doses compared with those who received low
P=0.0035). In Cox regression, active simvastatin use was independently associated with reduced risk for mortality (adjusted hazard ratio (HR) 0.56 (95% CI 0.38, 0.83), P=0.004) and risk for recurrence (adjusted HR 0.61 (0.41, 0.89), P=0.01). Survival improved significantly among patients who received moderate-high-intensity (median 42.1 months (24.0,52.7)) doses compared with those who received low-intensity doses of simvastatin (median 14.1 months (8.6,
Perspective highlights new mechanistic findings based on mouse models of diabetes. Importantly, some of the mechanisms revealed by mouse models are now being studied in human subjects.

[4] Retinoic acid induces macrophage cholesterol efflux and inhibits atherosclerotic plaque formation in apoE-deficient mice. Zhou W, Lin J, Chen H et al. *The British journal of nutrition* 2015:1-10. It has been suggested that retinoic acid (RA) has a potential role in the prevention of atherosclerotic CVD. In the present study, we used J774A.1 cell lines and primary peritoneal macrophages to investigate the protective effects of RA on foam cell formation and atherogenesis in apoE-deficient (apoE-/-) mice. A total of twenty male apoE-/- mice (n 10 animals per group), aged 8 weeks, were fed on a high-fat diet (HFD) and treated with vehicle or 9-cis-RA for 8 weeks. The atherosclerotic plaque area in the aortic sinus of mice in the 9-cis-RA group was 40.7% less than that of mice in the control group (P < 0.01). Mouse peritoneal macrophages from the 9-cis-RA group had higher protein expression levels of ATP-binding cassette transporter A1 (ABCA1) and G1 (ABCG1) than those from the control group. Serum total and LDL-cholesterol concentrations were lower in the 9-cis-RA group than in the control group (P < 0.05). In vitro studies showed that incubation of cholesterol-loaded J774A.1 macrophages with 9-cis-RA (0.1, 1 and 10 mumol/l) induced cholesterol efflux in a dose-dependent manner. The 9-cis-RA treatment markedly attenuated lipid accumulation in macrophages exposed to oxidised LDL. Moreover, treatment with 9-cis-RA significantly increased the protein expression levels of ABCA1 and ABCG1 in J774A.1 macrophages in a dose-dependent manner. Furthermore, 9-cis-RA dose-dependently enhanced the protein expression level of liver X receptor-alpha (LXRalpha), the upstream regulator of ABCA1 and ABCG1. Taken together, the present results show that 9-cis-RA suppresses foam cell formation and prevents HFD-induced atherogenesis via the LXRalpha-dependent up-regulation of ABCA1 and ABCG1.

[5] A Combination of Low Doses of Fluvastatin and Valsartan Decreases Arterial Stiffness in Patients After Myocardial Infarction: A Pilot Study. Hanzel J, Piletic Z, Turk M et al. *Current therapeutic research, clinical and experimental* 2015; 77: 63-65. BACKGROUND: Despite optimum treatment, patients who experience myocardial infarction are still at high risk for future events. OBJECTIVE: We evaluated the effect of 30 days of treatment with combination of low, subtherapeutic doses of fluvastatin and valsartan on arterial stiffness in patients after myocardial infarction, a therapy that has not been used yet. METHODS: Fourteen male patients with a history of myocardial infarction were enrolled into a pilot double-blind randomized controlled study. They were allocated to receive 10 mg fluvastatin and 20 mg valsartan or placebo for 30 days in addition to their regular pharmacotherapy. Carotid-femoral pulse wave velocity was measured on inclusion, after 30 days, and after 3 months. RESULTS: Mean (SD) carotid-femoral pulse wave velocity decreased significantly in the treatment group after 30 days and persisted at lower values after 3 months (from 8.4 [1.5] m/sec to 7.3 [1.1] m/sec to 7.2 [0.8] m/sec; P < 0.05). The 95% CI for decrease after 30 days in the treatment group was 0.5-1.6. Only nonsignificant changes were observed in the control group. Serum lipid levels and arterial blood pressure did not change significantly in any group. CONCLUSIONS: The treatment resulted in a significant and sustained improvement of arterial stiffness in male patients with a history of myocardial infarction, which highlights the need for further study of this new approach.

