[1] Improved cardiovascular outcomes following temporal advances in lipid-lowering therapy in a genetically-characterised cohort of familial hypercholesterolaemia homozygotes. Thompson GR, Seed M, Naoumova RP et al. Atherosclerosis 2015; 243:328-333. BACKGROUND AND AIMS: There is a paucity of data concerning the influence of lipid-lowering therapy on cardiovascular (CV) outcomes in patients with homozygous familial hypercholesterolaemia (FH). To redress this a retrospective analysis was undertaken of the demographic features, lipid levels, low density lipoprotein receptor and Autosomal Recessive Hypercholesterolaemia gene mutations, CV outcomes and vital status of 44 FH homozygotes referred to a single centre in the UK between 1964 and 2014. METHODS: Data were obtained from past publications, case records and death certificates. Differences in categorical and continuous variables between living and dead patients were analysed using Fisher's exact test and an independent t-test respectively. RESULTS: During the 50 years covered by this survey 13 patients have died, 30 are still alive and 1 was lost to follow up. The mean age of Alive patients was 32.6 +/- 11.5 versus 28.3 +/- 14.9 years in Dead ones (P = 0.31) and they were born 18 years later (P = 0.0001). Pre-treatment serum total cholesterol (TC) was similar in Alive and Dead (20.2 +/- 5.1 v 21.3 +/- 4.4 mmol/l, P = 0.52) but on-treatment TC was lower in Alive than Dead (8.1 +/- 2.8 v 14.5 +/- 6.0 mmol/l, P = 0.0001) and CV adverse events were far less frequent (eg aortic stenosis, 33% v 77%, P = 0.02). CONCLUSIONS: The lower on-treatment TC and fewer CV adverse events in FH homozygotes still living reflect advances in apheresis and drug therapy since the 1990s. Further improvements in prognosis can be expected with the impending introduction of novel lipid-lowering agents.

[2] A Novel Peroxisome Proliferator Response Element Modulates Hepatic Low Density Lipoprotein Receptor Gene Transcription in Response to PPARdelta Activation. Shende VR, Singh AB, Liu J. The Biochemical journal 2015. The hepatic expression of LDLR gene is regulated primarily at the transcriptional level by a sterol-regulatory element (SRE) in its proximal promoter region which is the site of action of SRE-binding protein 2 (SREBP2). However whether additional cis-regulatory elements contribute to LDLR transcription has not been fully explored. We investigated the function of a putative PPAR-response element (PPRE) sequence motif located at -768 to -752 bases upstream of the transcription start site of human LDLR gene in response to PPARdelta activation. Promoter luciferase reporter analyses showed that treating HepG2 cells with PPARdelta agonist L165041 markedly increased the activity of a full-length LDLR promoter construct (pLDLR-1192) without any effects on the shorter promoter reporter pLDLR-234 that contains only the core regulatory elements SRE-1 and SP1 sites. Importantly, mutation of the PPRE sequence greatly attenuated the induction of the full-length LDLR promoter activity by L165041 without affecting rosuvastatin mediated transactivation. Electrophoretic mobility shift and chromatin immunoprecipitation assays further confirmed the binding of PPARdelta to the LDLR-PPRE site. Treating HepG2 cells with L165041 elevated the mRNA and protein expressions of LDLR without affecting the LDLR mRNA decay rate. The induction of LDLR expression by PPARdelta agonist was further observed in liver tissue of mice and hamsters treated with L165041. Altogether, our studies identify a novel PPRE-mediated regulatory mechanism for LDLR transcription and suggest that combined treatment of statin with PPARdelta agonists may have advantageous effects on LDLR expression.

[3] How low should we target the LDL goal to improve survival for acute coronary syndrome patients in Hong Kong? Lee VW, Chau RY, Cheung HY et al. BMC cardiovascular disorders 2015; 15:117. BACKGROUND: Utilization of lipid-lowering agents has been associated with improved long-term outcomes in acute coronary syndrome (ACS) patients. However, updated data regarding local use and outcomes was lacking. METHODS: We retrospectively reviewed 696 hospitalized patients in the local ACS registry of Prince of Wales Hospital during 1 January 2008 to 31 December 2009 with data retrieved using computerized clinical records of all patients. RESULTS: Among the 402 MI patients included, 104 (25.9 %) were not prescribed with statins at discharge. Percutaneous coronary intervention (PCI) not performed or planned during discharge (OR: 0.324, p = 0.001) and latest lower LDL-C level before discharge (OR: 0.221 for an increment of 1 mmol/L, p = 0.009) were significant independent predictors of the absence of statin prescriptions at discharge. A significantly lower all-cause mortality rate (14.4 % vs 51.7 %, p < 0.001), fewer total hospitalizations (p < 0.001) and fewer hospitalizations due to cardiovascular problems (p < 0.001) were observed in patients discharged with statins. LDL-C goal attainment of < 2.6 mmol/L resulted in a significant reduction in mortality (10.8 % vs 24.2 %, p = 0.001), but not for goal attainment of < 1.8 mmol/L. Significant difference in survival existed only when LDL-C cut-off values were above 2.4 mmol/L. CONCLUSIONS: This study revealed the under-utilization of statin therapy in eligible MI
patients at discharge and unsatisfactory percentages of LDL-C goal attainment, and also reassured the role of low LDL-C reduction to < 2.6 mmol/L in the management of MI. However, the current study did not show that the lower LDL-C reduction improved survival of ACS patients. Further research should be conducted to assess the necessity of aggressive LDL-C reduction to < 1.8 mmol/L in local patients.

