETP (cholesteryl ester transfer protein) expression albeit that the underlying mechanism is disputed. We recently showed that plasma CETP is mainly derived from Kupffer cells (KCs). In this study, we investigated the role of KC subsets in the mechanism by which LPS reduces CETP expression. METHODS AND RESULTS: In CETP-transgenic mice, LPS markedly decreased hepatic CETP expression and plasma CETP

concentration without affecting hepatic macrophage number. This was paralleled by decreased expression of the resting KC markers C-type lectin domain family 4, member f (Clec4f) and V-set and immunoglobulin domain containing 4 (Vsig4), while expression of the infiltrating monocyte marker lymphocyte antigen 6 complex locus C (Ly6C) was increased. Simultaneously, the ratio of plasma high-density lipoprotein-cholesterol over non-high-density lipoprotein-cholesterol transiently increased. After ablation hepatic macrophages via injection with liposomal clodronate, the reappearance of hepatic gene and protein expression of CETP coincided with Clec4f and Vsig4, but not Ly6C. Double-immunofluorescence staining showed that CETP co-localized with Clec4f(+) KCs and not Ly6C(+) monocytes. In humans, microarray gene-expression analysis of liver biopsies revealed that hepatic expression and plasma level of CETP both correlated with hepatic VSIG4 expression. LPS administration decreased the plasma CETP concentration in humans. In vitro experiments showed that LPS reduced liver X receptor-mediated CETP expression. CONCLUSIONS: Hepatic expression of CETP is exclusively confined to the resting KC subset (ie, F4/80(+)Clec4f(+)Vsig4(+)Ly6C(-)). LPS activated resting KCs, leading to reduction of Clec4f and Vsig4 expression and reduction of hepatic CETP expression, consequently decreasing plasma CETP and raising high-density lipoprotein (HDL)-cholesterol. This sequence of events is consistent with the anti-inflammatory role of HDL in the response to LPS and may be relevant as a defense mechanism against bacterial infections.

[30] *Favari E, Thomas MJ, Sorci-Thomas MG*. **HDL Functionality As A New Pharmacological Target On CVD: Unifying Mechanism That Explains HDL Protection Towards The Progression Of Atherosclerosis**. Journal of cardiovascular pharmacology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29528874
ABSTRACT
The formation of the atherosclerotic plaque that is characterized by the accumulation of abnormal amounts of cholesterol-loaded macrophages in the artery wall is mediated by both inflammatory events and alterations of lipid/lipoprotein metabolism. Reverse transport of cholesterol (RCT) opposes the formation and development of atherosclerotic plaque through high density lipoprotein (HDL) metabolism, promoting the removal of cholesterol from peripheral macrophages and its delivery back to the liver for excretion into the bile. Although an inverse association between HDL plasma levels and the risk of CVD has been demonstrated over the years, several studies have recently shown that the antiatherogenic functions of HDL appear to be mediated by their functionality, not always associated to their plasma concentrations. Therefore, assessment of HDL function, evaluated as the capacity to promote cell cholesterol efflux may offer a better prediction of CVD than HDL levels alone. In agreement with this idea, it has recently shown that the assessment of serum cholesterol efflux capacity (CEC), as a metric of HDL functionality, may represents a predictor of atherosclerosis extent in humans. The purpose of this narrative review is to summarize the current evidence concerning the role of CEC that is important for evaluating cardiovascular disease (CVD) risk, focusing on pharmacological evidences and its relationship with inflammation. We conclude that HDL therapeutics are a promising area of investigation but strategies for identifying efficacy must move beyond the idea of simply raising static HDL-cholesterol levels and towards methods of measuring the dynamics of HDL particle remodeling and the generation of lipid-free

apolipoprotein A-I (apoA-I). In this way, apoA-I, unlike mature HDL can promote the greatest extent of cholesterol efflux relieving cellular cholesterol toxicity and the inflammation it causes.

[31] *Glueck CJ, Brown A, Goldberg AC et al.* **Alirocumab in high-risk patients: Observations from the open-label expanded use program**. Journal of clinical lipidology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29525445
ABSTRACT
BACKGROUND: The alirocumab expanded use program provided open-label access to alirocumab before its commercial availability to patients with severe hypercholesterolemia not controlled with maximally tolerated doses of standard-of-care lipid-lowering therapy. OBJECTIVE: To describe the safety and lipid-lowering efficacy of alirocumab in high-risk patients who were likely to be early users of proprotein convertase subtilisin/kexin type 9 inhibitors after approval. METHODS: Patients with heterozygous familial hypercholesterolemia (HeFH) and/or coronary heart disease (CHD) and baseline low-density lipoprotein cholesterol (LDL-C) of >/=160 mg/dL on maximally tolerated lipid-lowering therapy were enrolled and received alirocumab 150 mg every 2 weeks for 24 weeks. Patients were permitted use of all available statins; those not taking any dose of statin could also be enrolled. RESULTS: Of 100 enrolled patients, 93 were white, 62 were women, and overall mean age was 58 years; 61 had HeFH, 3 had unknown type of familial hypercholesterolemia, 66 had CHD, and 30 had both familial hypercholesterolemia and CHD. Sixty-four patients were identified by their providers to have some level of statin intolerance; of these, 47 were not on statin. Alirocumab reduced LDL-C on average from 221 mg/dL at baseline to 102 mg/dL by week 24 (-55%). Treatment-emergent adverse events were experienced in 61% of patients and treatment-emergent adverse events leading to permanent treatment discontinuation in 3% of patients; no deaths occurred. CONCLUSIONS: Safety and efficacy observations from the open-label alirocumab expanded use program of very high-risk patients with HeFH and/or CHD and baseline LDL-C of >/=160 mg/dL uncontrolled by maximally tolerated lipid-lowering therapy were consistent with those in the placebo/ezetimibe-controlled ODYSSEY trials.

[32] *Maulucci G, Cipriani F, Russo D et al.* **Improved endothelial function after short-term therapy with evolocumab**. Journal of clinical lipidology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29544724
ABSTRACT
BACKGROUND: The reduction of cholesterol levels with cholesterol-lowering therapy may improve endothelial function. Lipid-lowering therapy has been greatly enhanced by the introduction of proprotein convertase subtilisin/kexin type 9 (PCSK9) antibodies. Less is known of the effect of PCSK9 inhibitors on endothelial function of subjects with hypercholesterolemia. OBJECTIVE: To assess whether treatment with PCSK9 inhibitors may improve endothelial function evaluated by brachial artery vasoreactivity test. METHODS: Brachial artery vasoreactivity test was performed in 14 consecutive patients with previous myocardial infarction before and after 2 months of therapy with evolocumab 140 mg twice in a month. Mean brachial artery diameter, velocity time integral, flow-mediated dilation (FMD) and low-density lipoprotein (LDL) cholesterol levels were also evaluated. RESULTS: After 2 months of treatment with evolocumab, mean total cholesterol levels decreased from 245 +/- 41 to 128 +/-

30 mg/dL (P < .001, -48%), and LDL levels from 176 +/- 43 to 71 +/- 26 mg/dL (P = .001, -59%); FMD conversely increased from 6.3 +/- 4.1% to 8.8 +/- 6.3% (P = .004, +40%). Improvement in FMD was proportional to reduction of LDL levels (r = 0.69, P = .006). Therapy with evolocumab increased brachial artery diameter during vasoreactivity test (peak values 0.39 +/- 0.09 vs 0.36 +/- 0.11 cm, P = .010; final values 0.36 +/- 0.10 vs 0.34 +/- 0.10 cm, P = .001), and velocity time integral (peak levels 96 +/- 1 vs 85 +/- 9 cm, P = .045). CONCLUSIONS: Two months of treatment with evolocumab 140 mg may improve endothelial function in subjects with increased cardiovascular risk. The improvement in endothelial function is proportional to LDL reduction.

