Literature update week 49 (2018)

[1] *Ennezat PV, Le Jemtel T, Cosgrove S et al.* **Outcome postponement as a potential patient centred measure of therapeutic benefit: examples in cardiovascular medicine**. Acta Cardiol 2018:1-10.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30513258
ABSTRACT
BACKGROUND: The impact of randomised controlled trials (RCTs) depends heavily on the presentation of the findings. OBJECTIVE: Classically, RCT findings are presented in the form of absolute risk reduction (ARR), number needed to treat (NNT) to prevent one adverse outcome, and relative risk reduction (RRR) or hazard ratio (the most favourable means for drug marketing). However, the estimation of average survival gain (i.e. outcome postponement between a trial intervention and comparator) is an alternative and informative means of presenting the findings of RCTs. STUDY SELECTION: Recent cardiovascular RCTs evaluating ezetimibe added to simvastatin, evolocumab, canakinumab, ticagrelor, rivaroxaban, ivabradine, LCZ 696 (sacubitril/valsartan), and transfemoral aortic valve replacement are analysed and discussed. FINDINGS: The average survival gains ranged between 4.9 days on a composite end point with ticagrelor versus clopidogrel in randomised patients with acute coronary syndrome and 117 days of life expectancy obtained with TAVR versus standard therapy in patients with severe aortic stenosis deemed ineligible for surgery. CONCLUSIONS: Using outcome postponement as an additional measure of treatment effect is likely to be more easily understood than hazard ratio or RRR by both patients and physicians and could help when evaluating drugs.

[2] *Tang Y, Zhang X, Chen Z et al.* **Novel benzamido derivatives as PTP1B inhibitors with anti-hyperglycemic and lipid-lowering efficacy**. Acta pharmaceutica Sinica. B 2018; 8:919-932.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30505661
ABSTRACT
Based on a non-competitive and selective PTP1B inhibitor reported by us previously, thirty-nine benzamido derivatives were designed and synthesized as novel PTP1B inhibitors. Among them, twelve compounds exhibited IC50 values at micromolar level against human recombinant PTP1B, and most of them exhibited significant selectivity to PTP1B over TC-PTP and CD45. Further evaluation of the most potent compound 27 on high-fat diet (HFD)-induced insulin-resistant (IR) obese mice indicated that 27 could modulate glucose metabolism and ameliorate dyslipidemia simultaneously.

[3] *Yebyo HG, Aschmann HE, Puhan MA*. **Finding the Balance Between Benefits and Harms When Using Statins for Primary Prevention of Cardiovascular Disease: A Modeling Study**. Annals of internal medicine 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30508425
ABSTRACT
Background: Many guidelines use expected risk for cardiovascular disease (CVD) during the next 10 years as a basis for recommendations on use of statins for primary prevention of CVD. However, how harms were considered and weighed against benefits is often unclear. Objective: To identify the expected risk above which statins provide net benefit. Design: Quantitative benefit-harm balance modeling study. Data Sources: Network meta-analysis of primary

prevention trials, a preference survey, and selected observational studies. Target Population: Persons aged 40 to 75 years with no history of CVD. Time Horizon: 10 years. Perspective: Clinicians and guideline developers. Intervention: Low- or moderate-dose statin versus no statin. Outcome Measures: The 10-year risk for CVD at which statins provide at least a 60% probability of net benefit, with baseline risk, frequencies of and preferences for statin benefits and harms, and competing risk for non-CVD death taken into account. Results of Base-Case Analysis: Younger men had net benefit at a lower 10-year risk for CVD than older men (14% for ages 40 to 44 years vs. 21% for ages 70 to 75 years). In women, the risk required for net benefit was higher (17% for ages 40 to 44 years vs. 22% for ages 70 to 75 years). Atorvastatin and rosuvastatin provided net benefit at lower 10-year risks than simvastatin and pravastatin. Results of Sensitivity Analysis: Most alternative assumptions led to similar findings. Limitation: Age-specific data for some harms were not available. Conclusion: Statins provide net benefits at higher 10-year risks for CVD than are reflected in most current guidelines. In addition, the level of risk at which net benefit occurs varies considerably by age, sex, and statin type. Primary Funding Source: Swiss Government Excellence Scholarship Office, Beatrice Ederer-Weber Foundation, and North-South Cooperation at the University of Zurich.

[4] *Masson W, Lobo M, Huerin M et al.* **Plasma proprotein convertase subtilisin/kexin type 9 inhibitors and cataract risk: A systematic review and meta-analysis**. Archivos de la Sociedad Espanola de Oftalmologia 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30502968
ABSTRACT
BACKGROUND: The marked decrease in LDL-C levels produced by the inhibitors of the plasma proprotein convertase subtilisin/kexin type 9 (iPCSK9) could be associated with an increased risk of cataracts. METHODS: A meta-analysis was performed that included randomised clinical trials controlled with iPCSK9, alone, or in combination with other lipid-lowering drugs, which reported new cases of cataracts, by searching PubMed/Medline, databases of EMBASE and Cochrane Clinical Trials. A fixed-effect model was used, and a meta-regression was carried out evaluating the relationship between intra-treatment LDL-C and the risk of developing cataracts. RESULTS: Five eligible studies of iPCSK9 including 83,492 patients were taken into account for the analysis, and 531 new cases of cataracts in iPCSK9 group vs. 532 in placebo group were diagnosed. The iPCSK9 therapy was not associated with an increased risk of cataracts [OR: 0.96, 95% CI: 0.85-1.08; P=.86, I(2): 0%]. Likewise, no significant association was found between on-treatment LDL-C levels, differences between study arms, and new cases of cataracts. CONCLUSION: In this analysis, the use of iPCSK9 was not associated with an increased risk of cataracts.

[5] *Singh F, Zoll J, Duthaler U et al.* **PGC-1beta modulates statin-associated myotoxicity in mice**. Archives of toxicology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30511338
ABSTRACT
Statins inhibit cholesterol biosynthesis and lower serum LDL-cholesterol levels. Statins are generally well tolerated, but can be associated with potentially life-threatening myopathy of unknown mechanism. We have shown previously that statins impair PGC-1beta expression in

human and rat skeletal muscle, suggesting that PGC-1beta may play a role in statin-induced myopathy. PGC-1beta is a transcriptional co-regulator controlling the expression of important genes in mitochondrial biogenesis, antioxidative capacity and energy metabolism. The principle aim of the current study was to investigate the interaction between atorvastatin and PGC-1beta in more detail. We therefore treated wild-type mice and mice with selective skeletal muscle knockout of PGC-1beta (PGC-1beta((i)skm-/-) mice) with oral atorvastatin (5 mg/kg/day) for 2 weeks. At the end of treatment, we determined body parameters, muscle function, structure, and composition as well as the function of muscle mitochondria, mitochondrial biogenesis and activation of apoptotic pathways. In wild-type mice, atorvastatin selectively impaired mitochondrial function in glycolytic muscle and caused a conversion of oxidative type IIA to glycolytic type IIB myofibers. Conversely, in oxidative muscle of wild-type mice, atorvastatin enhanced mitochondrial function via activation of mitochondrial biogenesis pathways and decreased apoptosis. In PGC-1beta((i)skm-/-) mice, atorvastatin induced a switch towards glycolytic fibers, caused mitochondrial dysfunction, increased mitochondrial ROS production, impaired mitochondrial proliferation and induced apoptosis in both glycolytic and oxidative skeletal muscle. Our work reveals that atorvastatin mainly affects glycolytic muscle in wild-type mice and demonstrates the importance of PGC-1beta for oxidative muscle integrity during long-term exposure to a myotoxic agent.