[4] Statin effects on atherosclerotic plaques: regression or healing? Bittencourt MS, Cerri RJ. BMC medicine 2015; 13:260. Despite the well-documented improved survival of coronary heart disease with the use of statins, their effects on atherosclerotic plaques are not yet fully understood. While some studies suggest statins may reduce plaque volume, the reduction is small even with the use of high-dose statins. Due to this small change in plaque volume, other effects of statin therapy on plaques have been proposed. A large meta-analysis by Banach et al. explored statin effects on plaque composition detected by intravascular ultrasound (IVUS). We discuss the mechanisms of plaque composition modification demonstrated in their study and its implications on atherosclerotic plaque stabilization. Please see related article: http://www.biomedcentral.com/1741-7015/13/229.

[5] Lipid-lowering treatment patterns among patients with type 2 diabetes mellitus with high cardiovascular disease risk. Quek RG, Fox KM, Wang L et al. BMJ open diabetes research & care 2015; 3:e000132. OBJECTIVE: To examine real-world treatment patterns of lipid-lowering treatment and their possible associated intolerance and/or ineffectiveness among patients with type 2 diabetes mellitus initiating statins and/or ezetimibe. RESEARCH DESIGN AND METHODS: Adult (aged >/=18 years) patients diagnosed with type 2 diabetes who initiated statins and/or ezetimibe from January 1, 2007 to June 30, 2011 were retrospectively identified from the IMS LifeLink Pharmetrics Plus commercial claims database. Patients were further classified into 3 high-risk cohorts: (1) history of cardiovascular event (CVE); (2) two risk factors (age and hypertension); (3) aged >/=40 years. Patients had continuous health plan enrolment >/=1 year preindex and postindex date (statin and/or ezetimibe initiation date). Primary outcomes were index statin intensity, treatment modification(s), possible associated statin/non-statin intolerance and/or ineffectiveness issues (based on treatment modification type), and time-to-treatment modification(s). Analyses for each cohort were stratified by age groups (<65 and >/=65 years). RESULTS: A total of 9823 (history of CVE), 62 049 (2 risk factors), and 128 691 (aged >/=40 years) patients were included. Among patients aged <65 years, 81.4% and 51.8% of those with history of CVE, 75.6% and 44.4% of those with 2 risk factors, and 77.9% and 47.1% of those aged >/=40 years had >/=1 and 2 treatment modification(s), respectively. Among all patients, 23.2-28.4% had possible statin intolerance and/or ineffectiveness issues after accounting for second treatment modification (if any). CONCLUSIONS: Among patients with type 2 diabetes with high cardiovascular disease risk, index statin treatment modifications that potentially imply possible statin intolerance and/or ineffectiveness were frequent.


[7] Lipophilic Statins and Aldosterone Secretion: A Bridge Too Far? Andersson C, Vasan RS. Circulation 2015. Statins have been hypothesized to have pleiotropic effects that may mitigate the risks of developing arterial and venous thromboembolic events, 1, 2 heart failure, 3 and immune-related diseases including pneumonia. 4 Statins have been observed also to lower blood pressure in short-term, double-blinded, randomized clinical trials, 5-7 and to attenuate cardiac remodeling in mice with myocardial infarction or hypertension. 8-10 While the latter effects may relate to improvements in vascular stiffness (secondary to reduced lipid accumulation within the arterial intima-media layer), other biological features of statins that are distinctive from their cholesterol-lowering effects may contribute to both the attenuation of blood pressure elevation and cardiac remodeling. 11.
[8] Statin Use and Adrenal Aldosterone Production in Hypertensive and Diabetic Subjects. Baudrand R, Pogoya LH, Vaidya A et al. Circulation 2015. BACKGROUND: -Statins substantially reduce cardiovascular mortality and appear to have beneficial effects independent of their lipid lowering properties. We evaluated the hypothesis that statin use may modulate the secretion of aldosterone, a well-known contributor to cardiovascular disease. METHODS AND RESULTS: -We measured adrenal hormones in two intervention studies. In study 1 in hypertensive subjects, aldosterone was analyzed at baseline and after angiotensin-II stimulation (AngII) on both high (HS) and low sodium (LS) diets (1122 observations, 15% on statins > 3 months). Statin users had 33% lower aldosterone levels in adjusted models (p < 0.001). Cortisol was not modified by statins. In secondary analyses, the lowest aldosterone levels were seen with lipophilic statins and with higher doses. Statin users had lower blood pressure (BP) and reduced salt sensitivity of BP (p=0.001). In study 2, aldosterone was measured in diabetic patients on a HS diet, before and after AngII stimulation (143 observations, 79% statin users). Again, statin users had 26% lower aldosterone levels (p =0.006), particularly those using lipophilic statins. Ex vivo studies in rat adrenal glomerulosa cells confirmed that lipophilic statins acutely inhibited aldosterone, but not corticosterone, in response to different secretagogues. CONCLUSIONS: -Statin use among hypertensive and diabetic subjects was associated with lower aldosterone secretion in response to AngII and LS diet in two human intervention studies. This effect appeared to be most pronounced with lipophilic statins and higher doses. Future studies to evaluate whether aldosterone inhibition may partially explain the robust cardioprotective effects of statins are warranted.

[9] Gemfibrozil disrupts the metabolism of circulating lipids in bobwhite quails. Bussiere-Cote S, Omlin T, de Cassia Pinheiro E, Weber JM. Comparative biochemistry and physiology. Toxicology & pharmacology : CBP 2015. The circulating lipids of birds play essential roles for egg production and as an energy source for flight and thermogenesis. How lipid-lowering pharmaceuticals geared to prevent heart disease in humans and that are routinely released in the environment affect their metabolism is unknown. This study assesses the impact of the popular drug gemfibrozil (GEM) on the plasma phospholipids (PL), neutral lipids (NL), and nonesterified fatty acids (NEFA) of bobwhite quails (Colinus virginianus). Results show that bird lipoproteins are rapidly altered by GEM, even at environmentally-relevant doses. After 4 days of exposure, pharmacological amounts cause an 83% increase in circulating PL levels, a major decrease in average lipoprotein size measured as a 56% drop in the NL/PL ratio, and important changes in the fatty acid composition of PL and NEFA (increases in fatty acid unsaturation). The levels of PL carrying all individual fatty acids except arachidonate are strongly stimulated. The large decrease in bird lipoprotein size may reflect the effects seen in humans: lowering of LDL that can cause atherosclerosis and stimulation of HDL that promote cholesterol disposal. Lower (environmental) doses of GEM cause a reduction of %palmitate in all the plasma lipid fractions of quails, but particularly in the core triacylglycerol of lipoproteins (NL). No changes in mRNA levels of bird peroxisome proliferator-activated receptor (PPAR) could be demonstrated. The disrupting effects of GEM on circulating lipids reported here suggest that the pervasive presence of this drug in the environment could jeopardize reproduction and migratory behaviours in wild birds.