[33] *Malik M, Tasnim N, Mahmud G*. **Effect of Metformin Alone Compared with Metformin Plus Simvastatin on Polycystic Ovarian Syndrome in Pakistani Women**. Journal of the College of Physicians and Surgeons--Pakistan : JCPSP 2018; 28:184-187.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29544572
ABSTRACT
OBJECTIVE: To determine the efficacy of metformin alone versus metformin plus simvastatin for treatment of polycystic ovariansyndrome (PCOS). STUDY DESIGN: Randomized controlled trial. PLACE AND DURATION OF STUDY: Maternal and Child Health Centre, Unit II, Pakistan Institute of Medical Sciences (PIMS), from November 2014 to April 2015. METHODOLOGY: One hundred and eight patients (108) were randomly divided into metformin group (n=54) and metformin plus simvastatin group (n=54), detailed clinical history, including menstrual details, was taken with thorough examination performed. Baseline ultrasound was performed to evaluate ovarian size and these were considered enlarged with volume >10cc or with >12 follicles in any one ovary. Blood samples were taken at baseline and after three months of therapy to determine the LH/FSH ratio and lipid profile. Efficacy was defined as >15% decrease in the baseline values. RESULTS: The mean age of patients was 28.82 +/-7.18 years. Mean BMI of the patients was 22.41 +/-1.55 Kg/m2. Efficacy was achieved in 66.7% patients with metformin alone, while in 92.6% with combination medication (p=0.001). CONCLUSION: The combination of metformin plus simvastatin is more efficacious as compared to metformin alone for management of females with PCOS.

[34] *Meester EJ, Krenning BJ, de Blois RH et al.* **Imaging of atherosclerosis, targeting LFA-1 on inflammatory cells with (111)In-DANBIRT**. Journal of nuclear cardiology : official publication of the American Society of Nuclear Cardiology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29536351
ABSTRACT
BACKGROUND: (111)In-DOTA-butylamino-NorBIRT (DANBIRT) is a novel radioligand which binds to Leukocyte Function-associated Antigen-1 (LFA-1), expressed on inflammatory cells. This study evaluated (111)In-DANBIRT for the visualization of atherosclerotic plaque inflammation in mice. METHODS AND RESULTS: ApoE(-/-) mice, fed an atherogenic diet up to 20 weeks (n = 10), were imaged by SPECT/CT 3 hours post injection of (111)In-DANBIRT (~ 200 pmol, ~ 40 MBq). Focal spots of (111)In-DANBIRT were visible in the aortic arch of all animals, with an average Target-to-Background Ratio (TBR) of 1.7 +/- 0.5. In vivo imaging results were validated by ex vivo SPECT/CT imaging, with a TBR up to 11.5 (range 2.6 to 11.5). Plaques, identified by Oil Red O lipid-staining on excised arteries, co-localized with (111)In-DANBIRT uptake as determined by

ex vivo autoradiography. Subsequent histological processing and in vitro autoradiography confirmed (111)In-DANBIRT uptake at plaque areas containing CD68 expressing macrophages and LFA-1 expressing inflammatory cells. Ex vivo incubation of a human carotid endarterectomy specimen with (111)In-DANBIRT (~ 950 nmol, ~ 190 MBq) for 2 hours showed heterogeneous plaque uptake on SPECT/CT, after which immunohistochemical analysis demonstrated co-localization of (111)In-DANBIRT uptake and CD68 and LFA-1 expressing cells. CONCLUSIONS: Our results indicate the potential of radiolabeled DANBIRT as a relevant imaging radioligand for non-invasive evaluation of atherosclerotic inflammation.

[35] *Jackson JC, Mozaffarian D, Graves AJ et al.* **Fish Oil Supplementation Does Not Affect Cognitive Outcomes in Cardiac Surgery Patients in the Omega-3 Fatty Acids for Prevention of Post-Operative Atrial Fibrillation (OPERA) Trial**. The Journal of nutrition 2018; 148:472-479.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29546292
ABSTRACT
Background: Cognitive decline has been reported following cardiac surgery, leading to great interest in interventions to minimize its occurrence. Long-chain n-3 (omega-3) polyunsaturated fatty acids (PUFAs) have been associated with less cognitive decline in observational studies, yet no trials have tested the effects of n-3 PUFAs on cognitive decline after surgery. Objective: We sought to determine whether perioperative n-3 PUFA supplementation reduces postoperative cognitive decline in patients postcardiac surgery. Methods: The study comprised a randomized, double-blind, placebo-controlled, multicenter, clinical trial conducted on cardiac surgery recipients at 9 tertiary care medical centers across the United States. Patients were randomly assigned to receive fish oil (1-g capsules containing >/=840 mg n-3 PUFAs as ethyl esters) or placebo, with preoperative loading of 8-10 g over 2-5 d followed postoperatively by 2 g/d until hospital discharge or postoperative day 10, whichever came first. Global cognition was assessed using in-person testing over 30 d with the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (primary outcome), Mini-Mental State Exam (secondary outcome), and Trails A and B (secondary outcome) tests. All end points were prespecified. Statistical methods were employed, including descriptive statistics, logistic regression, and various sensitivity analyses. Results: A total of 320 US patients were enrolled in the Omega-3 Fatty Acids for Prevention of Post-Operative Atrial Fibrillation (OPERA) Cognitive Trial (OCT), a substudy of OPERA. The median age was 62 y (IQR 53, 70 y). No differences in global cognition were observed between placebo and fish oil groups at day 30 (P = 0.32) for the primary outcome, a composite neuropsychological RBANS score. The population demonstrated resolution of initial 4-d cognitive decline back to baseline function by 30 d on the RBANS. Conclusion: Perioperative supplementation with n-3 PUFAs in cardiac surgical patients did not influence cognition </=30 d after discharge. Modern anesthetic, surgical, and postoperative care may be mitigating previously observed long-term declines in cognitive function following cardiac surgery. This trial was registered at clinicaltrials.gov as NCT00970489.