[6] Uncomplicating the Macrovascular Complications of Diabetes: The 2014 Edwin Bierman Award Lecture. Bornfeldt KE. *Diabetes* 2015; 64:2689-2697. The risk of cardiovascular events in humans increases in the presence of type 1 or type 2 diabetes mellitus, in large part due to exacerbated atherosclerosis. Genetically engineered mouse models have begun to elucidate cellular and molecular mechanisms responsible for diabetes-exacerbated atherosclerosis. Research on these mouse models has revealed that diabetes independently accelerates initiation and progression of lesions of atherosclerosis and also impairs the regression of lesions following aggressive lipid lowering. Myeloid cell activation in combination with proatherogenic changes allowing for increased monocyte recruitment into arteries of diabetic mice has emerged as an important mediator of the effects of diabetes on the three stages of atherosclerosis. The effects of diabetes on atherosclerosis appear to be dependent on an interplay between glucose and lipids, as well as other factors, and result in increased recruitment of monocytes into both progressing and regression lesions of atherosclerosis. Importantly, some of the mechanisms revealed by mouse models are now being studied in human subjects. This Perspective highlights new mechanistic findings based on mouse models of diabetes-exacerbated atherosclerosis and...
most patients with CKD disease (CKD) is highly prevalent worldwide and represents a major cardiovascular risk factor. Dyslipidemia is present in T2DM patients. apoB is significantly related to MetS independently of LDL-C level. Of the components of MetS, TG, and systolic blood pressure appeared to be determinants of apoB.

[7] Glycemic and Cholesterol Control Versus Single-Goal Control in US Veterans with Newly Diagnosed Type 2 Diabetes: A Retrospective Observational Study. Shi L, Ye X, Lu M et al. Diabetes Ther 2015. INTRODUCTION: A majority of patients with diabetes do not have levels of glycated hemoglobin (HbA1c) and low-density lipoprotein cholesterol (LDL-C) under control, either individually or in combination. The objective was to assess the clinical benefits and patient characteristics associated with dual-goal achievement [HbA1c <7% (53 mmol/mol) and LDL-C <100 mg/dL] versus only LDL-C goal achievement in adults with newly diagnosed type 2 diabetes. METHODS: Newly diagnosed patients with >/=2 measures of LDL-C and HbA1c were identified in the South Central Veterans Affairs Health Care Network (01/2004-06/2010). The index date was the first HbA1c assessment within 3 months of the first type 2 diabetes diagnosis. Multivariate Cox proportional hazards models were used to assess the association between time-varying goal achievement and post-index microvascular and cardiovascular complications. Patient characteristics associated with dual-goal achievement in the 7-12 months post-index were identified using a logistic regression. RESULTS: The sample included 16,829 patients. Compared with LDL-C goal achievement, dual-goal achievement was associated with lower risk of microvascular complications [hazard ratio (95% confidence interval): 0.69 (0.63, 0.76)]. Other outcomes did not differ between those two groups. Characteristics associated with dual-goal achievement (44.2% of patients) include prior dual-goal achievement, older age, and use of lipid-lowering drugs. CONCLUSION: Dual-goal achievement in newly diagnosed type 2 diabetes is associated with a lower risk of microvascular complications versus only LDL-C goal achievement. Although dual-goal achievement rates are suboptimal, early and regular intervention will increase its likelihood. FUNDING: Daiichi Sankyo, Inc., Parsippany, NJ, USA.


[9] Apolipoprotein B Is Related to Metabolic Syndrome Independently of Low Density Lipoprotein Cholesterol in Patients with Type 2 Diabetes. Lim Y, Yoo S, Lee SA et al. Endocrinol Metab (Seoul) 2015; 30:208-215. BACKGROUND: Increased low density lipoprotein cholesterol (LDL-C) level and the presence of metabolic syndrome (MetS) are important risk factors for cardiovascular disease (CVD) in type 2 diabetes mellitus (T2DM). Recent studies demonstrated apolipoprotein B (apoB), a protein mainly located in LDL-C, was an independent predictor of the development of CVD especially in patients with T2DM. The aim of this study was to investigate the relationship between apoB and MetS in T2DM patients. METHODS: We analyzed 912 patients with T2DM. Fasting blood samples were taken for glycated hemoglobin, high-sensitivity C-reactive protein, total cholesterol, triglyceride (TG), high density lipoprotein cholesterol, LDL-C, and apoB. MetS was defined by the modified National Cholesterol Education Program Adult Treatment Panel III criteria. We performed a hierarchical regression analysis with apoB as the dependent variable. Age, sex, the number of components of MetS and LDL-C were entered at model 1, the use of lipid-lowering medications at model 2, and the individual components of MetS were added at model 3. RESULTS: Seventy percent of total subjects had MetS. ApoB level was higher in subjects with than those without MetS (104.5+/ -53.3 mg/dL vs. 87.7+/ -33.7 mg/dL, P<0.01) even after adjusting for LDL-C. ApoB and LDL-C were positively correlated to the number of MetS components. The hierarchical regression analysis showed that the increasing number of MetS components was associated with higher level of apoB at step 1 and step 2 (beta=0.120, P<0.001 and beta=0.110, P<0.001, respectively). At step 3, TG (beta=0.116, P<0.001) and systolic blood pressure (beta=0.099, P<0.05) were found to significantly contribute to apoB. CONCLUSION: In patients with T2DM, apoB is significantly related to MetS independently of LDL-C level. Of the components of MetS, TG, and systolic blood pressure appeared to be determinants of apoB.