[10] Effect of high-dose atorvastatin on the cardiovascular risk associated with individual components of metabolic syndrome: A subanalysis of the Treating to New Targets (TNT) study. Deedwania PC, Shepherd J, Breazna A, DeMicco DA. Diabetes Obes Metab 2015. AIMS: This analysis of the Treating to New Targets study investigated the impact of intensive lipid-lowering with high-dose atorvastatin on the cardiovascular risk associated with individual metabolic syndrome (MetS) components (high body mass index [BMI], elevated triglycerides, low high-density lipoprotein cholesterol [HDL-C], hypertension and elevated fasting glucose) in patients with coronary heart disease (CHD). MATERIALS AND METHODS: Patients with clinically evident, stable CHD and low-density lipoprotein cholesterol (LDL-C) <3.4 mmol/l (130 mg/dl) were randomized to double-blind therapy with atorvastatin 10 mg/day (ATV10, n=5006) or 80 mg/day (ATV80, n=4995) after an 8-week open-label run-in with ATV10. Median follow-up was 4.9 years. The impact of individual MetS risk factors was tested on the primary endpoint, which was the occurrence of a first major cardiovascular event (MCVE). RESULTS: On-treatment LDL-C was 2.6 mmol/l (101 mg/dl) with ATV10 and 2.0 mmol/l (77 mg/dl) with ATV80. Among patients receiving ATV10, the presence of each individual MetS component significantly increased the risk of MCVEs compared with the absence of each (BMI, p=0.014; triglycerides, p=0.006; HDL-C, p=0.0006; hypertension, p<0.0001; and fasting glucose p<0.0001). In patients receiving ATV80, elevated triglycerides and fasting
glucose were no longer significant predictors of MCVEs. The predictive power of hypertension on the risk of MCVEs was reduced in patients treated with ATV80, although it remained a significant predictor. CONCLUSIONS: Treatment with high-dose atorvastatin to a mean LDL-C level of 2.0 mmol/l (77 mg/dl) considerably attenuated the predictive power associated with three MetS components.

[11] **Functional Characterization of Carrier-Mediated Transport of Pravastatin across the Blood-Retinal Barrier in Rats.** Fujii S, Setoguchi C, Kawazu K, Hosoya KI. Drug metabolism and disposition: the biological fate of chemicals 2015. Systemically administered pravastatin effectively treats diabetic retinopathy without central nervous system side effects. The efflux transport mechanism of pravastatin from the brain has already been clarified. In this study, the influx of pravastatin across the blood-retinal and blood-brain barriers (BRB and BBB), as well as the efflux of pravastatin from the retina, were investigated using rats. Pravastatin influx (blood-to-tissues) was assessed using the retinal and brain uptake index (RUI and BUI) methods, and microdialysis was performed to investigate the efflux (retina-to-blood) transport of pravastatin. The RUI and BUI values for [3H]pravastatin were lower than those expected based on its lipophilicity, suggesting that the influx transport across the BRB and BBB was less than the reverse direction transport. The RUI and BUI values for [3H]pravastatin were significantly decreased by pravastatin, digoxin, and probenecid, indicating that pravastatin undergoes carrier-mediated influx transport in the blood-to-tissues direction across the BRB and BBB. Following intravitreal injection, [3H]pravastatin and the bulk flow marker [14C]D-mannitol were found to be eliminated bi-exponentially from the vitreous humor. The elimination rate constant of [3H]pravastatin during the terminal phase was 1.66-fold greater than that of [14C]D-mannitol. Efflux transport was reduced in the retinal presence of pravastatin, digoxin, and benzylpenicillin, suggesting that pravastatin is transported via efflux transporters. In conclusion, pravastatin is transported across the BRB via uptake and efflux transporters in both the blood-to-retina and retina-to-blood directions, and the retina-to-blood transporters are dominant, based on the lower values of the RUI compared with the values expected from the lipophilicity.

[12] **Treating hypercholesterolemia - when and how.** Vogt A. Deutsche medizinische Wochenschrift (1946) 2015; 140:1490-1493. Treating hypercholesterolemia reduces cardiovascular events in secondary and primary prevention. Familial hypercholesterolemia is a high risk constellation per se and LDL-cholesterol should be lowered early in life and significantly. Some novel agents will broaden our therapeutic options. The MTP-inhibitor Lomitapide, that reduces LDL-cholesterol independently of the LDL-receptor, and PCSK9-inhibitors, that reduce LDL-cholesterol by blocking the degradation of the LDL-receptor, were approved recently. Both novel therapeutic principles are promising. Further trials have to address long term safety and - as first data suggest in case of PCSK9-inhibitors - the reduction of cardiovascular events. One can expect that these novel agents will improve the risk adapted therapy - in combination with well-established therapies or in case of intolerances as mono-therapy.