[36] *Song H, Moon C, Lee BJ, Oh E*. **Mesoporous pravastatin solid dispersion granules incorporable into orally disintegrating tablets**. Journal of pharmaceutical sciences 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29530714
ABSTRACT

Herein, we aimed to prepare porous granules of pravastatin and evaluate their applicability to orally disintegrating tablets (ODTs). Pravastatin solid dispersion granules (PSDGs-A) were prepared by dispersing pravastatin sodium in D-mannitol (the dispersion medium) in the presence of ammonium bicarbonate (the sublimation agent) using a spray-drying process. The PSDGs-A were round, irregularly shaped, mesoporous agglomerates with appropriate particle size, bulk density, and flowability for the tableting process. The mesopore formation in PSDGs-A resulted from the complete sublimation of ammonium bicarbonate during spray-drying and resulted in a notably high surface area. When the PSDGs-A were blended with ODT excipients and then directly compressed into ODTs (PSDGs-A-ODTs), they were readily incorporated into ODTs without tableting problems and had desirable ODT characteristics. They demonstrated rapid disintegration times because of the fast water uptake of mesoporous PSDGs-A caused by their high surface area. This rapid disintegration of PSDGs-A-ODTs was reflected also by their quick initial dissolution. The mesoporous pravastatin solid dispersion granules prepared with ammonium bicarbonate using the spray-drying process can be used to develop pravastatin ODTs. This spray-dried, mannitol-based solid dispersion of drugs employing sublimation solids is a potential formulation technology for ODT product development.

[37] *Ni YF, Wang H, Gu QY et al.* **Gemfibrozil has antidepressant effects in mice: Involvement of the hippocampal brain-derived neurotrophic factor system**. Journal of psychopharmacology (Oxford, England) 2018:269881118762072.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29534628
ABSTRACT
Major depressive disorder has become one of the most serious neuropsychiatric disorders worldwide. However, currently available antidepressants used in clinical practice are ineffective for a substantial proportion of patients and always have side effects. Besides being a lipid-regulating agent, gemfibrozil is an agonist of peroxisome proliferator-activated receptor-alpha (PPAR-alpha). We investigated the antidepressant effects of gemfibrozil on C57BL/6J mice using the forced swim test (FST) and tail suspension test (TST), as well as the chronic unpredictable mild stress (CUMS) model of depression. The changes in brain-derived neurotrophic factor (BDNF) signaling cascade in the brain after CUMS and gemfibrozil treatment were further assessed. Pharmacological inhibitors and lentivirus-expressed short hairpin RNA (shRNA) were also used to clarify the antidepressant mechanisms of gemfibrozil. Gemfibrozil exhibited significant antidepressant actions in the FST and TST without affecting the locomotor activity of mice. Chronic gemfibrozil administration fully reversed CUMS-induced depressive-like behaviors in the FST, TST and sucrose preference test. Gemfibrozil treatment also restored CUMS-induced inhibition of the hippocampal BDNF signaling pathway. Blocking PPAR-alpha and BDNF but not the serotonergic system abolished the antidepressant effects of gemfibrozil on mice. Gemfibrozil produced antidepressant effects in mice by promoting the hippocampal BDNF system.

[38] *Liu Y, Yang H, Jia G et al.* **The Synergistic Neuroprotective Effects of Combined Rosuvastatin and Resveratrol Pretreatment against Cerebral Ischemia/Reperfusion Injury**. Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association 2018.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29525080

ABSTRACT

BACKGROUND: It is well accepted that both rosuvastatin and resveratrol exert neuroprotective effects on cerebral ischemia/reperfusion injury through some common pathways. Resveratrol has also been demonstrated to protect against cerebral ischemia/reperfusion injury through enhancing autophagy. Thus, we hypothesized that combined rosuvastatin and resveratrol pretreatment had synergistic effects on cerebral ischemia/reperfusion injury. MATERIALS AND METHODS: Adult male Sprague Dawley rats receiving middle cerebral artery occlusion surgery as animal model of cerebral ischemia/reperfusion injury were randomly assigned to 4 groups: control, resveratrol alone pretreatment, rosuvastatin alone pretreatment, and combined rosuvastatin and resveratrol pretreatment. Rosuvastatin (10 mg/kg) or resveratrol (50 mg/kg) was administrated once a day for 7 days before cerebral ischemia onset. RESULTS: We found that combined rosuvastatin and resveratrol pretreatment not only significantly decreased the neurologic defective score, cerebral infarct volume, the levels of caspase-3, and Interleukin-1beta (IL-1beta) but also significantly increased the ratios of Bcl-2/Bax and LC3II/LC3I, as well as the level of Becline-1, compared with resveratrol alone or rosuvastatin alone pretreatment group. Rosuvastatin alone pretreatment significantly increased the ratio of LC3II/LC3I and the level of Beclin-1. However, there were no significant differences in the neurologic defective score, cerebral infarct volume, the levels of caspase-3, IL-1beta, and Beclin-1, and the ratios of Bcl-2/Bax and LC3II/LC3I between resveratrol pretreatment group and rosuvastatin pretreatment group. CONCLUSIONS: Synergistically enhanced antiapoptosis, anti-inflammation, and autophagy activation might be responsible for the synergistic neuroprotective effects of combining rosuvastatin with resveratrol on cerebral ischemia/reperfusion injury.

[39] *Hillaert MA, den Ruijter HM, Hoefer IE et al.* **Renin and aldosterone are not associated with vulnerable plaque characteristics in patients with carotid artery disease**. Journal of vascular surgery 2018.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29548814

ABSTRACT

BACKGROUND: The renin-angiotensin-aldosterone system is increasingly being recognized to play an important role in the development and clinical course of cardiovascular diseases. Renin-angiotensin-aldosterone system activation is associated with clinical outcome in various populations of cardiovascular patients, such as patients with coronary artery, peripheral artery, and cerebrovascular disease. In this study, we investigated the associations between plasma renin and aldosterone concentrations and atherosclerotic plaque characteristics and secondary vascular events in patients undergoing carotid endarterectomy. METHODS AND RESULTS: Baseline plasma renin and aldosterone concentrations from 506 subjects undergoing carotid endarterectomy (mean age, 67 +/- 9 years; 65% male) were correlated with histopathologic characteristics and inflammatory protein concentrations of the excised atherosclerotic plaque. Ordinal logistic regression (for ordinal outcome parameters) or linear regression (for linear outcome) analysis did not show a statistically significant relationship between plasma renin or aldosterone concentrations and plaque fat, thrombus, calcifications, collagen, smooth muscle cells, or macrophage content. Neither could any association be found with intraplaque inflammatory mediators. During a median follow-up of 3 years, 102 (20%) patients experienced

a major secondary vascular event (composite of stroke, myocardial infarction, leg amputation, vascular death, or coronary revascularization or peripheral intervention). In multivariable Cox regression analysis, including both renin and aldosterone, baseline renin concentrations were associated with the occurrence of secondary events. CONCLUSIONS: In patients with established atherosclerotic disease undergoing carotid endarterectomy, plasma renin and aldosterone concentrations were not associated with atherosclerotic plaque characteristics. Plasma renin concentration was positively associated with the occurrence of major secondary vascular events.