[6] *Hasanvand A, Ahmadizar F, Abbaszadeh A et al.* **The Antinociceptive Effects of Rosuvastatin in Chronic Constriction Injury Model of Male Rats**. Basic and clinical neuroscience 2018; 9:251-260.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30519383
ABSTRACT
Introduction: According to studies, statins possess analgesics and anti-inflammatory properties. In the present study, we examined the antinociceptive, anti-inflammatory and antioxidative effects of rosuvastatin in an experimental model of Chronic Constriction Injury (CCI). Methods: Our study was conducted on four groups; sham, CCI (the control group), CCI+rosuvastatin (i.p. 5 mg/kg), and CCI+rosuvastatin (i.p. 10 mg/kg). We performed heat hyperalgesia, cold and mechanical allodynia tests on the 3(rd), 7(th), 14(th), and 21(st) after inducing CCI. Blood samples were collected to measure the serum levels of Tumor Necrosis Factor (TNF)-alpha, and Interleukin (IL)-6. Rats' spinal cords were also examined to measure tissue concentration of Malondialdehyde (MDA), Superoxide Dismutase (SOD), and Glutathione Peroxidase (GPx) enzymes. Results: Our findings showed that CCI resulted in significant increase in heat hyperalgesia, cold and mechanical allodynia on the 7(th), 14(th) and 21(st) day. Rosuvastatin use attenuated the CCI-induced hyperalgesia and allodynia. Rosuvastatin use also resulted in reduction of TNF-alpha, IL-6, and MDA levels. However, rosuvastatin therapy increased the concentration of SOD and GPx in the CCI+Ros (5 mg/kg) and the CCI+Ros (10 mg/kg) groups compared to the CCI group. Conclusion: Rosuvastatin attenuated the CCI-induced neuropathic pain and inflammation. Thus, antinociceptive effects of rosuvastatin might be channeled through inhibition of inflammatory biomarkers and antioxidant properties.

[7] *Gurzeler E, Aavik E, Laine A et al.* **Therapeutic effects of rosuvastatin in hypercholesterolemic prediabetic mice in the absence of low density lipoprotein receptor**. Biochimica et biophysica acta. General subjects 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30508567
ABSTRACT
Statins are effective drugs used to prevent and treat cardiovascular diseases but their effects in the absence of low density lipoprotein receptor (LDLR) and on the risk of diabetes are not yet well characterized. The aim of this study was to clarify systemic and pleiotropic effects of rosuvastatin on cardiovascular and diabetic phenotypes. IGF-II/LDLR(-/-)ApoB(100/100) hypercholesterolemic prediabetic mice were used to test the effects of rosuvastatin on plasma glucose, insulin, lipids, atherosclerosis and liver steatosis. To get a more comprehensive view about changes in gene expression RNA-sequencing was done from the liver. Rosuvastatin significantly reduced plasma cholesterol in hypercholesterolemic mice in the absence of LDLR but had no effects on atherosclerosis at aortic sinus level or in coronary arteries. Rosuvastatin also significantly reduced liver steatosis without any harmful effects on glucose or insulin metabolism. RNA-sequencing showed relatively specific effects of rosuvastatin on genes involved in cholesterol metabolism together with a significant anti-inflammatory gene expression profile in the liver. In addition, significant changes were found in the expression of Perilipin 4 and 5 which are involved in lipid droplet formation in the liver. For the first time it could be shown that Tribbles proteins are affected by rosuvastatin treatment in the hyperlipidemic mice. Rosuvastatin had several positive effects on hypercholesterolemic mice showing early signs of diabetes, many of which are unrelated to cholesterol and lipoprotein metabolism. These results increase our understanding about the systemic and pleiotropic effects of rosuvastatin in the absence of LDLR expression.

[8] *Torii H, Shimizu R, Tanizaki Y et al.* **Effects of Ramelteon and Other Sleep-Promoting Drugs on Serum Low-Density Lipoprotein and Non-high-density Lipoprotein Cholesterol: A Retrospective Comparative Pilot Study**. Biological & pharmaceutical bulletin 2018; 41:1778-1790.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30504680
ABSTRACT
Melatonin has been suggested to play important roles in lipid metabolism as well as circadian rhythm; however, very few studies explored the effects of ramelteon, a selective melatonin receptor agonist, on serum lipid profiles. In this study effects of ramelteon on serum lipid profiles were explored, comparing to those of other sleep-promoting drugs including benzodiazepines and non-benzodiazepines, in patients with insomnia. We retrospectively reviewed medical charts of outpatients who were treated with ramelteon (8 mg/d) or other sleep-promoting drugs for no less than 8 weeks during the period between October 1st, 2011 and September 30th, 2014, and compared the changes in serum lipid profiles between the two groups. Patients with regular dialysis or malignant diseases treated with cytotoxic anti-cancer drugs, or whose lipid-lowering drugs were altered during the study period, were excluded. Among 365 or 855 outpatients treated with ramelteon or other sleep-promoting drugs, 35 or 46 patients, respectively, had complete serum low-density lipoprotein cholesterol (LDL-C) or non-high-density lipoprotein cholesterol (non-HDL-C) data. Serum LDL-C was significantly

reduced from 103.1+/-4.4 to 94.6+/-4.2 mg/dL (8.2% reduction, p<0.05, n=31) in the ramelteon group, and was not significantly changed (p=0.23, n=40) in the other sleep-promoting drug group. Non-HDL-C was significantly decreased from 138.8+/-6.0 to 130.6+/-4.9 mg/dL (5.9% reduction, p<0.05, n=32) in the ramelteon group, and was not significantly altered (p=0.29, n=42) in the other sleep-promoting drug group. Ramelteon, but not other sleep-promoting drugs, specifically lowers serum LDL-C and non-HDL-C levels.

[9] *Otrocka-Domagala I, Pazdzior-Czapula K, Maslanka T*. **Simvastatin Impairs the Inflammatory and Repair Phases of the Postinjury Skeletal Muscle Regeneration**. BioMed research international 2018; 2018:7617312.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30519583
ABSTRACT
Background: Recent clinical data have suggested that the chronic use of high-lipophilic statins impairs the regenerative capacity of skeletal muscle. Because this activity of statins is poorly understood, we aimed to investigate the effect of simvastatin (SIM) on postinjury myofibre regeneration. Methods: The porcine model was used in this study. The animals were divided into two groups: nontreated (control; n=24) and SIM-treated (40 mg/day; n=24). On the 15th day (day 0) of the experiment, a bupivacaine hydrochloride- (BPVC-) induced muscle injury was established, and the animals were sacrificed in the following days after muscle injury. The degree of regeneration was assessed based on histopathological and immunohistochemical examinations. The presence and degree of extravasation, necrosis, and inflammation in the inflammatory phase were assessed, whereas the repair phase was evaluated based on the numbers of muscle precursor cells (MPCs), myotube and young myofibres. Results: In the inflammatory phase, SIM increased the distribution and prolonged the period of extravasation, prolonged the duration of necrosis, and prolonged and enhanced the infiltration of inflammatory cells. In the repair phase, SIM delayed and prolonged the activity of MPCs, delayed myotube formation, and delayed and decreased the formation of young myofibres. Our results indicated that SIM did not improve blood vessel stabilization at the site of the injury, did not exert an anti-inflammatory effect, prolonged and enhanced the inflammatory response, and impaired MPC activity, differentiation, and fusion. Moreover, SIM appeared to reduce M1 macrophage activity, resulting in slower removal of necrotic debris and sustained necrosis. Conclusion: This study shows that SIM negatively affects the inflammatory and repair phases of the postinjury muscle regeneration. These findings are unique, strengthen the available knowledge on the side effects of SIM, and provide evidence showing that statin therapy is associated with an increased risk of impairment of the regenerative capacity of muscle.