[13] **Cryotherapy increases features of plaque stability in atherosclerotic rabbits.** Verheyse S, Roth L, De Meyer I et al. EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology 2015; 11. AIMS: In the last 10 years, cryotherapy has been investigated as a new technology to treat vascular disease. The efficiency of cryotherapy in stabilising atherosclerotic plaques has never been described. The purpose of the present study was to evaluate the effect of catheter-based cryotherapy on atherosclerotic plaque composition in a rabbit model of atherosclerosis. METHODS AND RESULTS: Twenty-four New Zealand white rabbits were fed a 0.3% cholesterol-supplemented diet for 24 weeks. At two predefined sites of the atherosclerotic thoracic aorta, catheter-based cryotherapy, applying either single-dose, double-dose cryotherapy or control inflation, was performed after randomisation. Rabbits were continued on a cholesterol-supplemented diet for one day (acute) or four weeks (chronic). One day after cryotherapy, apoptotic cell death of smooth muscle cells (SMCs) and endothelial cells (ECs) was observed, whereas macrophages were unaffected. Four weeks later, the amount of SMCs was restored, the EC layer was regenerated, and a subendothelial macrophage-free layer was formed, indicative of a more stable plaque. In addition, both the thickness and the type I collagen content of the fibrous cap were increased. CONCLUSIONS:
The present study demonstrated that cryotherapy is feasible and appears to stabilise atherosclerotic plaques in a rabbit model.

[14] Characteristics and functions of lipid droplets and associated proteins in enterocytes. Beilstein F, Carriere V, Letorque A, Demignot S. Experimental cell research 2015. Cytosolic lipid droplets (LDs) are observed in enterocytes of jejunum during lipid absorption. One important function of the intestine is to secrete chylomicrons, which provide dietary lipids throughout the body, from digested lipids in meals. The current hypothesis is that cytosolic LDs in enterocytes constitute a transient pool of stored lipids that provides lipids during interprandial period while lowering chylomicron production during the post-prandial phase. This smoothens the magnitude of peaks of hypertriglyceridemia. Here, we review the composition and functions of lipids and associated proteins of enteroctye LDs, the known physiological functions of LDs as well as the role of LDs in pathological processes in the context of the intestine.

[15] [Ezetimibe in clinical practice: from laboratory investigations to the IMPROVE-IT trial results]. Borghi C, Filardi PP. Giornale italiano di cardiologia (2006) 2015; 16:3s-14s. The impact of low density lipoprotein (LDL) cholesterol levels on cardiovascular risk has been extensively studied. Statins have been demonstrated to significantly reduce LDL cholesterol levels, contributing to cardiovascular risk reduction particularly in patients with high cardiovascular risk. However, low adherence to statin therapy, often due to adverse effects, has raised the need for new pharmacological approaches to combine with statin therapy in order to reach the target levels of LDL cholesterol. Ezetimibe is a selective inhibitor of Niemann-Pick C1-like 1 (NPC1L1) protein that regulates the cholesterol uptake from the small intestine into the enterocytes. Ezetimibe has been demonstrated to significantly reduce LDL cholesterol levels in combination with statins and recent trials support its role in reducing the risk of cardiovascular events.

[16] LDL Cholesterol, Statins And PCSK 9 Inhibitors. Gupta S. Indian Heart J 2015; 67:419-424. Reduction of low density lipoprotein cholesterol (LDLc) is of vital importance for the prevention of atherosclerotic cardiovascular disease (ASCVD). Statin is the most effective therapy today to lower LDLc by inhibiting HMG-CoA-reductase. However despite intensive statin therapy, there remains a residual risk of recurrent myocardial infarction in about 20-30% cases. Moreover a few patients develop statin intolerance. For severe hypercholesterolemia, statins alone or in combination of ezetimibe, niacin and fenofibrate have been advocated. For homozygous familial hypercholesterolemia (HOFH), a microsomal triglyceride transfer protein MTP inhibitor (Lopitamide) and antisense oligonucleotide (ASO) (Mipomersen) have recently been approved by FDA, USA through 'Risk evaluation and Mitigation Strategy (REMS)'. Possible future therapies include PCSK-9 inhibitors which have excellent lipid lowering properties. Three monoclonal antibodies (PCSK 9 Inhibitors) alirocumab, evolocumab and Bococizumab are under advanced clinical stage IV trials and awaiting approval by FDA and European Medicines Agency.


[18] Associations between serum lipid levels and suicidal ideation among Korean older people. Shin HY, Kang G, Kang HJ et al. Journal of affective disorders 2015; 189:192-198. INTRODUCTION: There have been inconsistent reports on the relationships between lipids and suicidality, and studies conducted in older adults are rare. This study examined associations between serum lipid levels and suicidal ideation in an older population. METHODS: This study used data obtained from a representative Korean sample of 4265 people age 65 years or older who completed a self-administered questionnaire about suicidal ideation over the last year. The fasting serum concentrations of total cholesterol, high-
density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglycerides were measured and categorized into lower, intermediate (reference), and upper quartiles. A complex sample logistic regression stratified by gender was performed to determine the associations between serum lipid levels and suicidal ideation after controlling for covariates including age, education, marital status, current smoking, alcohol drinking, body mass index, hypertension, diabetes, diagnosed depression, antidepressant use, and lipid-lowering therapies. RESULTS: In this study, the prevalence of suicidal ideation in an older Korean population was 22.9% (SE=0.9%). The prevalence was significantly higher in women than in men, 27.7% (1.2%) vs. 15.9% (1.1%) respectively. After adjusting for covariates, lower triglyceride levels were significantly associated with a decreased risk of suicidal ideation (OR=0.65; 95% CI=0.43-0.99) among men but no significant associations were observed among women. Additionally, there were no significant associations between any other measure of cholesterol levels and suicidal ideation in either men or women. LIMITATIONS: Cross-sectional design cannot infer temporality or the effects of changes in variables. CONCLUSIONS: These results support the association between lower triglyceride levels and a reduced risk of suicidal ideation among Korean men over 65. Further studies are necessary to investigate gender difference and the biological mechanism.