Vascular and metabolic effects of ezetimibe combined with simvastatin in patients with hypercholesterolemia.
Koh KK, Oh PC, Sakuma I et al. International journal of cardiology 2015; 199:126-131. BACKGROUND: Ezetimibe decreases visceral fat and improving insulin sensitivity (IS) in animals and humans. We first reported that simvastatin dose-dependently worsens insulin sensitivity. Whether ezetimibe may compensate untoward effects of simvastatin, depending on dosages of simvastatin has not been investigated in patients with hypercholesterolemia, compared with simvastatin alone. METHODS: This was a randomized, single-blind, placebo-controlled, parallel study. Fifty-one in each group were given placebo, ezetimibe 10mg combined with simvastatin 10mg (Vyto10), ezetimibe 10mg combined with simvastatin 20mg (Vyto20), or simvastatin 20mg alone (Simva20) daily for 2months. RESULTS: Placebo, Vyto10, Vyto20, and Simva20 improved flow-mediated dilation relative to baseline measurements. Placebo therapy did not significantly change insulin and IS and adiponecins level and visceral fat area (VFA) and VFA/subcutaneous fat area (SFA) relative to baseline measurements. Vyto10 therapy significantly decreased CRP and insulin levels and increased adiponecin levels and IS, and reduced VFA, VFA/SFA, and blood pressure. Vyto20 therapy did not significantly change insulin levels and IS and adiponecin levels but significantly reduced CRP levels and VFA, VFA/SFA, and blood pressure. Simva20 therapy significantly decreased adiponecin levels and IS but did not significantly change VFA, VFA/SFA, and blood pressure. Of note, these different effects of each therapy were significant by ANOVA. CONCLUSIONS: Vyto10, Vyto20, and Simva20 showed significant reduction of LDL cholesterol levels and improvement of flow-mediated dilation in patients with hypercholesterolemia. However, Vyto10, Vyto20, and Simva20 showed significantly differential metabolic effects, depending on dosages of simvastatin.

Increasing HDL levels by inhibiting cholesteryl ester transfer protein activity in rabbits with hindlimb ischemia is associated with increased angiogenesis. Wu BJ, Shrestha S, Ong KL et al. International journal of cardiology 2015; 199:204-212. BACKGROUND: High density lipoprotein (HDL) infusions increase new blood vessel formation (angiogenesis) in rodents with ischemic injury. This study asks if increasing HDL levels by inhibiting cholesteryl ester transfer protein (CETP) activity increases angiogenesis in New Zealand White (NZW) rabbits with hindlimb ischemia. METHODS AND RESULTS: NZW rabbits were maintained for 6weeks on chow or chow supplemented with 0.07% or 0.14% (wt/wt) of the CETP inhibitor, des-fluoro-anacetrapib. The left femoral artery was ligated after 2weeks of des-fluoro-anacetrapib treatment. The animals were sacrificed 4weeks after femoral artery ligation. Treatment with 0.07% and 0.14% (wt/wt) des-fluoro-anacetrapib reduced CETP activity by 63+/-12% and 81+/-8.6%, increased plasma apoA-I levels by 1.3+/-0.1- and 1.4+/0.1-fold, and increased plasma HDL-cholesterol levels by 1.4+/-0.1- and 1.7+/-0.2-fold, respectively. Treatment with 0.07% and 0.14% (wt/wt) des-fluoro-anacetrapib increased the number of collateral arteries by 60+/-16% and 84+/-27%, and arteriole wall area in the ischemic hindlimbs by 84+/-16% and 94+/-13%, respectively. Capillary density in the ischemic hindlimb adductor muscle increased from 1.1+/-0.2 (control) to 2.1+/-0.3 and 2.2+/-0.4 in the 0.07% and 0.14% (wt/wt) des-fluoro-anacetrapib-treated animals, respectively. Incubation of HDLs from des-fluoro-anacetrapib-treated animals with human coronary artery endothelial cells at apoA-I concentrations comparable with their plasma levels increased tubule network formation. These effects were abolished by knockdown of scavenger receptor-B1 (SR-B1) and PDZK1, and pharmacological inhibition of PI3K/Akt. CONCLUSION: Increasing HDL levels by inhibiting CETP activity is associated with increased collateral blood vessel formation in NZW rabbits with hindlimb ischemia in an SR-B1- and PI3K/Akt-dependent manner.