[10] *Chen L, Zhan Q, Peng W et al.* **Comparison of two different measurement methods in evaluating basilar atherosclerotic plaque using high-resolution MRI at 3 tesla**. BMC medical imaging 2018; 18:49.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30509197
ABSTRACT
BACKGROUND: To compare the Self-referenced and Referenced measurement methods in assessing basilar artery (BA) atherosclerotic plaque employing dark blood high-resolution MRI at 3 Tesla. METHODS: Forty patients with > 20% stenosis as identified by conventional MRA

were recruited and evaluated on a 3 Tesla MRI system. The outer wall, inner wall and lumen areas of maximal lumen narrowing site and the outer wall and lumen areas of sites that were proximal and distal to the maximal lumen narrowing site were manually traced. Plaque area (PA), stenosis rate (SR) and percent plaque burden (PPB) were calculated using the Self-referenced and Referenced measurement methods, respectively. To assess intra-observer reproducibility, BA plaque was measured twice with a 2-week interval in between measurements. RESULTS: Thirty-seven patients were included in the final analysis. There were no significant differences in PA, SR and PPB measurements between the two methods. The intra-class coefficients and coefficient of variations (CV) ranged from 0.976 to 0.990 and from 3.73 to 5.61% for the Self-referenced method and ranged from 0.928 to 0.971 and from 4.64 to 9.95% for the Referenced method, respectively. Both methods are effective in the evaluation of BA plaque. However, the CVs of the Self-referenced method is lower than the Referenced measurement method. Moreover, Bland-Altman plots showed that the Self-referenced method has a narrower interval than the Referenced measurement method. CONCLUSIONS: The Self-referenced method is better and more convenient for evaluating BA plaque, and it may serve as a promising method for evaluation of basilar atherosclerotic plaque.

[11] *Miura K, Ohnishi H, Morimoto N et al.* **Ezetimibe suppresses development of liver tumors by inhibiting angiogenesis in mice fed a high-fat diet**. Cancer science 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30520543

ABSTRACT

Nonalcoholic steatohepatitis (NASH) is a common cause of liver cirrhosis and hepatocellular carcinoma (HCC). However, effective therapeutic strategies for preventing and treating NASH-mediated liver cirrhosis and HCC are lacking. Cholesterol is closely associated with vascular endothelial growth factor (VEGF), a key factor that promotes HCC. Recent reports have demonstrated that statins could prevent HCC development. In contrast, we have little information on ezetimibe, an inhibitor of cholesterol absorption, in the prevention for NASH-related liver cirrhosis and HCC. In the present study, a steatohepatitis-related HCC model, hepatocyte-specific phosphatase and tensin homolog (Pten)-deficient (Pten(Deltahep)) mice were fed a high-fat (HF) diet with/without ezetimibe. In the standard-diet group, ezetimibe did not reduce the development of liver tumors in Pten(Deltahep) mice, in which the increase of serum cholesterol levels was mild. Feeding of a HF diet increased serum cholesterol levels markedly and subsequently increased serum levels of VEGF, a crucial component of angiogenesis. The HF diet increased the number of VEGF-positive cells and vascular endothelial cells in the tumors of Pten(Deltahep) mice. Kupffer cells, macrophages in the liver, increased VEGF expression in response to fat overload. Ezetimibe treatment lowered cholesterol levels and these angiogenetic processes. As a result, ezetimibe also suppressed inflammation, liver fibrosis, and tumor growth in Pten(Deltahep) mice on the HF diet. Tumor cells were highly proliferative by HF-diet feeding, which was inhibited by ezetimibe. In conclusion, ezetimibe suppressed development of liver tumors by inhibiting angiogenesis in Pten(Deltahep) mice with hypercholesterolemia.

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[12] *Kim J, Lee HS, Lee KY*. **Effect of statins on fasting glucose in non-diabetic individuals: nationwide population-based health examination in Korea**. Cardiovascular diabetology 2018; 17:155.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30518364
ABSTRACT
BACKGROUND: Increasing evidence suggest that statin therapy has a diabetogenic effect. Individual types of statin may have a different effect on glucose metabolism. Using the repeated nationwide population-based health screening data in Korea, we investigated the longitudinal changes in fasting glucose level of non-diabetic individuals by use of statins. METHODS: From the National Health Screening Cohort, we included 379,865 non-diabetic individuals who had >/= 2 health screening examinations with fasting blood glucose level measured in 2002-2013. Using the prescription records of statins in the database, we calculated the proportion of days covered (PDC) and average number of defined daily doses per day (anDDD) by statins. We constructed multivariate linear mixed models to evaluate the effects of statins on the changes in fasting glucose (Deltaglu). RESULTS: High PDC by statins had a significant positive effect on Deltaglu (coefficient for PDC 0.093 mmol/L, standard error 0.007, $p < 0.001$). anDDD by statins was also positively associated with Deltaglu (coefficient for anDDD 0.119 mmol/L, standard error 0.009, $p < 0.001$). Unlike statins, the PDC by fibrate and ezetimibe were not significantly associated with Deltaglu. There was no significant interaction effect on Deltaglu between time interval and statin. Considering individual types of statins, use of atorvastatin, rosuvastatin, pitavastatin, and simvastatin were significantly associated with increase of Deltaglu. Pravastatin, lovastatin, and fluvastatin were also positively associated with Deltaglu, but were not statistically significant. CONCLUSIONS: More adherent and intensive use of statins was significantly associated with an increase in fasting glucose of non-diabetic individuals. In subgroup analysis of individual statins, use of atorvastatin, rosuvastatin, pitavastatin and simvastatin had significant association with increase in fasting glucose. Pravastatin, lovastatin, and fluvastatin had non-significant trend toward an increased fasting glucose. Our findings suggest the medication class effect of statins inducing hyperglycemia.

[13] *Geladari E, Tsamadia P, Vallianou NG*. **ANGPTL3 Inhibitors- Their Role in Cardiovascular Disease Through Regulation of Lipid Metabolism**. Circulation journal : official journal of the Japanese Circulation Society 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30504621
ABSTRACT
Elevated plasma lipid levels are linked to atherosclerosis, a hallmark for coronary artery disease (CAD), documented by animal studies as well as angiographic and clinical studies. The ability to treat hyperlipidemia through lifestyle changes and lipid-lowering agents has been related to the slow progression of atherosclerosis and decreased incidence of major coronary events. Angiopoietin-like proteins (ANGPTLs) are a family of secreted glycoproteins expressed in the liver that share common domain characteristics with angiopoietins, the main regulators of angiogenesis. Although ANGPTLs cannot bind the angiopoietin receptors expressed on endothelial cells, 2 ANGPTL family members (ANGPTL3 and ANGPTL4) have clinical importance because of their unambiguous effects on lipoprotein metabolism in mice and humans. The regulation of plasma lipid levels by ANGPTL3 is controlled via affecting lipoprotein lipase and

endothelial lipase-mediated hydrolysis of triglycerides (TGs) and phospholipids. ANGPTL 3, along with the other 2 members, 4 and 8, is a key to balancing the distribution of circulating TGs between white adipose tissue (WAT) and oxidative tissues. Thus, ongoing trials with newly discovered medications in the form of monoclonal antibodies or antisense oligonucleotides with novel targets are under analysis and may represent a fresh frontier in the treatment of hyperlipidemia and CAD.

[14] *Holden RM, Hetu MF, Li TY et al.* **Circulating Gas6 is associated with reduced human carotid atherosclerotic plaque burden in high risk cardiac patients**. Clinical biochemistry 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30508521
ABSTRACT
OBJECTIVE: Pre-clinical studies suggest that growth arrest-specific protein 6 (Gas6), a member of the vitamin K dependent family of proteins, is implicated in atherosclerosis. A role for Gas6 in stabilizing atherosclerotic plaque has been suggested. Our aim was to determine the association between Gas6 and measures of carotid artery atherosclerosis in humans undergoing elective coronary angiography. Secondary aims were to determine the association between Gas6 and sex, diabetes, and obesity. METHODS: In 204 outpatients referred for coronary angiography, EDTA plasma was collected and a focused carotid ultrasound performed. Degree of angiographic coronary artery disease was scored. Carotid intima media thickness as well as maximum plaque height, plaque area, and grayscale median were measured by vascular sonography. Gas6 was assessed by enzyme-linked immunosorbent assay. RESULTS: We found that Gas6 concentrations were lower in males and were associated with diabetes, obesity, and lower kidney function. After adjustment for age, sex, kidney function, BMI and traditional cardiac risk factors; diabetes was associated with higher levels of Gas6, whilst there was a significant inverse relationship between Gas6 and total plaque area. Gas6 was inversely associated with maximum plaque height and total plaque area in adjusted multi-variable models. CONCLUSIONS: We observed higher levels of Gas6 in participantswith adverse cardiovascular risk profiles (e.g. diabetes, obesity) yet Gas6 was independently associated with reduced plaque height and total plaque area. These findings suggest that Gas6 may play a role in human atherosclerotic plaque remodeling.