[40] *Berwanger O, Santucci EV, de Barros ESPGM et al.* **Effect of Loading Dose of Atorvastatin Prior to Planned Percutaneous Coronary Intervention on Major Adverse Cardiovascular Events in Acute Coronary Syndrome: The SECURE-PCI Randomized Clinical Trial**. Jama 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29525821

ABSTRACT

Importance: The effects of loading doses of statins on clinical outcomes in patients with acute coronary syndrome (ACS) and planned invasive management remain uncertain. Objective: To determine if periprocedural loading doses of atorvastatin decrease 30-day major adverse cardiovascular events (MACE) in patients with ACS and planned invasive management. Design, Setting, and Participants: Multicenter, double-blind, placebo-controlled, randomized clinical trial conducted at 53 sites in Brazil among 4191 patients with ACS evaluated with coronary angiography to proceed with a percutaneous coronary intervention (PCI) if anatomically feasible. Enrollment occurred between April 18, 2012, and October 6, 2017. Final follow-up for 30-day outcomes was on November 6, 2017. Interventions: Patients were randomized to receive 2 loading doses of 80 mg of atorvastatin (n = 2087) or matching placebo (n = 2104) before and 24 hours after a planned PCI. All patients received 40 mg of atorvastatin for 30 days starting 24 hours after the second dose of study medication. Main Outcomes and Measures: The primary outcome was MACE, defined as a composite of all-cause mortality, myocardial infarction, stroke, and unplanned coronary revascularization through 30 days. Results: Among the 4191 patients (mean age, 61.8 [SD, 11.5] years; 1085 women [25.9%]) enrolled, 4163 (99.3%) completed 30-day follow-up. A total of 2710 (64.7%) underwent PCI, 333 (8%) underwent coronary artery bypass graft surgery, and 1144 (27.3%) had exclusively medical management. At 30 days, 130 patients in the atorvastatin group (6.2%) and 149 in the placebo group (7.1%) had a MACE (absolute difference, 0.85% [95% CI, -0.70% to 2.41%]; hazard ratio, 0.88; 95% CI, 0.69-1.11; P = .27). No cases of hepatic failure were reported; 3 cases of rhabdomyolysis were reported in the placebo group (0.1%) and 0 in the atorvastatin group. Conclusions and Relevance: Among patients with ACS and planned invasive management with PCI, periprocedural loading doses of atorvastatin did not reduce the rate of MACE at 30 days. These findings do not support the routine use of loading doses of atorvastatin among unselected patients with ACS and intended invasive management. Trial Registration: clinicaltrials.gov Identifier: NCT01448642.

[41] *Nicholls SJ, Psaltis PJ*. **Lipid Lowering in Acute Coronary Syndrome: Is Treatment Early Enough?** Jama 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29525819

Literature update week 11 (2018)

ABSTRACT

[42] *Nissen SE, Pillai SG, Nicholls SJ et al.* **ADCY9 Genetic Variants and Cardiovascular Outcomes With Evacetrapib in Patients With High-Risk Vascular Disease: A Nested Case-Control Study**. JAMA cardiology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29525816
ABSTRACT
Importance: A pharmacogenetic analysis of dalcetrapib, a cholesteryl ester transfer protein inhibitor, reported an association between a single-nucleotide polymorphism (SNP) in the ADCY9 gene (rs1967309) and reduction in major adverse cardiovascular events despite a neutral result for the overall trial. Objective: To determine whether the association between the SNP in the ADCY9 gene and a reduction in major adverse cardiovascular events could be replicated for another cholesteryl ester transfer protein inhibitor, evacetrapib, in patients with high-risk vascular disease. Design, Setting, and Participants: A nested case-control study examining the rs1967309 SNP in 1427 cases and 1532 matched controls selected from the 12092-patient Assessment of Clinical Effects of Cholesteryl Ester Transfer Protein Inhibition with Evacetrapib in Patients at a High Risk for Vascular Outcomes (ACCELERATE) trial, a randomized, double-blind, placebo-controlled phase 3 trial conducted in patients with high-risk vascular disease randomized from October 2012 through December 2013. The genotyping was conducted from January 2017 to March 2017, and the data analyses were conducted from July 2017 to November 2017. Exposures: Evacetrapib, 130 mg, or matching placebo. Main Outcomes and Measures: The primary analyses used a conditional logistic regression model to assess the odds ratio (OR) for major adverse cardiovascular events for evacetrapib compared with placebo for each genotype. The basic model included adjustment for age, sex, and the top 5 principal components. An additional model included cardiovascular risk factors to adjust for potential bias in selecting control patients. The primary major adverse cardiovascular event end point was the composite of death from cardiovascular causes, myocardial infarction, stroke, coronary revascularization, or hospitalization for unstable angina. Results: For patients with the AA genotype reported to demonstrate a beneficial effect from dalcetrapib, the OR for evacetrapib compared with placebo was 0.88 (95% CI, 0.69-1.12). For patients with the AG genotype, the OR was 1.04 (95% CI, 0.90-1.21). For patients with the GG genotype reported to show evidence for a harmful effect from dalcetrapib, the OR for evacetrapib was 1.18 (95% CI, 0.98-1.41). The interaction P value among the 3 genotypes was P = .17 and the trend P value was P = .06. When adjusted for cardiovascular risk factors, the OR for evacetrapib was 0.93 (95% CI, 0.73-1.19) for the AA genotype, 1.05 (95% CI, 0.91-1.22) for the AG genotype, and 1.02 (95% CI 0.85-1.24) for the GG genotype; interaction P = .71 and trend P = .59. Conclusions and Relevance: Pharmacogenetic analysis did not show a significant association between the ADCY9 SNP (rs1967309) and cardiovascular benefit or harm for the cholesteryl ester transfer protein inhibitor evacetrapib.

[43] *Warraich HJ, Salami JA, Khera R et al.* **Trends in Use and Expenditures of Brand-name Atorvastatin After Introduction of Generic Atorvastatin**. JAMA internal medicine 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29525818
ABSTRACT

[44] *Toth PP, Dwyer JP, Cannon CP et al.* **Efficacy and safety of lipid lowering by alirocumab in chronic kidney disease**. Kidney international 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29526502
ABSTRACT
Individuals with chronic kidney disease are at increased risk of premature cardiovascular disease. Among them, many with elevated low-density lipoprotein cholesterol (LDL-C) are unable to achieve optimal LDL-C on statins and require additional lipid-lowering therapy. To study this, we compared the LDL-C-lowering efficacy and safety of alirocumab in individuals with hypercholesterolemia with impaired renal function, defined as eGFR 30-59 ml/min/1.73 m(2), to those without impaired renal function eGFR >/=60 ml/min/1.73 m(2). A total of 4629 hypercholesterolemic individuals without or with impaired renal function, pooled from eight phase 3 ODYSSEY trials (double-blind treatments of 24-104 weeks), were on alirocumab 150 mg or 75/150 mg every two weeks vs. placebo or ezetimibe. Overall, 10.1% had impaired renal function and over 99% were receiving statin treatment. Baseline LDL-C in alirocumab and control groups was comparable in subgroups analyzed. LDL-C reductions at week 24 ranged from 46.1 to 62.2% or 48.3 to 60.1% with alirocumab among individuals with or without impaired renal function, respectively. Similar reductions were observed for lipoprotein (a), non-high-density lipoprotein cholesterol, apolipoprotein B, and triglycerides. Safety data were similar in both treatment subgroups, regardless of the degree of CKD. Renal function did not change over time in response to alirocumab. This post hoc efficacy analysis is limited by evaluation of alirocumab treatment effects on renal and lipid parameters by serum biochemistry. Thus, alirocumab consistently lowered LDL-C regardless of impaired renal function, with safety comparable to control, among individuals with hypercholesterolemia who nearly all were on statin treatment.