Plasma membrane CD81 complexes with PCSK9 and LDLR and its levels are reduced by PCSK9. Le QT, Blanchet M, Seidah NG, Labonte P. The Journal of biological chemistry 2015. Proprotein convertase subtilisin/kexin type 9 (PCSK9) is an important factor in plasma cholesterol regulation through modulation of low-density lipoprotein receptor (LDLR)
levels. Naturally occurring mutation can lead to hyper- or hypo-cholesterolemia in human. Recently, we reported that PCSK9 was also able to modulate CD81 in Huh7 cells. In the present study, several gain-of-function (GOF) and loss-of-function (LOF) as well as engineered mutants of PCSK9 were compared for their ability to modulate the cell surface expression of LDLR and CD81. While PCSK9 GOF D374Y enhances the degradation both receptors, D374H and D129N seem to only reduce LDLR levels. In contrast, mutations in the C-terminal hinge-CHRD segment primarily affect the PCSK9-induced CD81 degradation. Furthermore, when C-terminally fused to an ACE2-transmembrane anchor, the secretory N-terminal catalytic or hinge-CHRD domains of PCSK9 were able to reduce CD81 and LDLR levels. These data confirm that PCSK9 reduces CD81 levels via an intracellular pathway, as reported for LDLR. Using immunocytochemistry, a proximity ligation assay and coimmunoprecipitation, we found that the cell surface level of PCSK9 was enhanced upon overexpression of CD81, and that both PCSK9 and LDLR interact with this tetraspanin protein. Interestingly, using CHO-A7 cells lacking LDLR expression, we revealed that LDLR was not required for the degradation of CD81 by PCSK9, but its presence strengthened the PCSK9 effect.


BACKGROUND: To examine the effects of pitavastatin on atherosclerotic plaque in Watanabe heritable hyperlipidemic (WHHL) rabbits using serial in vivo tissue-characterizing intravascular ultrasound. METHODS: A total of 11 WHHL rabbits of 10-12 weeks of age were divided into two groups, control and pitavastatin-administered groups. A total of 29 atherosclerotic plaque segments from control group and 43 plaque segments from the pitavastatin group were serially imaged by 40MHz intravascular ultrasound in vivo with a tissue characterization software (iMAP, Boston Scientific, Natick, MA, USA) at the baseline and the follow-up (16th week). RESULTS: The level of low-density lipoprotein cholesterol was significantly decreased in pitavastatin group. During the follow-up period, plaque area was significantly increased in the control group, whereas it was not significantly changed in the pitavastatin group. The fibrotic, necrotic, and necrotic plus lipidic areas were significantly increased in the control group, while no significant change was revealed for tissue profile in pitavastatin group. The change in the percent areas of fibrotic and lipidic plus necrotic tissues were significantly different between the two groups especially in the superficial half portion of plaque. CONCLUSIONS: These data indicate that pitavastatin could attenuate atherosclerotic plaque formation and that it could stabilize the plaque in WHHL rabbits. Considering the fact that these were observed even with a high follow-up level of cholesterol, these data might come from the pleiotropic effects of pitavastatin.