[15] *Casula M, Pirillo A, Catapano AL*. **Lipid Lowering and Incidence of Cataract, a Role for Fibrates**. Clinical pharmacology and therapeutics 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30520012
ABSTRACT
Cataract is a pathological eye condition with loss of lens transparency. Age-related cataract is the most common type in adults, and opacity is believed to result from oxidative stress. According to estimates by the World Health Organization, cataract affects approximately 100 million people worldwide. There has been discussion on the role of lipid-lowering drugs in inducing cataract. Herein, we comment on an article suggesting a role for fibrates.

[16] *Chilton RJ, Oliveros R, Gallegos KM, Pham S*. **PCSK9 inhibitors and diabetes: translational biology to clinical practice**. Diabetes Obes Metab 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30520245

ABSTRACT
Improving patient care incorporates well done translational science with excellent clinical trials. The development of new medications beyond statins to reduce low-density lipoprotein (LDL) in patients who are at high risk for cardiovascular (CV) events has ushered in new concerns by physicians from recent clinical trials. This article is protected by copyright. All rights reserved.

[17] *Mamdooh N, Kasabri V, Al-Hiari Y et al.* **Evaluation of selected commercial pharmacotherapeutic drugs as potential pancreatic lipase inhibitors and antiproliferative compounds**. Drug development research 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30511444
ABSTRACT
In this study, 15 commercial acidic drugs have been evaluated for pancreatic lipase (PL) inhibitory activity using an in vitro spectrophotometric method. The acidity was the basis of selection, since most PL inhibitors exhibit acidic groups and high lipophilicity. Orlistat was the robust reference agent for potency and efficacy determinations. In comparison to the cisplatin, the evaluation of the antineoplastic activities of selected drugs in a panel of colorectal cancer cell lines (HT-29, HCT-116, SW620, CACO-2, and SW480) and normal periodontal ligament fibroblasts for safety examination was performed by using a sulforhodamine procuring ascorbic acid as a reference in diphenyl-2-picryl-hydrazyl assay of radical scavenging properties was performed. This research revealed three highly acidic pharmacological classes with reasonable PL inhibitory activity in comparison to orlistat out of 15 selected drugs, namely sulfonylureas, fluoroquinolones, and proton pump inhibitors. Docking studies supported the hypothesis of a selection based on acidity, since it showed that the sulfonamide acid group (glyburide) is a remarkably potent interacting group with the enzyme. Failing to fulfill other structure-activity relationship requirements (lipophilicity) led to weak activity. Since the drugs are of different chemical classes with unknown mechanisms, they showed diverse antiproliferative activity. Some drugs such as atorvastatin and gemifloxacin showed higher antiproliferative activity than cisplatin with high-safety profiles against SW620 and SW480 cell lines, respectively, whereas lansoprazole and clopidogrel revealed comparable activity to cisplatin against HCT-116 and SW480, respectively. Unfortunately, selected tested drugs exhibited negligible radical scavenging activity versus ascorbic acid. Hit, Lead & Candidate Discovery.

[18] *Kosmas CE, Silverio D, Sourlas A et al.* **Impact of lipid-lowering therapy on glycemic control and the risk for new-onset diabetes mellitus**. Drugs in context 2018; 7:212562.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30515229
ABSTRACT
Lipid-lowering therapy is used very commonly nowadays not only for the optimization of the lipid profile but also to reduce cardiovascular risk. However, some studies have linked the use of certain lipid-lowering agents with an increased risk for impaired glycemic control and new-onset diabetes mellitus, a condition well established as an important risk factor for cardiovascular disease. On the other hand, some other lipid-lowering agents have been shown to have a beneficial effect on glucose metabolism. Profound knowledge of these differences would enable the clinician to choose the right lipid-lowering medication for each individual patient, so that the benefits would outweigh the risk of side effects. This review aims to present

and discuss the clinical and scientific data pertaining to the impact of lipid-lowering therapy on glycemic control and the risk for new-onset diabetes mellitus.

[19] *Kandzia I, Kowar M, Frackowiak M, Jacobs AH*. **[Simvastatin-Induced Myopathy after Dose Increase]**. Deutsche medizinische Wochenschrift (1946) 2018; 143:1791-1794.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30508862
ABSTRACT
HISTORY AND CLINICAL FINDINGS: We present a 86-year-old patient who suffered from progressive weakness in his right leg. Due to a hypercholesterinemia he had received Simvastatin for a few years. Because of higher cholesterine levels the dosis had been increased from 40 to 80 mg 6 months ago. INVESTIGATIONS AND DIAGNOSIS: We saw elevated levels of creatinine kinase and creatinine. In the EMG, a neuromuscular impairment was detected. In context with the medical history we could make the diagnosis of a statin-induced myopathy with rhabdomyolysis. TREATMENT AND COURSE: After stopping the medication with statin and under liquid substitution, creatinine kinase and creatinine levels dropped. After therapy the weakness of the leg was totally recurrent. CONCLUSION: In case of unclear neurological symptoms and under therapy with statins, a myopathy should be considered.

[20] *Schwaab B, Zeymer U, Jannowitz C et al.* **Improvement of low-density lipoprotein cholesterol target achievement rates through cardiac rehabilitation for patients after ST elevation myocardial infarction or non-ST elevation myocardial infarction in Germany: Results of the PATIENT CARE registry**. European journal of preventive cardiology 2018:2047487318817082.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30509144
ABSTRACT
AIMS: The PATIENT CARE registry aimed to document clinical characteristics of patients during cardiac rehabilitation after myocardial infarction, including the current pharmacological treatment, risk factor modification and achievement of treatment targets for low-density lipoprotein cholesterol (LDL-C). METHODS: Multicentre, prospective non-interventional study at 20 cardiac rehabilitation in-patient centres across Germany. RESULTS: A total of 1408 patients post myocardial infarction were analysed. Patients' mean age was 62 +/- 11 years and 27.0% were women. ST elevation myocardial infarction (n = 657; 48.7%), and non-ST elevation myocardial infarction (n = 617; 45.8%) were equally balanced causes for hospitalization, while previous coronary artery bypass grafting was reported in n = 134 patients (9.9%). On average, cardiac rehabilitation began 19 +/- 10 days after the index event and lasted for 22 +/- 4 days. At discharge, 96.7% of patients received statins, 13.0% another lipid-lowering medication in addition to a statin, 98.5% antithrombotic drugs and 22.3% antidiabetic medication. The rate of patients with LDL-C on target according to the European Society of Cardiology/European Atherosclerosis Society dyslipidaemia guidelines 2011 (<70 mg/dl (1.8 mmol/l) or at least 50% reduction of baseline value) was increased from 21.4% at admission to cardiac rehabilitation to 41.9% at discharge after cardiac rehabilitation. Most patients (95.2%) completed the cardiac rehabilitation and 88% returned to their former work at full time. CONCLUSION: During cardiac rehabilitation, the modifiable cardiovascular risk factors, in particular the LDL-C, were substantially improved in patients after myocardial infarction. The great majority were able to

return to work. However, less than 50% reached the LDL-C guideline targets during short-term cardiac rehabilitation.