[45] *Avci E, Kiris T, Demirtas AO, Kadi H*. **Relationship between high-density lipoprotein cholesterol and the red cell distribution width in patients with coronary artery disease**. Lipids in health and disease 2018; 17:53.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29548288
ABSTRACT
BACKGROUND: The red cell distribution width (RDW) is a numerical measurement of variability in the size of red blood cells. Many studies have shown that high-density lipoprotein cholesterol (HDL-C), has an anti-inflammatory effect. The aim of this study was to investigate the relationship between the serum HDL-C level and RDW in patients with coronary artery disease (CAD). METHODS: Patients who underwent coronary angiography were reviewed. Patients who had moderate or severe heart failure, moderate or severe renal failure, significant systemic disease, anemia, a blood transfusion within the last 3 months, or a hematologic disease, as well as those who were taking lipid-lowering medication, were excluded from the study. The Gensini scoring system was used to determine the severity of CAD. Biochemical and hematological parameters were measured from venous blood samples taken after the patient fasted for at least 8 h. The RDW was routinely obtained from a hemogram. RESULTS: In total, 328 patients were included in the study. The patients were categorized according to quartiles. There were 80 patients in Quartile 1 (RDW < 13.2), 84 patients in Quartile 2 (13.2 >/= RDW < 14.15), 81

patients in Quartile 3 (14.15 >/= RDW < 16), and 83 patients in Quartile 4 (RDW >/= 16). There was a significant and inverse relationship between the serum HDL level and RDW. Regression analysis showed that the HDL-C, hemoglobin, and hs-CRP levels and Gensini score were predictors for the RDW. CONCLUSION: We found an inverse and gradual association between the serum HDL-C level and RDW, and the serum HDL-C level was an independent predictor for the RDW.

[46] *Hadj Ahmed S, Kharroubi W, Kaoubaa N et al.* **Correlation of trans fatty acids with the severity of coronary artery disease lesions**. Lipids in health and disease 2018; 17:52.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29544473
ABSTRACT
BACKGROUND: Nutritional choices, which include the source of dietary fatty acids (FA), have an important significant impact on coronary artery disease (CAD). We aimed to determine on patients with CAD the relationships between Trans fatty acids (Trans FA) and different CAD associated parameters such as inflammatory and oxidative stress parameters in addition to Gensini score as a vascular severity index. METHODS: Fatty acid profiles were established by gas chromatography from 111 CAD patients compared to 120 age-matched control group. Lipid peroxidation biomarkers, oxidative stress, inflammatory parameters and Gensini score were studied. RESULTS: Our study showed a significant decrease of the antioxidant parameters levels such as erythrocyte glutathione peroxydase (GPx) and superoxide dismutase (SOD) activities, plasma antioxidant status (FRAP) and thiol (SH) groups in CAD patients. On the other hand, catalase activity, conjugated dienes and malondialdehyde were increased. Plasmatic and erythrocyte Trans FA were also increased in CAD patients compared to controls. Furthermore, divergent associations of these Trans FA accumulations were observed with low-density lipoprotein-cholesterol/ high-density lipoprotein-cholesterol (LDL-C/HDL-C) ratio, Apolipoprotein B (ApoB), lipid peroxidation parameters, high-sensitivity C Reactive Protein (hs-CRP), Interleukin 6 (IL-6), tumor necrosis factor alpha (TNF-alpha) and Gensini score. Especially, elaidic acid (C18:1 trans 9), trans C18:2 isomers and trans 11 eicosanoic acid are correlated with these parameters. Trans FA are also associated with oxidative stress, confirmed by a positive correlation between C20:1 trans 11 and GPx in erythrocytes. CONCLUSIONS: High level of Trans FA was highly associated with the induction of inflammation, oxidative stress and lipoperoxidation which appear to be based on the vascular severity and might be of interest to assess the stage and progression of atherosclerosis. The measurement of these Trans FA would be of great value for the screening of lipid metabolism disorders in CAD patients.

[47] *Pares A*. **Primary biliary cholangitis**. Medicina clinica 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29526309
ABSTRACT
Primary cholangitis (cirrhosis) is a chronic cholestatic disease with an unquestionable female predominance. It is characterised by inflammation of the small and medium size bile ducts, and can eventually progress to cirrhosis. Most patients remain asymptomatic and are diagnosed by the casual finding of an anicteric biochemical cholestasis with increased alkaline phosphatase. The pathogenesis is unknown and of presumed autoimmune origin in genetic susceptible subjects. M2-type antimitochondrial antibodies, and specific antinuclear antibodies (gp210 and

Sp100) are typical and specific of the disease. The positivity of these antibodies and a biochemical cholestasis are sufficient for diagnosis, without the need for liver biopsy. Ursodeoxycholic acid is the specific treatment with an excellent response in more than 60% of patients. When this optimal response is not observed, it can be combined with new agents, but those that have shown to be effective are those that improve cholestasis such as fibrates and obeticholic acid.

[48] *Xiao YH, He XY, Han Q et al.* **Atorvastatin prevents glomerular extracellular matrix formation by interfering with the PKC signaling pathway**. Molecular medicine reports 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29532876
ABSTRACT
Platelet-activating factor (PAF) promotes glomerular extracellular matrix (ECM) deposition, primarily through activation of the protein kinase C (PKC) pathway. The present study was designed to investigate whether atorvastatin, which mediates a protective effect against glomerular ECM deposition and diabetic neuropathy, may interfere with the PKCtransforming growth factorbeta1 (TGFbeta1) pathway in a model of human mesangial cells (HMCs) exposed to a high glucose (HG) and lysophosphatidylcholine (LPC) environment. HMCs were divided into three treatment groups: Control, high glucose and lysophosphatidylcholine (HG+LPC), and HG+LPC+atorvastatin. Cells were cultured for 24 h. The levels of the ECMassociated molecules collagen IV (Col IV) and fibronectin (Fn) in the supernatant were detected using an ELISA kit. PKCbeta1, TGFbeta1 and PAFreceptor gene expression was detected by reverse transcriptionquantitative polymerase chain reaction. PKCbeta1 and TGFbeta1 protein expression was detected by western blotting, and the subcellular localization of PKCbeta1 was assessed using immunofluorescence. The results indicated that atorvastatin may reduce the secretion of ECM components (Fn and Col IV) in HMCs in a HG and LPC environment, by inhibiting the increase in PAF secretion and the activation of the PKCTGFbeta1 signaling pathway.