[19] Implications of Coronary Artery Calcium Testing Among Statin Candidates According to American College of Cardiology/American Heart Association Cholesterol Management Guidelines: MESA (Multi-Ethnic Study of Atherosclerosis). Nasir K, Bittencourt MS, Blaha MJ et al. Journal of the American College of Cardiology 2015; 66:1657-1668. BACKGROUND: The American College of Cardiology (ACC)/American Heart Association (AHA) cholesterol management guidelines have significantly broadened the scope of candidates eligible for statin therapy. OBJECTIVES: This study evaluated the implications of the absence of coronary artery calcium (CAC) in reclassifying patients from a risk stratum in which statins are recommended to one in which they are not. METHODS: MESA (Multi-Ethnic Study of Atherosclerosis) is a longitudinal study of 6,814 men and women 45 to 84 years of age without clinical atherosclerotic cardiovascular disease (ASCVD) risk at enrollment. We excluded 1,100 participants (16%) on lipid-lowering medication, 87 (1.3%) without low-density lipoprotein levels, 26 (0.4%) with missing risk factors for calculation of 10-year risk of ASCVD, 633 (9%) >75 years of age, and 209 (3%) with low-density lipoprotein <70 mg/dl from the analysis. RESULTS: The study population consisted of 4,758 participants (age 59 +/- 9 years; 47% males). A total of 247 (5.2%) ASCVD and 155 (3.3%) hard coronary heart disease events occurred over a median (interquartile range) follow-up of 10.3 (9.7 to 10.8) years. The new ACC/AHA guidelines recommended 2,377 (50%) MESA participants for moderate- to high-intensity statins; the majority (77%) was eligible because of a 10-year estimated ASCVD risk >/=7.5%. Of those recommended statins, 41% had CAC = 0 and had 5.2 ASCVD events/1,000 person-years. Among 589 participants (12%) considered for moderate-intensity statin, 338 (57%) had a CAC = 0, with an ASCVD event rate of 1.5 per 1,000 person-years. Of participants eligible (recommended or considered) for statins, 44% (1,316 of 2,966) had CAC = 0 at baseline and an observed 10-year ASCVD event rate of 4.2 per 1,000 person-years. CONCLUSIONS: Significant ASCVD risk heterogeneity exists among those eligible for statins according to the new guidelines. The absence of CAC reclassifies approximately one-half of candidates as not eligible for statin therapy.

[20] Hypercholesterolemia, low density lipoprotein receptor and proprotein convertase subtilisin/kexin-type 9. Gu HM, Zhang DW. Journal of biomedical research 2015; 29:356-361. Atherosclerotic cardiovascular disease is the main cause of mortality and morbidity in the world. Plasma levels of low density lipoprotein cholesterol (LDL-C) are positively correlated with the risk of atherosclerosis. High plasma LDL concentrations in patients with hypercholesterolemia lead to build-up of LDL in the inner walls of the arteries, which becomes oxidized and promotes the formation of foam cells, consequently initiating atherosclerosis. Plasma LDL is mainly cleared through the LDL receptor (LDLR) pathway. Mutations in the LDLR cause familiar hypercholesterolemia and increase the risk of premature coronary heart disease. The expression of LDLR is regulated at the transcriptional level via the sterol regulatory element binding protein 2 (SREBP-2) and at the posttranslational levels mainly through proprotein convertase subtilisin/kexin-type 9 (PCSK9) and inducible degrader of the LDLR (IDOL). In this review, we summarize the latest advances in the studies of PCSK9.
[21] Role of oxidative stress and serum lipid levels in stable chronic obstructive pulmonary disease. Can U, Yerlikaya FH, Yosunkaya S. Journal of the Chinese Medical Association : JCMA 2015. BACKGROUND: Chronic obstructive pulmonary disease (COPD) has been associated with increased oxidative stress or reduced antioxidant resources. The main goal of this study was to evaluate the levels of serum ischemia-modified albumin (IMA), oxidized low-density lipoprotein (ox-LDL), total oxidant status (TOS), and total antioxidant status in patients with stable COPD, compared with a control group. METHODS: This study was performed on 51 patients with stable COPD (42 men and 9 women; mean age 56.92 +/- 3.0 years) and 45 healthy control participants (32 men and 13 women; 54.8 +/- 3.8 years). The levels of serum lipids, IMA, total antioxidant status, TOS, and ox-LDL were measured in all participants. RESULTS: The levels of serum IMA, ox-LDL, and TOS were significantly higher in patients with COPD than those in control individuals. There was no difference between the levels of serum total antioxidant status, triglycerides, total cholesterol, and low-density lipoprotein cholesterol (LDL-C) of patients with COPD and those of control individuals. Serum high-density lipoprotein cholesterol levels were significantly lower in patients with COPD than in control individuals. CONCLUSION: Our study indicated that serum IMA, ox-LDL, and TOS may be increased as a result of chronic hypoxia, inflammation, and oxidative stress in patients with severe and very severe stable COPD. Our findings also revealed that IMA is higher in patients with Global Initiative for Chronic Obstructive Lung Disease Stages II, III, and IV, while TOS and ox-LDL are higher in patients with Global Initiative for Chronic Obstructive Lung Disease Stage IV. Measurements of serum IMA, TOS, and ox-LDL levels may be useful markers in the evaluation of stable COPD.

[22] Development and validation of methodologies for the quantification of phytosterols and phytosterol oxidation products in cooked and baked food products. Menendez-Carreno M, Knol D, Janssen HG. Journal of chromatography. A 2015. Chromatography-mass spectrometry (GC-MS) methodologies for the analysis of the main phytosterols (PS) and phytosterol oxidation products (POPs) present in 19 different foodstuffs cooked or baked using margarines with or without added plant sterols are presented. Various methods for fat extraction were evaluated to allow the GC-MS analysis of large numbers of prepared vegetable, fish and meat products, egg and bakery items in a practically feasible manner. The optimized methods resulted in a good sensitivity and allowed the analysis of both PS and POPs in the broad selection of foods at a wide range of concentrations. Calibration curves for both PS and POPs showed correlation coefficients (R2) better than 0.99. Detection limits were below 0.24mgkg-1 for PS and 0.02mgkg-1 for POPs, respectively. Average recovery data were between 81% and 105.1% for PS and between 65.5 and 121.8% for POPs. Good results were obtained for within- and between-day repeatability, with most values being below 10%. Entire sample servings were analyzed, avoiding problems with inhomogeneity and making the method an exact representation of the typical use of the food by the consumer.