[21] *Nikolic D, Corina A, Toth PP et al.* **Choosing an ideal pharmacotherapeutic strategy for dyslipidemia in children**. Expert opinion on pharmacotherapy 2018:1-4.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30521406
ABSTRACT

[22] *Nakamura A, Sato K, Kanazawa M et al.* **Impact of decreased insulin resistance by ezetimibe on postprandial lipid profiles and endothelial functions in obese, non-diabetic-metabolic syndrome patients with coronary artery disease**. Heart Vessels 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30519809
ABSTRACT
The association between insulin resistance and lipid dysmetabolism after consuming a meal is unclear. We aimed at assessing the effects of ezetimibe on postprandial hyperlipidemia and hyperinsulinemia and to find out whether the medication improves endothelial function in obese metabolic syndrome (MetS) patients with coronary artery disease (CAD). We obtained oral fat loading test results (4 and 6 h after load) and brachial flow-mediated vasodilation (FMD) measurements before and 24 weeks after ezetimibe treatment initiation from 27 MetS patients with CAD and from 68 control patients with CAD alone. Serum triglyceride (TG) and insulin levels (2 h after the loading dose) were significantly higher in MetS patients than in control patients. The incremental areas under the curve (iAUCs) for these levels decreased significantly after ezetimibe treatment in MetS patients but not in control patients. Treatment with ezetimibe resulted in significant FMD changes in MetS patients (from 3.4 to 4.9%, P = 0.002), but not in control patients (from 5.1 to 5.4%, P = 0.216). When MetS patients were divided into two groups based on the median insulin iAUC reduction rate (higher group >/= 34%, n = 14; lower group < 34%, n = 13), those in the higher group showed a significantly higher rate of change in the iAUCs of TG and FMD than those in the lower group (TG, 31.0% vs. 10.8%; P = 0.033; FMD, 39.2% vs. 9.8%; P = 0.037). These results suggest that ezetimibe may reverse insulin resistance, reducing lipid dysmetabolism after a meal and endothelial dysfunction in MetS patients with CAD.

[23] *McGettigan B, McMahan R, Orlicky D et al.* **Dietary Lipids Differentially Shape NASH Progression and the Transcriptome of Kupffer Cells and Infiltrating Macrophages**. Hepatology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30516830
ABSTRACT
BACKGROUND: A crucial component of non-alcoholic fatty liver disease (NAFLD) pathogenesis is lipid stress, which may contribute to hepatic inflammation and activation of innate immunity in the liver. However, little is known regarding how dietary lipids, including fat and cholesterol, may facilitate innate immune activation in vivo. We hypothesized that dietary fat and cholesterol drive NAFLD progression to steatohepatitis and hepatic fibrosis by altering the transcription and phenotype of hepatic macrophages METHODS: This hypothesis was tested by using RNA-seq methods to characterize and analyze sort-purified hepatic macrophage

populations that were isolated from mice fed diets with varying amounts of fat and cholesterol RESULTS: The addition of cholesterol to a high fat diet triggered hepatic pathology reminiscent of advanced non-alcoholic steatohepatitis (NASH) in humans characterized by signs of cholesterol dysregulation, generation of oxidized LDL, increased recruitment of hepatic macrophages, and significant fibrosis. RNA-seq analyses of hepatic macrophages in this model revealed that dietary cholesterol induced a tissue repair and regeneration phenotype in Kupffer cells and recruited infiltrating macrophages to a greater degree than fat. Furthermore, comparison of diseased Kupffer cells and infiltrating macrophages revealed that these two macrophage subsets are transcriptionally diverse. Finally, direct stimulation of murine and human macrophages with oxidized LDL recapitulated some of the transcriptional changes observed in the RNA-seq study. These findings indicate that fat and cholesterol synergize to alter macrophage phenotype, and they also challenge the dogma that Kupffer cells are purely pro-inflammatory in NASH CONCLUSION: This comprehensive view of macrophage populations in NASH indicates novel mechanisms by which cholesterol contribute to NASH progression and identifies potential therapeutic targets for this common disease.

[24] *Zreik M, van Hamersvelt RW, Wolterink JM et al.* **A Recurrent CNN for Automatic Detection and Classification of Coronary Artery Plaque and Stenosis in Coronary CT Angiography**. IEEE transactions on medical imaging 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30507498
ABSTRACT
Various types of atherosclerotic plaque and varying grades of stenosis could lead to different management of patients with coronary artery disease. Therefore, it is crucial to detect and classify the type of coronary artery plaque, as well as to detect and determine the degree of coronary artery stenosis. This study includes retrospectively collected clinically obtained coronary CT angiography (CCTA) scans of 163 patients. In these, the centerlines of the coronary arteries were extracted and used to reconstruct multi-planar reformatted (MPR) images for the coronary arteries. To define the reference standard, the presence and the type of plaque in the coronary arteries (no plaque, non-calcified, mixed, calcified), as well as the presence and the anatomical significance of coronary stenosis (no stenosis, nonsignificant i.e. < 50% luminal narrowing, significant i.e. >/= 50% luminal narrowing) were manually annotated in the MPR images by identifying the start- and end-points of the segment of the artery affected by the plaque. To perform automatic analysis, a multi-task recurrent convolutional neural network is applied on coronary artery MPR images. First, a 3D convolutional neural network is utilized to extract features along the coronary artery. Subsequently, the extracted features are aggregated by a recurrent neural network that performs two simultaneous multiclass classification tasks. In the first task, the network detects and characterizes the type of the coronary artery plaque. In the second task, the network detects and determines the anatomical significance of the coronary artery stenosis. The network was trained and tested using CCTA images of 98 and 65 patients, respectively. For detection and characterization of coronary plaque, the method achieved an accuracy of 0.77. For detection of stenosis and determination of its anatomical significance, the method achieved an accuracy of 0.80. The results demonstrate that automatic detection and classification of coronary artery plaque and stenosis are feasible. This may enable

automated triage of patients to those without coronary plaque and those with coronary plaque and stenosis in need for further cardiovascular workup.

[25] *Gori T*. **Endothelial Function: A Short Guide for the Interventional Cardiologist**. International journal of molecular sciences 2018; 19.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30513819
ABSTRACT
An impaired function of the coronary endothelium is an important determinant of all stages of atherosclerosis, from initiation, to mediation of functional phenomena-such as spasm and plaque erosion, to atherothrombotic complications. Endothelial function is modified by therapies, including stent implantation. Finally, endothelial function changes over time, in response to physical stimuli and pharmocotherapies, and its assessment might provide information on how individual patients respond to specific therapies. In this review, we describe the role of the endothelium in the continuum of coronary atherosclerosis, from the perspective of the interventional cardiologist. In the first part, we review the current knowledge of the role of endothelial (dys)function on atherosclerotic plaque progression/instabilization and on the mechanisms of ischemia, in the absence of coronary artery stenosis. In the second part of this review, we describe the impact of coronary artery stenting on endothelial function, platelet aggregation, and inflammation.

[26] *Singh L, Rana S, Mehan S*. **Role of adenylyl cyclase activator in controlling experimental diabetic nephropathy in rats**. International journal of physiology, pathophysiology and pharmacology 2018; 10:144-153.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30515257
ABSTRACT
The present study aimed to investigate the role of adenylyl cyclase activator in preventing diabetic nephropathy in rats. Renal function parameters, renal hypertrophy, lipid profile, markers of oxidative stress and free radical scavenging activities were assessed. Histopathology was performed to confirm Streptozotocin induced renal morphological changes in diabetic rats. Male Wistar rats were used in the present study to reduce the effect of estrogen. Rats were subjected to high fat diet (HFD) for two weeks followed by low dose of Streptozotocin (STZ) [35 mg/kg, i.p.] to develop experimental diabetic nephropathy in eight weeks. Two weeks treatment with low dose of Forskolin (10 mg/kg) reduced the level of diabetic nephropathy markers but results observed were not significant. Whereas, Forskolin intermediate dose (20 mg/kg) and high dose (30 mg/kg) treated rats significantly attenuated diabetes induced elevated renal function parameters and endogenous antioxidants enzymatic activities. High dose of Forskolin was found to be more effective in attenuating the renal structural and functional abnormalities. Forskolin prevented renal structural and functional abnormalities in diabetic rats. Histopathological evaluation revealed that Forskolin (20 mg/kg and 30 mg/kg) treated diabetic rats demonstrated reduced vacuolar degeneration of tubules and glomerulosclerosis. In the present study, Glibenclamide (0.6 mg/kg) and Atorvastatin (0.5 mg/kg) were used as standard drugs. Our results demonstrated synergistic effects, when high dose of Forskolin was co-administered with standard drugs. In conclusion, treatment with adenylyl cyclase activator, Forskolin in diabetic rats reduced the elevated serum glucose level,

biomarkers of renal morphological dysfunction, renal hypertrophy, dyslipidaemia, oxidative stress and improved renal structure, function and enhanced level of endogenous antioxidants. Forskolin has a potential to prevent nephropathy without showing any effect on body weight in diabetic rats.