[49] *Cui X, Fu Z, Wang M et al.* **Pitavastatin treatment induces neuroprotection through the BDNF-TrkB signalling pathway in cultured cerebral neurons after oxygen-glucose deprivation**. Neurol Res 2018:1-7.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29544396
ABSTRACT
OBJECTIVES: Along with their lipid-lowering effect, statins have been reported to have neuroprotective function in both in vivo and in vitro models of neurodegenerative diseases. We conducted this study in order to uncover the he neuroprotective effect of the lipophilic statin pitavastatin (PTV) and investigate the underlying molecular mechanisms using primary cultured cerebral neurons exposed to oxygen-glucose deprivation (OGD). METHODS: The primary cultured cerebral neurons were randomly assigned into four groups: the control group, the pitavastatin treatment group, the OGD group and the OGD + pitavastatin treatment group. The pitavastatin's concentration were set as follows: 1muM, 15muM, 30muM. After 3 hours OGD treatment, we use MTT method to assessment cell viability, immunofluorescence to observe neuron morphology and western blot method analysis the BDNF, TrkB. RESULTS: PTV at concentrations of 1 muM and 15 muM elevated the survival rate of cortical neurons exposed to

OGD, whereas 30 muM PTV did not show such an effect. Moreover, PTV promoted neuronal dendrite growth at concentrations of 1 muM and 15 muM. Increased expression levels of brain-derived neurotrophic factor (BDNF) and tropomyosin-related kinase B (TrkB) were observed in both of the following two scenarios: when neurons were treated with PTV for 48 hours and when PTV was added after the OGD procedure. CONCLUSION: Pitavastatin treatment induces neuroprotection in cultured cerebral neurons after oxygen-glucose deprivation this neuroprotection induced by PTV involves the BDNF-TrkB signalling pathway.

[50] *Lepretti M, Martucciello S, Burgos Aceves MA et al.* **Omega-3 Fatty Acids and Insulin Resistance: Focus on the Regulation of Mitochondria and Endoplasmic Reticulum Stress**. Nutrients 2018; 10.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29538286
ABSTRACT
Mitochondrial dysfunction and endoplasmic reticulum (ER) stress have been suggested to play a key role in insulin resistance development. Reactive oxygen species (ROS) production and lipid accumulation due to mitochondrial dysfunction seemed to be important mechanisms leading to cellular insulin resistance. Moreover, mitochondria are functionally and structurally linked to ER, which undergoes stress in conditions of chronic overnutrition, activating the unfolded protein response, which in turn activates the principal inflammatory pathways that impair insulin action. Among the nutrients, dietary fats are believed to play key roles in insulin resistance onset. However, not all dietary fats exert the same effects on cellular energy metabolism. Dietary omega 3 polyunsaturated fatty acids (PUFA) have been suggested to counteract insulin resistance development by modulating mitochondrial bioenergetics and ER stress. In the current review, we summarized current knowledge on the role played by mitochondrial and ER stress in inflammation and insulin resistance onset, focusing on the modulation role of omega 3 PUFA on these stress pathways. Understanding the mechanisms by which omega 3 PUFA modulates cellular metabolism and insulin resistance in peripheral tissues may provide additional details on the potential impact of omega 3 PUFA on metabolic function and the management of insulin resistance in humans.

[51] *Yamamoto K, Iwagaki Y, Watanabe K et al.* **Effects of a moderate-fat diet that is enriched with fish oil on intestinal lipid absorption in a senescence-accelerated prone mouse model**. Nutrition 2017; 50:26-35.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29547795
ABSTRACT
OBJECTIVES: We examined a moderate-fat (MF) diet that is enriched with fish oil (FO) and assessed whether lipid absorption was inhibited in senescence-accelerated prone mice (SAM-P8). METHODS: All mice (N = 70) were fed a normal diet that contained 4 g soybean oil/100 g of diet for 6 mo and then divided the mice into four groups (n = 10 or 20/group). Mice in the baseline group were euthanized at 6 mo old, those in the control group continued on a normal diet until 15 mo of age, those in the MF diet group switched to an MF diet (8 g soybean oil/100 g of diet) until 15 mo of age, and those in the MF + FO group switched to an MF diet that was enriched with FO (6.4 g soybean oil + 1.6 g FO/100 g of diet) until 15 mo of age. RESULTS: The area under the curve for lipid absorption decreased with age but lipid absorption tended to be

less attenuated with an MF diet that contained FO. Messenger RNA (mRNA) levels of apolipoprotein B, fatty acid transport protein 4, and microsomal triacylglycerol transfer protein in the small intestine decreased with age but tended to be maintained with an MF diet with or without FO. A histologic analysis of the small intestine showed that villi degenerated with age but the decline was less in mice in the MF + FO group. CONCLUSIONS: The results of this study suggest that MF + FO diets can inhibit the attenuation of lipid absorption commensurate with aging in SAM-P8 via a delay of the natural degeneration that occurs in small intestinal villi over time.

[52] *Moloudizargari M, Mortaz E, Asghari MH et al.* **Effects of the polyunsaturated fatty acids, EPA and DHA, on hematological malignancies: a systematic review**. Oncotarget 2018; 9:11858-11875.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29545942
ABSTRACT
Omega-3 polyunsaturated fatty acids (PUFAs) have well established anti-cancer properties. Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are among this biologically active family of macromolecules for which various anti-cancer effects have been explained. These PUFAs have a high safety profile and can induce apoptosis and inhibit growth of cancer cells both in vitro and in vivo, following a partially selective manner. They also increase the efficacy of chemotherapeutic agents by increasing the sensitivity of different cell lines to specific anti-neoplastic drugs. Various mechanisms have been proposed for the anti-cancer effects of these omega-3 PUFAs; however, the exact mechanisms still remain unknown. While numerous studies have investigated the effects of DHA and EPA on solid tumors and the responsible mechanisms, there is no consensus regarding the effects and mechanisms of action of these two FAs in hematological malignancies. Here, we performed a systematic review of the beneficial effects of EPA and DHA on hematological cell lines as well as the findings of related in vivo studies and clinical trials. We summarize the key underlying mechanisms and the therapeutic potential of these PUFAs in the treatment of hematological cancers. Differential expression of apoptosis-regulating genes and Glutathione peroxidase 4 (Gp-x4), varying abilities of different cancerous and healthy cells to metabolize EPA into its more active metabolites and to uptake PUFAS are among the major factors that determine the sensitivity of cells to DHA and EPA. Considering the abundance of data on the safety of these FAs and their proven anti-cancer effects in hematological cell lines and the lack of related human studies, further research is warranted to find ways of exploiting the anticancer effects of DHA and EPA in clinical settings both in isolation and in combination with other therapeutic regimens.