[23] Use of a Cholestyramine Washout in a Patient With Septic Shock on Leflunomide Therapy: A Case Report and Review of the Literature. Laub M, Fraser R, Kurche J et al. Journal of intensive care medicine 2015. Patients presenting with infections while receiving disease-modifying antirheumatic agents (DMARD) may be predisposed to a higher degree illness due to immunosuppression. This can be particularly problematic in patients who are receiving DMARDs with prolonged pharmacokinetic profiles. Leflunomide is a DMARD that has a prolonged half-life due to enterohepatic recirculation. We report a case of a patient with severe septic shock secondary to a prosthetic joint infection in which therapeutic levels of leflunomide were discovered, despite the patient ceasing therapy several weeks prior to admission. An orogastric cholestyramine washout was given to the patient to expedite the removal of the drug. Serum levels rapidly declined over the next several days, corresponding with resolution of her sepsis. A review of the literature relevant to the incidence of DMARD-related infections was conducted as well as discussion regarding the role of leflunomide drug monitoring and cholestyramine-facilitated removal of the drug in episodes of acute infectious syndromes.

[24] Simvastatin inhibits neural cell apoptosis and promotes locomotor recovery via activation of Wnt/beta-catenin signaling pathway after spinal cord injury. Gao K, Shen Z, Yuan Y et al. Journal of neurochemistry 2015. Statins exhibit neuroprotective effects after spinal cord injury (SCI). However, the molecular mechanism underlying these effects
remains unknown. This study demonstrates that the hydroxymethylglutaryl-coenzyme-A reductase inhibitor simvastatin exhibits neuroprotective effects on neuronal apoptosis and supports functional recovery in a rat SCI model by activating the Wnt/beta-catenin signaling pathway. In specific, simvastatin administration after SCI significantly upregulated the expression of low-density lipoprotein receptor-related protein-6 (LRP-6) phosphorylation and beta-catenin protein, increased the mRNA expression of lymphoid enhancer factor-1 (LEF-1) and T-cell factor-1 (TCF-1), and suppressed the expression of beta-catenin phosphorylation in the spinal cord neurons. Simvastatin enhanced motor neuronal survival in the spinal cord anterior horn, decreased the lesion of spinal cord tissues after SCI. Simvastatin administration after SCI also evidently reduced the expression levels of Bax, active caspase-3, and active caspase-9 in the spinal cord neurons and the proportion of TUNEL-positive neuron cells but increased the expression level of Bcl-2 in the spinal cord neurons. However, the anti-apoptotic effects of simvastatin were reduced in cultured spinal cord nerve cells when the Wnt/beta-catenin signaling pathway was suppressed in the lipopolysaccharide-induced model. Furthermore, the Basso, Beattie, and Bresnahan scores indicated that simvastatin treatment significantly improved the locomotor functions of rats after SCI. This study is the first to report that simvastatin exerts neuroprotective effects by reducing neuronal apoptosis and promoting functional and pathological recovery after SCI by activating the Wnt/beta-catenin signaling pathway. This article is protected by copyright. All rights reserved.

[25] Rosuvastatin 1.2 mg In Situ Gel Combined With 1:1 Mixture of Autologous Platelet-Rich Fibrin and Porous-Hydroxyapatite Bone Graft in Surgical Treatment of Mandibular Degree II Furcation Defects: A Randomized Clinical Control Trial. Pradeep AR, Karvekar S, Nagpal K et al. Journal of periodontology 2015;1:15. BACKGROUND: A wide range of regenerative materials have been tried and tested in the treatment of furcation defects. Rosuvastatin (RSV) is a new synthetic, second-generation, sulfur-containing, hydrophilic statin, that have potent anti-inflammatory and osseo-differentiation mechanism of action. Platelet-rich fibrin (PRF) is a platelet concentrate with sustained release of various growth factors, having regenerative potential to treat periodontal defects. Porous hydroxyapatite (HA) bone grafting material has clinically satisfactory response, when used to fill periodontal intrabony defects. This double-masked randomized study is designed to evaluate the potency of combination of RSV 1.2mg in situ gel with 1:1 mixture of autologous PRF and HA bone graft in the surgical treatment of mandibular degree II furcation defects when compared with autologous PRF and HA bone graft placed after open flap debridement (OFD). MATERIAL AND METHODS: 105 mandibular furcation defects were treated either with OFD + Placebo gel (Group 1) or PRF+HA with OFD (Group 2) or RSV 1.2mg gel+PRF+HA with OFD (Group 3). Clinical and radiological parameters i.e probing depth (PD), and relative vertical (RVAL) and horizontal (RHAL) attachment levels, intrabony defect depth and %defect fill were recorded at baseline and at 9 months postoperatively. RESULTS: Mean PD reduction was greater in Group 2 (3.68 +/- 1.07 mm) and Group 3 (4.62 +/- 1.03mm) than Group 1 (2.11 +/- 1.25 mm) while mean RVAL and RHAL gain was also found to be greater in Group 2 (3.31 +/- 0.52 and 2.97 +/- 0.56 mm) and Group 3 (4.17 +/- 0.70 and 4.05 +/- 0.76 mm) compared to Group 1 (1.82 +/- 0.78 and 1.62 +/- 0.64 mm respectively). Furthermore, significantly greater percentage of mean bone fill was found in the Group 2 (54.69 +/- 1.93 %) and Group 3 (61.94 +/- 3.54%) compared to Group 1 (10.09 +/- 4.28 %). CONCLUSION: Treatment of furcation defects with RSV 1.2mg in situ gel combined with autologous PRF and porus-HA bone graft, results in significant improvements of clinical and radiographic parameters when compared with OFD alone. Combining RSV with PRF and HA, implies their synergistic effects explaining their role as a regenerative material in the treatment of furcation defects.