[27] *Dincer N, Dagel T, Afsar B et al.* **The effect of chronic kidney disease on lipid metabolism**. International urology and nephrology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30519980
ABSTRACT
The major cause of death among chronic kidney disease patients is cardiovascular diseases. Cardiovascular and kidney disease are interrelated and increase the severity of each other. Dyslipidemia is one the major causes of cardiovascular disease among chronic kidney disease patients along with diabetes and hypertension. The relationship between dyslipidemia and chronic kidney disease is reciprocal. Dyslipidemia is known to be a risk factor for chronic kidney disease and chronic kidney disease causes major alterations on lipoprotein profile, defined as the "dyslipidemic profile" of chronic kidney disease patients. Increased triglyceride, very low density lipoprotein and oxidized low density lipoprotein as well as decreased high density lipoprotein and changes in the composition of lipoproteins contribute to the "dyslipidemic profile." Treatment strategies targeting the "dyslipidemic profile" of chronic kidney disease could contribute to prevent cardiovascular diseases. Current therapy is based on the patient kidney function and consist mainly of statins. This review focuses on the effects of chronic kidney disease on the lipoprotein profile and how this may impact novel therapeutic approaches to cardiovascular risk.

[28] *Yang B, Shi L, Wang AM et al.* **Lowering effects of n-3 fatty acid supplements on blood pressure by reducing plasma angiotensin II in Inner Mongolia hypertensive patients: A double-blind randomized controlled trial**. Journal of agricultural and food chemistry 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30511840
ABSTRACT
Whether n-3 fatty acid (FA) has hypotensive actions among Chinese adults remains inconclusive. Hypertensive patients from Inner Mongolia, China (n=126) were recruited to a double-blind, randomized controlled trial. We investigated the effects of n-3 FA supplements on blood pressure (BP, mm Hg), plasma concentrations of angiotensin II (Ang II, pg/mL) and nitric oxygen (NO, micromol/L), using fish oil (n=41, 4 capsules/day, equivalent to 2 grams of eicosapentaenoic acid plus docosahexaenoic acid) and flaxseed oil (n=42, 4 capsules/day, equivalent to 2.5 grams of alpha-linolenic acid). Comparing to the control group (corn oil, n=43), the mean systolic BP (-4.52+/-9.28 vs. -1.51+/-9.23, P=0.040) and the plasma Ang II levels (-12.68+/-10.87 vs. -4.93+/-9.08, P=0.023) were significantly lowered in fish oil group, whereas diastolic BP (P=0.285) and plasma NO levels (P=0.220) were not. Such findings suggest that marine-based n-3 FA has a hypotensive efficacy in Chinese hypertensive patients possibly through inhibiting Ang II-dependent vasoconstrictions.

[29] *Nakamura M, Ako J, Arai H et al.* **Investigation into Lipid Management in Acute Coronary Syndrome Patients from the EXPLORE-J Study**. Journal of atherosclerosis and thrombosis 2018.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30518728

ABSTRACT

AIMS: The EXPLORE-J study aimed to assess lipid management in patients hospitalized for acute coronary syndrome (ACS) and their cardiovascular risk despite undergoing standard therapy. Here, we focused on background characteristics of patients in the EXPLORE-J study to elucidate the current lipid-lowering therapy and its issues in Japan. METHODS: In this multicenter, prospective, observational study (UMIN000018946), consecutive Japanese ACS patients who required hospitalization were registered between April 2015 and August 2016. Background and lipid profile data collected within 14 days of hospitalization were analyzed according to risk factors such as diabetes mellitus status. RESULTS: In total, 1944 patients were analyzed (80.3% male). The mean and standard deviation (SD) age and body mass index of all patients were 66.0 years (SD: 12.2) and 24.24 kg/m(2) (SD: 3.59), respectively. The most common lipid-modifying medication used at the time of ACS was statins (27.3%). The low-density lipoprotein cholesterol (LDL-C) level (first measurement after hospitalization) of patients overall was 121.3 mg/dL (SD: 40.0); 30.3% had an LDL-C level 100 mg/dL (current target level for secondary prevention of cardiovascular events in Japan), compared with 52.1% of patients with a previous history of coronary artery disease (CAD), and 57.2% of patients with a history of diabetes. CONCLUSIONS: Many patients were not meeting Japanese LDL-C target levels at the time of ACS, and a large proportion of patients meeting target levels developed ACS; therefore, more stringent management and further evaluation of the target LDL-C levels is warranted in high-risk patients and those with previous history of CAD.

[30] *Teramoto T, Kiyosue A, Ishigaki Y et al.* **Efficacy and safety of alirocumab 150mg every 4 weeks in hypercholesterolemic patients on non-statin lipid-lowering therapy or lowest strength dose of statin: ODYSSEY NIPPON**. J Cardiol 2018.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30509509

ABSTRACT

BACKGROUND: Alirocumab, a fully human monoclonal antibody to proprotein convertase subtilisin/kexin type 9, given every 2 weeks (Q2W), significantly reduced low-density lipoprotein cholesterol (LDL-C) levels in Japanese hypercholesterolemic patients on background statin. We evaluated alirocumab 150mg every 4 weeks (Q4W) in patients on lowest-dose statin or non-statin lipid-lowering therapy (LLT). METHODS: ODYSSEY NIPPON was a double-blind study conducted in Japanese patients with LDL-C >/=100mg/dL (heterozygous familial hypercholesterolemia or non-familial hypercholesterolemia with coronary heart disease) or >/=120mg/dL (non-familial hypercholesterolemia, Japan Atherosclerosis Society category III) on atorvastatin 5mg/day or non-statin LLT. Patients were randomized (1:1:1) to subcutaneous alirocumab 150mg Q4W, alirocumab 150mg Q2W, or placebo for the 12-week double-blind treatment period (DBTP), followed by a 52-week open-label treatment period (OLTP). At entry into the OLTP, patients received alirocumab 150mg Q4W, with possible up-titration to 150mg Q2W at Week 24. RESULTS: Least-square mean percent change in LDL-C from baseline at Week 12 (primary efficacy endpoint) was -43.8% for alirocumab Q4W, -70.1% for Q2W, and -4.3% for placebo. During the OLTP, mean LDL-C change from baseline was -45.1% at Week 20, with a further reduction at Week 36, with achieved levels maintained to Week 64. Percent of patients with >/=1 adverse event (DBTP) was 51.9% with alirocumab Q4W, 47.2% with Q2W, and 46.4%

with placebo. Most common adverse events were infections and infestations (25.9%, 22.6%, 17.9%, respectively), gastrointestinal disorders (13.0%, 9.4%, 12.5%), nervous system disorders (5.6%, 7.5%, 10.7%), and general disorders and administration-site conditions (3.7%, 11.3%, 5.4%). CONCLUSIONS: Hypercholesterolemic Japanese patients who tolerate only lowest-strength dose statin or non-statin LLT can achieve robust LDL-C reduction with alirocumab 150mg Q4W, in addition to their current LLT. Alirocumab 150mg Q4W dosing was efficacious and generally well tolerated without new safety concerns. (ClinicalTrials.gov number: NCT02584504).