[53] *Caltabiano S, Mahar KM, Lister K et al.* **The drug interaction potential of daprodustat when coadministered with pioglitazone, rosuvastatin, or trimethoprim in healthy subjects**. Pharmacol Res Perspect 2018; 6:e00327.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29545948
ABSTRACT
This study was conducted to evaluate the likelihood of daprodustat to act as a perpetrator in drug-drug interactions (DDI) with the CYP2C8 enzyme and OATP1B1 transporter using the probe substrates pioglitazone and rosuvastatin as potential victims, respectively. Additionally,

this study assessed the effect of a weak CYP2C8 inhibitor, trimethoprim, as a perpetrator of a DDI with daprodustat. This was a two-part study: Part A assessed the effect of coadministration of daprodustat on the pharmacokinetics of pioglitazone and rosuvastatin in 20 subjects; Part B assessed the coadministration of trimethoprim on the pharmacokinetics of daprodustat in 20 subjects. Coadministration of 100 mg of daprodustat with pioglitazone or rosuvastatin had no effect on the plasma exposures of either probe substrate. When trimethoprim was coadministered with 25-mg daprodustat plasma daprodustat AUC and Cmax increased by 48% and 28%, respectively. Additionally, AUC and Cmax for the metabolite GSK2531401 were decreased by 32% and 40%, respectively. Cmax for the other metabolites was slightly decreased (~8-15%) but no changes in AUC were observed. As 100-mg daprodustat exceeds the planned top therapeutic dose, interaction potential of daprodustat as a perpetrator with substrates of the CYP2C8 enzyme and OATP1B1 transporters is very low. Conversely, daprodustat exposure (AUC and Cmax) is likely to increase moderately with coadministration of weak CYP2C8 inhibitors.

[54] *Shinozawa E, Amano Y, Yamakawa H et al.* **Antidyslipidemic potential of a novel farnesoid X receptor antagonist in a hamster model of dyslipidemia: Comparative studies of other nonstatin agents**. Pharmacol Res Perspect 2018; 6:e00390.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29541476
ABSTRACT
We attempted to clarify the therapeutic capability of antagonists of the farnesoid X receptor (FXR), a nuclear receptor that regulates lipid and bile acid metabolism. Herein, we report the antidyslipidemic effects of a novel synthesized FXR antagonist, compound-T1, utilizing a dyslipidemic hamster model. Compound-T1 selectively inhibited chenodeoxycholic acid-induced FXR activation (IC 50, 2.1 nmol.L(-1)). A hamster model of diet-induced hyperlipidemia was prepared to investigate the antidyslipidemic effects of compound-T1 through comparative studies of the nonstatin lipid-modulating agents ezetimibe, cholestyramine, and torcetrapib. In the hamster model, compound-T1 (6 mg.kg(-1).day(-1), p.o.) increased the level of plasma high-density lipoprotein (HDL)-cholesterol (+22.2%) and decreased the levels of plasma non-HDL-cholesterol (-43.6%) and triglycerides (-31.1%). Compound-T1 also increased hepatic cholesterol 7alpha-hydroxylase expression and fecal bile acid excretion, and decreased hepatic cholesterol content. Moreover, the hamster model could reflect clinical results of other nonstatin agents. Torcetrapib especially increased large HDL particles compared with compound-T1. Additionally, in the human hepatoma Huh-7 cells, compound-T1 enhanced apolipoprotein A-I secretion at a concentration close to its IC 50 value for FXR. Our results indicated the usefulness of the hamster model in evaluating FXR antagonists and nonstatin agents. Notably, compound-T1 exhibited beneficial effects on both blood non-HDL-cholesterol and HDL-cholesterol, which are thought to involve enhancement of cholesterol catabolism and apolipoprotein A-I production. These findings aid the understanding of the antidyslipidemic potential of FXR antagonists with a unique lipid and bile acid modulation.

[55] *Haslacher H, Fallmann H, Waldhausl C et al.* **Type 1 diabetes care: Improvement by standardization in a diabetes rehabilitation clinic. An observational report**. PloS one 2018; 13:e0194135.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29529063

ABSTRACT

BACKGROUND: T1D treatment requires informed self-responsible patients, who, however, frequently miss their therapeutic goals, providing considerable potential for improvement. METHODS: This observational report evaluates T1D patients [N = 109], aged >/=18 years (range 22-82), poorly controlled at home, at and 3 weeks after their admission to our diabetes rehabilitation clinic [DRC], where they were offered standardized, but unmonitored life-style modification. RESULTS: At admission, patients displayed elevated HbA1c values (66 mmol/mol [57; 81]), a high prevalence of co-morbidities (88%), lipodystrophies due to monolocal insulin injections (42%), a low rate of influenza (16%) and pneumococcal (7%) immunization, and underuse of lipid-lowering drugs (-38%). Standardization of life-style improved glucose ($p<0.0001$) and lipid metabolism (LDL/HDL ratio $p<0.01$) permitting reduction of insulin dose and reduction of add-on glucose-lowering drugs (GLDs) other than metformin. Outcome was independent of the mode of insulin treatment strategy and more marked at initially high HbA1c, with DRC-costs/d less than 25% of those encountered at standard hospitals. CONCLUSION: Type 1 diabetes care requires i) insulin treatment, food intake and life style to be handled in concert, ii) this need cannot be replaced by arbitrary addition of add-on GLDs, and iii) training to this end is 75% cheaper at a DRC than in standard hospitals.

[56] *Hindy G, Engstrom G, Larsson SC et al.* **Role of Blood Lipids in the Development of Ischemic Stroke and its Subtypes: A Mendelian Randomization Study**. Stroke 2018.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29535274

ABSTRACT

BACKGROUND AND PURPOSE: Statin therapy is associated with a lower risk of ischemic stroke supporting a causal role of low-density lipoprotein (LDL) cholesterol. However, more evidence is needed to answer the question whether LDL cholesterol plays a causal role in ischemic stroke subtypes. In addition, it is unknown whether high-density lipoprotein cholesterol and triglycerides have a causal relationship to ischemic stroke and its subtypes. Our aim was to investigate the causal role of LDL cholesterol, high-density lipoprotein cholesterol, and triglycerides in ischemic stroke and its subtypes through Mendelian randomization (MR). METHODS: Summary data on 185 genome-wide lipids-associated single nucleotide polymorphisms were obtained from the Global Lipids Genetics Consortium and the Stroke Genetics Network for their association with ischemic stroke (n=16 851 cases and 32 473 controls) and its subtypes, including large artery atherosclerosis (n=2410), small artery occlusion (n=3186), and cardioembolic (n=3427) stroke. Inverse-variance-weighted MR was used to obtain the causal estimates. Inverse-variance-weighted multivariable MR, MR-Egger, and sensitivity exclusion of pleiotropic single nucleotide polymorphisms after Steiger filtering and MR-Pleiotropy Residual Sum and Outlier test were used to adjust for pleiotropic bias. RESULTS: A 1-SD genetically elevated LDL cholesterol was associated with an increased risk of ischemic stroke (odds ratio: 1.12; 95% confidence interval: 1.04-1.20) and large artery atherosclerosis stroke (odds ratio: 1.28; 95% confidence interval: 1.10-1.49) but not with small artery occlusion or cardioembolic stroke in multivariable MR. A 1-SD genetically elevated high-density lipoprotein cholesterol was associated with a decreased risk of small artery occlusion stroke (odds ratio: 0.79; 95% confidence interval: 0.67-0.90) in multivariable MR. MR-Egger