[27] Molecular mechanisms of insulin resistance in chronic kidney disease. Thomas SS, Zhang L, Mitch WE. Kidney international 2015. Insulin resistance refers to reduced sensitivity of organs to insulin-initiated biologic processes that result in metabolic defects. Insulin resistance is common in patients with end-stage renal disease but also occurs in patients with chronic kidney disease (CKD), even when the serum creatinine is minimally increased. Following insulin binding to its receptor, auto-phosphorylation of the insulin receptor is followed by kinase reactions that phosphorylate
insulin receptor substrate-1 (IRS-1), phosphatidylinositol 3-kinase (PI3K), and Akt. In fact, low levels of Akt phosphorylation (p-Akt) identify the presence of the insulin resistance that leads to metabolic defects in insulin-initiated metabolism of glucose, lipids, and muscle proteins. Besides CKD, other complex conditions (e.g., inflammation, oxidative stress, metabolic acidosis, aging, and excess angiotensin II) reduce p-Akt resulting in insulin resistance. Insulin resistance in each of these conditions is due to the activation of different E3 ubiquitin ligases, which specifically conjugate ubiquitin to IRS-1 marking it for degradation in the ubiquitin-proteasome system (UPS). Consequently, IRS-1 degradation suppresses insulin-induced intracellular signaling, causing insulin resistance. Understanding mechanisms of insulin resistance could lead to therapeutic strategies that improve the metabolism of patients with CKD.Kidney International advance online publication, 7 October 2015; doi:10.1038/ki.2015.305.

[28] ABCB1 C3435T polymorphism and the lipid-lowering response in hypercholesterolemic patients on statins: a meta-analysis. Su J, Xu H, Yang J et al. Lipids in health and disease 2015; 14:122. BACKGROUND: A number of researches have evaluated the association between the ABCB1 polymorphism and the lipid-lowering response of statins, but the results have been inconclusive. To examine the lipid-lowering efficacy and safety associated with the ABCB1 C3435T polymorphism in hypercholesterolemic patients receiving statin, all available studies were included in this meta-analysis. METHODS: A systematic search for eligible studies in the Cochrane library database, Scopus and PubMed was performed. Articles meeting the inclusion criteria were comprehensively reviewed, and the available data were accumulated by the meta-analysis. RESULTS: The results indicated that the comparisons of CC+CT vs. TT were associated with a significant elevation of the serum HDL-C levels after statin treatment (CC+CT vs. TT: MD, 2.46; 95 % CI, 0.36 to 4.55; P = 0.02), and the ABCB1 C3435T variant in homozygotes was correlated with decreases in LDL-C (CC vs. TT: MD, 2.29; 95 % CI, 0.37 to 4.20; P = 0.02) as well as TC (CC vs. TT: MD, 3.05; 95 % CI, 0.58 to 5.53; P = 0.02) in patients treated with statin. However, we did not observe a significant association in the TG group or an association between other genetic models serum lipid parameters. In addition, statin treatment more than 5 months led to a higher risk of muscle toxicity. CONCLUSIONS: The evidence from the meta-analysis demonstrated that the ABCB1 C3435T polymorphism may represent a pharmacogenomic biomarker for predicting treatment outcomes in patients on statins and that statin treatment for more than 5 months can increase the risk of myopathy.

[29] Evolocumab (Repatha)--a second PCSK9 inhibitor to lower LDL-Cholesterol. The Medical letter on drugs and therapeutics 2015; 57:140-141.

[30] Role of bioactive lipid mediators in obese adipose tissue inflammation and endocrine dysfunction. Lopategi A, Lopez-Vicario C, Alcaraz-Quiles J et al. Molecular and cellular endocrinology 2015. White adipose tissue is recognized as an active endocrine organ implicated in the maintenance of metabolic homeostasis. However, adipose tissue function, which has a crucial role in the development of obesity-related comorbidities including insulin resistance and non-alcoholic fatty liver disease, is dysregulated in obese individuals. This review explores the physiological functions and molecular actions of bioactive lipids biosynthesized in adipose tissue including sphingolipids and phospholipids, and in particular fatty acids derived from phospholipids of the cell membrane. Special emphasis is given to polyunsaturated fatty acids of the omega-6 and omega-3 families and their conversion to bioactive lipid mediators through the cyclooxygenase and lipooxygenase pathways. The participation of omega-3-derived lipid autacoids in the resolution of adipose tissue inflammation and in the prevention of obesity-associated hepatic complications is also thoroughly discussed.

[31] Specialty Pharmaceuticals for Hyperlipidemia - Impact on Insurance Premiums. Schulman KA, Balu S, Reed SD. The New England journal of medicine 2015. The Food and Drug Administration (FDA) recently approved alirocumab and evolocumab, PCSK9 inhibitors, for the treatment of hyperlipidemia. These novel biologic agents offer the promise of reductions in blood cholesterol levels. Specifically, the FDA approved alirocumab as an "adjunct to diet and maximally
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tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease, who require additional lowering of LDL [low-density lipoprotein]-cholesterol.1

This broad indication sets the practice of cardiology on a collision course with specialty pharmaceutical pricing models that were previously reserved for drugs that benefited relatively limited patient populations. Alirocumab was launched.