[31] *Cheng WP, Lo HM, Wang BW et al.* **Effect of atorvastatin on cardiomyocyte hypertrophy through suppressing MURC induced by volume overload and cyclic stretch**. Journal of cellular and molecular medicine 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30511410
ABSTRACT
MURC (muscle-restricted coiled-coil protein) is a hypertrophy-related gene. Hypertrophy can be induced by mechanical stress. The purpose of this research was to investigate the hypothesis that MURC mediates hypertrophy in cardiomyocytes under mechanical stress. We used the in vivo model of an aortocaval shunt (AV shunt) in adult Wistar rats to induce myocardial hypertrophy. We also used the in vitro model of cyclic stretch in rat neonatal cardiomyocytes to clarify MURC expression and the molecular regulation mechanism. The flexible membrane culture plate seeding with cardiomyocytes Cardiomyocytes seeded on a flexible membrane culture plate were stretched by vacuum pressure to 20% of maximum elongation at 60 cycles/min. AV shunt induction enhanced MURC protein expression in the left ventricular myocardium. Treatment with atorvastatin inhibited the hypertrophy induced by the AV shunt. Cyclic stretch markedly enhanced MURC protein and mRNA expression in cardiomyocytes. Addition of extracellular-signal-regulated kinase (ERK) inhibitor PD98059, ERK small interfering RNA (siRNA), angiotensin II (Ang II) antibody and atorvastatin before stretch, abolished the induction of MURC protein. An electrophoretic mobility shift assay showed that stretch enhanced the DNA binding activity of serum response factor. Stretch increased but MURC mutant plasmid, ERK siRNA, Ang II antibody and atorvastatin reversed the transcriptional activity of MURC induced by stretch. Adding Ang II to the cardiomyocytes also induced MURC protein expression. MURC siRNA and atorvastatin inhibited the hypertrophic marker and protein synthesis induced by stretch. Treatment with atorvastatin reversed MURC expression and hypertrophy under volume overload and cyclic stretch.

[32] *Zhang Y, Fang Q, Niu K et al.* **Time-dependently slow-released multiple-drug eluting external sheath for efficient long-term inhibition of saphenous vein graft failure**. J Control Release 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30521829
ABSTRACT
Coronary artery bypass graft surgery (CABG) is an effective therapeutic method for coronary artery disease. Great saphenous vein is the predominant graft due to the accessibility, sufficient length and suitable size matching with coronary artery. However, saphenous vein graft failure (SVGF) always restrict the long-term success of CABG. In this study, a complex external sheath

was prepared using multi-channel and coaxial electrospinning techniques. The sheath can slowly release fasudil dihydrochloride (100% at 63days), everolimus (100% at 84days) and simvastatin (31.87+/-1.55% at 20weeks) to match the time-dependent pathological changes of SVGF through a cocktail pattern. In 16weeks animal experiments, drug loaded sheath exhibited significantly greater efficacy in inhibiting neointima formation and ensuring graft patency than bare vein graft and empty sheath. Under the joint action of mechanical restriction of the sheath and the synergistic effect of loaded fasudil dihydrochloride and everolimus, the endothelium damage and the proliferation/migration of smooth muscle cells, which were thought to be the early cause of graft failure, could be efficiently alleviated. Moreover, the long-term patency could be expected due to the inhibition of atherosclerosis by the sustained released simvastatin.

[33] *Wang Z, Mansukhani NA, Emond ZM et al.* **Endoluminal Atherosclerotic Plaque Debulking Using Enzymatic and Ultrasonic Energy**. J Surg Res 2019; 233:335-344.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30502268
ABSTRACT
BACKGROUND: Current procedures to treat severe atherosclerosis are traumatic to the arterial wall and often result in restenosis due to neointimal hyperplasia. We developed a novel therapy using a specially designed double occlusion balloon catheter, ultrasonic wire, and enzymatic digestion solution to atraumatically debulk atherosclerotic plaques. MATERIALS AND METHODS: A combination of different enzymes, chemicals, and treatment conditions were evaluated for its effect at reducing atherosclerotic plaque harvested from human carotid artery endarterectomies ex vivo. The optimized digestion solution was examined in harvested intact human superficial femoral arteries in situ. A conventional Yorkshire/Landrace and a genetically modified Yucatan minipig homozygous for a nonfunctional LDLR mutation were used to evaluate the endovascular therapy in nonatherosclerotic and atherosclerotic environments in vivo. RESULTS: Ex vivo, the technology successfully digested human carotid artery plaques by 75%. In situ, the therapy successfully reduced plaque area in harvested superficial femoral arteries by 46%. In vivo, the endovascular therapy was technically feasible and demonstrated initial safety with no thrombosis, dissection, or aneurysmal dilatation in a nonatherosclerotic porcine model. In an atherosclerotic porcine model, the therapy demonstrated initial efficacy by successfully reducing atherosclerotic plaque while preserving the arterial wall with an intact internal elastic lamina. CONCLUSIONS: Using human plaque, human artery, and a normal and atherosclerotic pig model, we demonstrated that delivery of our therapy to the vasculature is technically feasible, appears safe, and shows initial efficacy. Our percutaneous plaque debulking method is a unique and promising therapy for the treatment of atherosclerosis and warrants further study.

[34] *Ritter P, Yousefi K, Ramirez J et al.* **LDL Cholesterol Uptake Assay Using Live Cell Imaging Analysis with Cell Health Monitoring**. Journal of visualized experiments : JoVE 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30507918
ABSTRACT
The regulation of LDL cholesterol uptake through LDLR-mediated endocytosis is an important area of study in various major pathologies including metabolic disorder, cardiovascular disease,

and kidney disease. Currently, there is no available method to assess LDL uptake while simultaneously monitoring for health of the cells. The current study presents a protocol, using a live cell imaging analysis system, to acquire serial measurements of LDL influx with concurrent monitoring for cell health. This novel technique is tested in three human cell lines (hepatic, renal tubular epithelial, and coronary artery endothelial cells) over a four-hour time course. Moreover, the sensitivity of this technique is validated with well-known LDL uptake inhibitors, Dynasore and recombinant PCSK9 protein, as well as by an LDL uptake promoter, Simvastatin. Taken together, this method provides a medium-to-high throughput platform for simultaneously screening pharmacological activity as well as monitoring of cell morphology, hence cytotoxicity of compounds regulating LDL influx. The analysis can be used with different imaging systems and analytical software.

[35] *Dai W, Zhang Z, Zhao S*. **Baseline levels of serum high sensitivity C reactive protein and lipids in predicting the residual risk of cardiovascular events in Chinese population with stable coronary artery disease: a prospective cohort study**. Lipids in health and disease 2018; 17:273.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30509306
ABSTRACT
BACKGROUND: The contributions of inflammation, triglyceride (TG) and high-density lipoprotein cholesterol (HDL-C) to the residual risk of cardiovascular events have not been determined in a large cohort of Chinese population before. This study was aimed to investigate the association of serum levels of high sensitive C reactive protein (hs-CRP), TG and HDL-C with the residual risk of cardiovascular events in patients with stable coronary artery disease (CAD). METHODS: We enrolled 4090 patients with stable CAD from 13 hospitals in China. All participants received optimal medical treatment (OMT) for stable CAD suggested by guidelines and were followed. The endpoint measures were the first occurrence of a major adverse cardiovascular event (MACE), defined as cardiovascular death, non-fatal myocardial infarction, non-fatal stroke or unplanned coronary revascularization. Cox proportional regression analysis was conducted to identify independent predictors of MACE. RESULTS: We found that hs-CRP and HDL-C levels were associated with coronary lesion severity at baseline (both $p < 0.001$). After 3 months OMT, 91.2% (3730/4090) patients achieved the therapeutic goal for low density lipoprotein cholesterol (LDL-C) (< 1.8 mmoL/L). During a mean follow-up period of 39.5 months, 11.5% (471/4090) patients suffered MACE. In multivariate Cox proportional regression analysis, the hazard ratio for MACE was 1.17 (95% confidence interval: 1.07-1.28, $p < 0.001$) per standardized deviation in the log-transformed hs-CRP levels after adjustment for other traditional cardiovascular risk factors. However, baseline TG and HDL-C levels were not associated with MACE in this study. CONCLUSIONS: Baseline hs-CRP level was an independent predictor of residual risk of cardiovascular events in Chinese population with stable CAD. However, TG and HDL-C levels were not associated with MACE.