indicated no pleiotropic bias, and results did not markedly change after sensitivity exclusion of pleiotropic single nucleotide polymorphisms. Genetically elevated triglycerides did not associate with ischemic stroke or its subtypes. CONCLUSIONS: LDL cholesterol lowering is likely to prevent large artery atherosclerosis but may not prevent small artery occlusion nor cardioembolic strokes. High-density lipoprotein cholesterol elevation may lead to benefits in small artery disease prevention. Finally, triglyceride lowering may not yield benefits in ischemic stroke and its subtypes.

[57] *Jafar TH, Tan NC, Allen JC et al.* **Management of hypertension and multiple risk factors to enhance cardiovascular health in Singapore: The SingHypertension cluster randomized trial**. Trials 2018; 19:180.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29540213
ABSTRACT
BACKGROUND: Hypertension is a serious public health problem in Singapore and is associated with significant morbidity and mortality from cardiovascular disease (CVD) with considerable implications for health-care resources. The goal of the trial is to compare a multicomponent intervention (MCI) to usual care to evaluate the effectiveness and cost-effectiveness of the MCI for lowering blood pressure (BP) among adults with uncontrolled hypertension in Singapore primary-care clinics. METHODS/DESIGN: The study is a cluster randomized trial in eight polyclinics in Singapore: four deliver a structured MCI and four deliver usual care. The components of the MCI are: (1) an algorithm-driven antihypertensive treatment for all hypertensive individuals using single-pill combination (SPC) and lipid-lowering medication for high-risk hypertensive individuals, (2) a motivational conversation for high-risk hypertensive individuals, (3) telephone-based follow-ups of all hypertensive individuals by polyclinic nurses, and (4) discounts on SPC antihypertensive medications. The trial will be conducted with 1000 individuals aged >/= 40 years with uncontrolled hypertension (systolic BP >/= 140 mmHg or diastolic BP >/= 90 mmHg, based on the mean of the last two of three measurements) in eight polyclinics in Singapore. The primary outcome is change in systolic BP from baseline to follow-up at 24 months post-randomization. The incremental cost of MCI per CVD disability adjusted life years (DALY) averted and quality adjusted life years (QALY) saved will be computed. DISCUSSION: The demonstration of an effective and cost-effective hypertension control program that is implementable in busy polyclinics would provide compelling evidence for upscaling the program across all primary-care centers in Singapore, and possibly other regional countries with a similar health-care structure. TRIAL REGISTRATION: Clinicaltrials.gov, NCT02972619 . Registered on 23 November 2016.

[58] *Sarfo FS, Sarfo-Kantanka O, Adamu S et al.* **Stroke Minimization through Additive Anti-atherosclerotic Agents in Routine Treatment (SMAART): study protocol for a randomized controlled trial**. Trials 2018; 19:181.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29540234
ABSTRACT
BACKGROUND: There is an unprecedented rise in the prevalence of stroke in sub-Saharan Africa (SSA). Secondary prevention guidelines recommend that antihypertensive, statin and antiplatelet therapy be initiated promptly after ischemic stroke and adhered to in a persistent

fashion to achieve optimal vascular-risk reduction. However, these goals are seldom realized in routine clinical care settings in SSA due to logistical challenges. We seek to assess whether a polypill containing fixed doses of three antihypertensive agents, a statin and antiplatelet therapy taken once daily per os for 12 months among recent stroke survivors would result in carotid intimal thickness regression compared with usual care (UC). METHODS: The Stroke Minimization through Additive Anti-atherosclerotic Agents in Routine Treatment (SMAART) trial is a phase 2, open-label, evaluator-blinded trial involving 120 Ghanaian recent-ischemic-stroke survivors. Using a computer-generated sequence, patients will be randomly allocated 1:1 into either the intervention arm or UC. Patients in the intervention arm will receive Polycap DS(R) (containing aspirin, 100 mg; atenolol, 50 mg; ramipril, 5 mg; thiazide, 12.5 mg; simvastatin, 20 mg) taken as two capsules once daily. Patients in the UC will receive separate, individual secondary preventive medications prescribed at the physician's discretion. Both groups will be followed for 12 months to assess changes in carotid intimal thickness regression - a surrogate marker of atherosclerosis - as primary outcome measure. Secondary outcome measures include adherence to therapy, safety and tolerability, health-related quality of life, patient satisfaction, functional status, depression and cognitive dysfunction. DISCUSSION: An efficacy-suggesting SMAART trial could inform the future design of a multi-center, double-blinded, placebo-controlled, parallel-group, randomized controlled trial comparing the clinical efficacy of the polypill strategy for vascular risk moderation among stroke survivors in SSA. TRIAL REGISTRATION: ClinicalTrials.gov , ID: NCT03329599 . Registered on 11 February 2017.

[59] *Moccetti F, Weinkauf CC, Davidson BP et al.* **Ultrasound Molecular Imaging of Atherosclerosis Using Small-Peptide Targeting Ligands Against Endothelial Markers of Inflammation and Oxidative Stress**. Ultrasound in medicine & biology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29548756

ABSTRACT

The aim of this study was to evaluate a panel of endothelium-targeted microbubble (MB) ultrasound contrast agents bearing small peptide ligands as a human-ready approach for molecular imaging of markers of high-risk atherosclerotic plaque. Small peptide ligands with established affinity for human P-selectin, VCAM-1, LOX-1 and von Willebrand factor (VWF) were conjugated to the surface of lipid-stabilized MBs. Contrast-enhanced ultrasound (CEUS) molecular imaging of the thoracic aorta was performed in wild-type and gene-targeted mice with advanced atherosclerosis (DKO). Histology was performed on carotid endarterectomy samples from patients undergoing surgery for unstable atherosclerosis to assess target expression in humans. In DKO mice, CEUS signal for all four targeted MBs was significantly higher than that for control MBs, and was three to sevenfold higher than in wild-type mice, with the highest signal achieved for VCAM-1 and VWF. All molecular targets were present on the patient plaque surface but expression was greatest for VCAM-1 and VWF. We conclude that ultrasound contrast agents bearing small peptide ligands feasible for human use can be targeted against endothelial cell adhesion molecules for inflammatory cells and platelets for imaging advanced atherosclerotic disease.