[32] Reducing LDL with PCSK9 Inhibitors - The Clinical Benefit of Lipid Drugs. Everett BM, Smith RJ, Hiatt WR. The New England journal of medicine 2015. In early June, the Endocrinologic and Metabolic Drugs Advisory Committee of the Food and Drug Administration (FDA), on which we serve, met to consider marketing applications for the new molecular entities alirocumab and evolocumab on the basis of their ability to lower low-density lipoprotein (LDL) cholesterol levels and their effects on other lipid fractions in patients at risk for cardiovascular disease. These first-in-class medications are fully humanized monoclonal antibodies that inactivate proprotein convertase subtilisin-kexin type 9 (PCSK9). That inactivation results in decreased LDL-receptor degradation, increased recirculation of the receptor to the surface of hepatocytes, and consequent lowering of LDL cholesterol.


Statins Promote Long-Term Recovery after Ischemic Stroke by Reconnecting Noradrenergic Neuronal Circuitry. Cho KJ, Cheon SY, Kim GW. Neural plasticity 2015; 2015:585783. Inhibitors of HMG-CoA reductase (statins), widely used to lower cholesterol in coronary heart and vascular disease, are effective drugs in reducing the risk of stroke and improving its outcome in the long term. After ischemic stroke, cardiac autonomic dysfunction and psychological problems are common complications related to deficits in the noradrenergic (NA) system. This study investigated the effects of statins on the recovery of NA neuron circuitry and its function after transient focal cerebral ischemia (tFCI). Using the wheat germ agglutinin (WGA) transgene technique combined with the recombinant adenoviral vector system, NA-specific neuronal pathways were labeled, and were identified in the locus coeruleus (LC), where NA neurons originate. NA circuitry in the atorvastatin-treated group recovered faster than in the vehicle-treated group. The damaged NA circuitry was partly reorganized with the gradual recovery of autonomic dysfunction and neurobehavioral deficit. Newly proliferated cells might contribute to reorganizing NA neurons and lead anatomic and functional recovery of NA neurons. Statins may be implicated to play facilitating roles in the recovery of the NA neuron and its function.

Excess of free fatty acids as a cause of metabolic dysfunction in skeletal muscle. Tumova J, Andel M, Trnka J. Physiological research / Academia Scientiarum Bohemoslovaca 2015. Obesity is often associated with metabolic impairments in peripheral tissues. Evidence suggests an excess of free fatty acids (FFA) as one factor linking obesity and related pathological conditions and the impact of FFA overload on skeletal muscle metabolism is described herein. Obesity is associated with dysfunctional adipose tissue unable to buffer the flux of dietary lipids. Resulting increased levels and fluxes of plasma FFA lead to ectopic lipid deposition and lipotoxicity. FFA accumulated in skeletal muscle are associated with insulin resistance and overall cellular dysfunction. Mechanisms supposed to be involved in these conditions include the Randle cycle, intracellular accumulation of lipid metabolites, inflammation and mitochondrial dysfunction or mitochondrial stress. These mechanisms are described and discussed in the view of current experimental evidence with an emphasis on conflicting theories of decreased vs. increased mitochondrial fat oxidation associated with lipid overload. Since different types of FFA may induce diverse metabolic responses in skeletal muscle cells, this review also focuses on cellular mechanisms underlying the different action of saturated and unsaturated FFA.

Acute Loss of miR-221 and miR-222 in the Atherosclerotic Plaque Shoulder Accompanies Plaque Rupture. Bazan HA, Hatfield SA, O’Malley CB et al. Stroke 2015. BACKGROUND AND PURPOSE: Atherosclerotic plaque vulnerability is accompanied by changes in the molecular and cellular function in the plaque shoulder, including a decrease in vascular smooth muscle cell proliferation. We aimed to determine whether the expression of 3 miRNAs that regulate vascular smooth muscle cell proliferation (miR-145, miR-221, and miR-222) is altered with plaque rupture, suggesting a role in regulating plaque stability. METHODS: miRNAs were measured in the plaque shoulder of carotid plaques obtained from patients undergoing carotid endarterectomy (CEA) for 3 distinct clinical scenarios: (1) patients without previous neurological events but high-grade carotid stenosis (asymptomatic), (2) patients with an acute neurological event within 5 days of the CEA (urgent), and (3) patients undergoing CEA>5 days after a neurological event (symptomatic). RESULTS: Mean time from plaque rupture event to CEA was 2.4 days in the urgent group. The urgent group exhibited a significant decrease in miR-221 and miR-222 expression in the plaque shoulder, whereas no significant differences were seen in miR-145 across the 3 groups. Regression analysis demonstrated a significant correlation between time from the neurological event to CEA and increasing miR-221 and miR-222, but not miR-145. mRNA encoding p27Kip1, a target of miR-221 and miR-222 that inhibits vascular smooth muscle cell proliferation, was increased in the urgent group. CONCLUSIONS: Atherosclerotic plaque rupture is accompanied by a loss of miR-221 and miR-222 and an increase in p27Kip1 mRNA expression in the plaque shoulder, suggesting an association between these miRNAs and atherosclerotic plaque stability.

Apolipoprotein C-III: From Pathophysiology to Pharmacology. Norata GD, Tsimikas S, Pirillo A, Catapano AL. Trends in pharmacological sciences 2015; 36:675-687. Apolipoprotein C-III (apoC-III) has a critical role in the metabolism of triglyceride (TG)-rich lipoproteins (TRLs). Animal models lacking the APOC3 gene exhibit reduced plasma TG levels,
whereas the overexpression of APOC3 leads to increased TG levels. In humans, loss-of-function mutations in APOC3 are associated with reduced plasma TG levels and reduced risk for ischemic vascular disease and coronary heart disease. Several hypolipidemic agents have been shown to reduce apoC-III, including fibrates and statins, and antisense technology aimed at inhibiting APOC3 mRNA to decrease the production of apoC-III is currently in Phase III of clinical development. Here, we review the pathophysiological role of apoC-III in TG metabolism and the evidence supporting this apolipoprotein as an emerging target for hypertriglyceridemia (HTG) and associated cardiovascular disorders.