[36] *Moreno Juste A, Gimeno Miguel A, Poblador Plou B et al.* **Adherence to treatment of hypertension, hypercholesterolaemia and diabetes in an elderly population of a Spanish cohort**. Medicina clinica 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30503066
ABSTRACT

BACKGROUND AND OBJECTIVE: Sub-optimal adherence to treatment in the general population has been highlighted in several studies, especially in the elderly and/or chronic patients. This study aims to describe the adherence to treatment of diabetes mellitus, dyslipidaemia and hypertension, and to identify the factors that influence adherence. MATERIAL AND METHOD: Retrospective, cross-sectional observational study on 16,208 patients aged >/=65 years from the EpiChron Cohort who initiated monotherapy treatment of an antidiabetic, a lipid-lowering or an antihypertensive medication in 2010. Adherence was measured by calculating the medication possession ratio during one year, considering those cases with medication possession ratio >/=80% to be adherent. We performed a descriptive study, and a logistic regression model was used to identify the predictors of low adherence. RESULTS: Adherence to antidiabetics, antihypertensive and lipid-lowering drugs was 72.4%, 50.7% and 44.3%, respectively. An increase in adherence of 3-8% was observed for each additional chronic disease suffered by the patient. The presence of mental illness did not affect adherence, and sex, age and number of prescribed drugs did not present consistent effects. CONCLUSION: The results obtained show a sub-optimal adherence to treatment for the 3chronic diseases studied. Adherence increased with the number of chronic diseases, while sex, age and number of drugs did not show a consistent effect. It is necessary to investigate if there are other factors that may influence therapeutic adherence, since improving adherence may have a greater impact on health than any progress in therapies.

[37] *Dirajlal-Fargo S, Kulkarni M, Bowman E et al.* **Serum Albumin Is Associated With Higher Inflammation and Carotid Atherosclerosis in Treated Human Immunodeficiency Virus Infection**. Open Forum Infect Dis 2018; 5:ofy291.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30515432
ABSTRACT
Background: This study was conducted to explore the associations between serum albumin and markers of inflammation and cardiovascular disease in treated human immunodeficiency virus (HIV)-infected adults. Methods: We conducted a nested study within in the SATURN-HIV trial in which 147 HIV(+) adults on stable antiretroviral therapy were (1) virally suppressed, (2) had a low-density lipoprotein (LDL)-cholesterol level <130 mg/dL, and (3) were randomized to 10 mg daily rosuvastatin or placebo. Measures of serum albumin, carotid intima media thickness ([cIMT] surrogate marker of atherosclerosis), inflammation, T cells, monocyte activation, and gut integrity were assessed at baseline, 48 and 96 weeks later. Spearman correlations and linear mixed-effect models were used to assess associations with serum albumin. Results: Mean age was 45 years, 80% of participants were male, and 69% were African American. Mean serum albumin was similar between the groups at all time points (4.01-4.09 g/dL in statin arm vs 4.02-4.11 g/dL in placebo arm; P = .08-0.35). Lower baseline serum albumin significantly predicted larger changes in cIMT, interleukin 6, D-dimer, tumor necrosis factor alpha receptor 1, fibrinogen, and high-sensitivity C-reactive protein (P </= .03) over 96 weeks independently of statin therapy. After adjusting for age, gender, smoking, body mass index, creatinine clearance, and LDL cholesterol, every 1 g/dL decrease in serum albumin at baseline remained associated with a 0.05-mm increase in cIMT over 96 weeks (P = .05). Conclusions: Lower serum albumin in controlled HIV is associated with higher markers of chronic inflammation and hypercoagulation, which could explain the prior observation that serum albumin predicts nonacquired immune

deficiency syndrome events in HIV. Serum albumin may predict progression of carotid atherosclerosis independent of traditional risk factors.

[38] *Buso G, Calanca L, Ney B et al.* **[Best medical treatment of lower extremity arterial disease in 2018]**. Revue medicale suisse 2018; 14:2202-2206.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30516887
ABSTRACT
Lower extremity artery disease is a very common disease, which is frequently associated with consistent disability in terms of both clinical symptoms and functioning. It is also associated with important morbidity and mortality, because of a significant increase in overall cardiovascular risk in affected patients. The establishment of an optimal medical treatment, including a careful management of the different cardiovascular risk factors through a healthy lifestyle, a regular and structured physical activity and the administration (if indicated) of antihypertensive, lipid-lowering, antidiabetic and antithrombotic drugs is a fundamental component in the clinical management of these patients and should always be considered by the clinicians facing the disease.

[39] *Cariou B, Smati S*. **LDL-cholesterol hypothesis:the lower is trully better**. Rev Prat 2016; 66:317-321.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30512645
ABSTRACT
LDL-cholesterol hypothesis : the lower is trully better. LDL-cholesterol (LDL-C) hypothesis is the concept that elevated LDL-C is a main risk factor in the development of atherosclerosis and consequently in cardiovascular diseases. By extension, the LDL-hypothesis also states that reducing LDL-C levels by nutritional and/or pharmacological approaches is an efficient strategy to reduce cardiovascular events. Concordant evidence supports the LDL-hypothesis, including epidemiologic and genetic studies. Importantly, randomized clinical trials with lipid-lowering drugs, mainly statins, have clearly demonstrated that the reduction of LDL-C levels is associated to a reduction of cardiovascular events. The results from recent clinical trials with ezetemibe (a non-statin hypolipidemic drug) further reinforce the LDL-hypothesis instead of the statin hypothesis. Thus, it seems more logical to define a LDL-target, which is tailored to the cardiovascular risk of each subject, rather than emphasize a therapeutic strategy with statins only. The oncoming results from cardiovascular outcomes studies with PCSK9 inhibitors will help to precise the optimal LDL-C target as well as the safety of achieving very-low LDL-C concentrations.

[40] *Borges IBP, Shinjo SK*. **Safety of statin drugs in patients with dyslipidemia and stable systemic autoimmune myopathies**. Rheumatology international 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30519709
ABSTRACT
Recent studies have shown a high prevalence of dyslipidemia in patients with systemic autoimmune myopathies (SAM). However, little is known about the safety of the use of statins in these patients, and this gap in research motivated the accomplishment of the present study. In a retrospective cohort study conducted from 2004 to 2018, 250 patients with SAM were

evaluated, and 24 patients had stable forms of SAM (16 dermatomyositis, 1 polymyositis and 7 antisynthetase syndrome) but had dyslipidemia and had received statins. Patients with clinically amyopathic dermatomyositis, immune-mediated necrotizing myopathy, dermatomyositis, or polymyositis induced by statins were excluded. The mean age of the patients was 50.6 years, and they were predominantly women. The median duration of the disease was 5.0 years. Twelve patients received simvastatin (10-60 mg/day), and 11 patients received atorvastatin (20-40 mg/day), and 1 patient received atorvastatin (10 mg/day) which was later replaced by simvastatin (20 mg/day). The median time of exposure to the statin was 22.5 months. The follow-up appointments showed that the patients' lipid profiles had improved and that there had been no recurrences of disease activity or clinical intercurrences. Despite the small sampling, the data showed that the use of statins in patients with SAM was safe. New studies with a larger sample and patients with different degrees of disease activity are necessary to corroborate the results of the present study.

[41] *Chodorge M, Celeste AJ, Grimsby J et al.* **Engineering of a GLP-1 analogue peptide/anti-PCSK9 antibody fusion for type 2 diabetes treatment**. Scientific reports 2018; 8:17545.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30510163

ABSTRACT
Type 2 diabetes (T2D) is a complex and progressive disease requiring polypharmacy to manage hyperglycaemia and cardiovascular risk factors. However, most patients do not achieve combined treatment goals. To address this therapeutic gap, we have developed MEDI4166, a novel glucagon-like peptide-1 (GLP-1) receptor agonist peptide fused to a proprotein convertase subtilisin/kexin type 9 (PCSK9) neutralising antibody that allows for glycaemic control and low-density lipoprotein cholesterol (LDL-C) lowering in a single molecule. The fusion has been engineered to deliver sustained peptide activity in vivo in combination with reduced potency, to manage GLP-1 driven adverse effects at high dose, and a favourable manufacturability profile. MEDI4166 showed robust and sustained LDL-C lowering in cynomolgus monkeys and exhibited the anticipated GLP-1 effects in T2D mouse models. We believe MEDI4166 is a novel molecule combining long acting agonist peptide and neutralising antibody activities to deliver a unique pharmacology profile for the management of T2D.

[42] Casale J, Bhimji SS. Fasting. In: StatPearls. Treasure Island (FL): StatPearls Publishing StatPearls Publishing LLC.; 2018.