[15] The Effect of oxLDL on Aortic Valve Calcification via the Wnt/ beta-catenin Signaling Pathway: An Important Molecular Mechanism. Gao X, Zhang L, Gu G et al. J Heart Valve Dis 2015; 24:190-196. BACKGROUND AND AIM OF THE STUDY: Calcific aortic valve disease (CAVD) is a commonly acquired valvular disease. Although previous studies have shown valve calcification to be mediated by a chronic inflammatory disease process, with many similarities to atherosclerosis that included inflammatory cell infiltrates, lipoproteins, lipids, extracellular bone-matrix proteins, and bone minerals, little is known of the mechanisms of the cellular and molecular components and processes. It has recently been hypothesized that the calcific aortic valve is a product of active inflammation, similar to the atherosclerosis pathological process. Thus, the cessation of statin therapy should, in theory, have an effect on the treatment of CAVD and on aortic valve myofibroblasts (AVMFs), which play an important role in aortic valvular calcification. The study aim was to determine if oxidized low-density lipoprotein (oxLDL) could stimulate the apoptosis of AVMFs and the calcific-related pathway, and whether atorvastatin could inhibit the effects of AVMFs induced by oxLDL. The Wnt/GSK-3beta/beta-catenin signaling pathway may play a key role in this process, thereby making a major contribution to aortic valve calcification. METHODS: AVMFs were successfully acquired using a combination of trypsin and collagenase enzyme digestion, and made phenotypic for the identification for alpha-smooth muscle actin (alpha-SMA). Cell apoptosis was monitored using flow cytometry, bone protein expression by Western blot, and related gene expression by reverse transcription polymerase chain reaction (RT-PCR). RESULTS: A positive identification of alpha-SMA, a myofibroblast marker, confirmed the successful harvesting of myofibroblasts. OxLDL significantly induced cell apoptosis (p < 0.05), and this became even more obvious after 48 h (p < 0.01). OxLDL also significantly increased the protein expression of all differentiation markers (p < 0.05), as confirmed through Western blotting and RT-PCR, while atorvastatin significantly reduced the effects of oxLDL (p < 0.05). CONCLUSION: Among the mechanisms of the cellular and molecular components and processes, oxLDL increased the valve calcification-related signaling pathway by
increasing extracellular bone-matrix protein that produces osteoblastic gene markers via the Wnt/GSK-3beta/beta-catenin pathway. And atorvastatin also prevented any oxLDL-induced effects through the same pathway, this may represent a new therapeutic target for CAVD, as an alternative to traditional valve replacement surgery.

[16] ABCA1 contributes to macrophage deposition of extracellular cholesterol. Jin X, Freeman SR, Vaisman B et al. Journal of lipid research 2015. We previously reported that cholesterol-enriched macrophages excrete cholesterol into the extracellular matrix. A monoclonal antibody that detects cholesterol microdomains labels the deposited extracellular particles. Macrophage deposition of extracellular cholesterol depends in part on ABCG1 and this cholesterol can be mobilized by HDL components of the reverse cholesterol transport process. The objective of the current study was to determine whether ABCA1 also contributes to macrophage deposition of extracellular cholesterol. ABCA1 functioned in extracellular cholesterol deposition. The LXR agonist, TO901317 (TO9), an ABCA1-inducing factor, restored cholesterol deposition that was absent in cholesterol-enriched ABCG1/- mouse macrophages. In addition, the ABCA1 inhibitor, probucol, blocked the increment in cholesterol deposited by TO9-treated, wild-type macrophages, and completely inhibited deposition from TO9-treated, ABCG1/- macrophages. Lastly, ABCA1/-macrophages deposited much less extracellular cholesterol than wild-type macrophages. These findings demonstrate a novel function of ABCA1 in contributing to macrophage export of cholesterol into the extracellular matrix.

[17] The Effect of Atorvastatin on Habitual Physical Activity among Healthy Adults. Panza GA, Taylor BA, Thompson PD et al. Med Sci Sports Exerc 2015. PURPOSE: Statin therapy can result in muscle pain, cramps, and weakness that may limit physical activity although reports are mixed. We conducted a randomized control trial to examine the effect of atorvastatin on habitual physical activity levels among a large sample of healthy adults. METHODS: Participants (n=418) were statin-naive adults [44.0±16.1yr (X+/−SD)] that were randomized and double-blinded to 80mg per day of atorvastatin or placebo for 6 months. Accelerometers were worn for 96hr before and after drug treatment. Repeated measures analysis test physical activity levels after versus before drug treatment among groups with age and VO2max as covariates. RESULTS: Among the total sample, sedentary behavior increased (19.5+/−5.1min*d), while light (9.1+/−3.0min*d) and moderate intensity (9.7+/−2.8min*d) physical activity decreased, as did total activity counts (17.8+/−6.3*dx10) over 6 months (P<0.01), with no differences between groups. The atorvastatin group increased sedentary behavior (19.8+/−7.4min*d), and decreased light (10.7+/−4.3min*d) and moderate (8.5+/−4.0min*d) intensity physical activity (P<0.05); while the placebo group increased sedentary behavior (19.2+/−7.1min*d), and decreased moderate intensity (11.0+/−3.8min*d) and total physical activity counts (-23.8+/−8.8x10*d) (p<0.05). CONCLUSION: Time being sedentary increased and physical activity levels decreased among the total sample over 6 months of drug treatment, independent of group assignment. Our results suggest that statins do not influence physical activity levels any differently than placebo, and the lack of inclusion of a placebo condition may provide insight into the inconsistencies in the literature.

[18] Simvastatin Enhances Spatial Memory and Long-Term Potentiation in Hippocampal CA1 via Upregulation of alpha7 Nicotinic Acetylcholine Receptor. Chen T, Wang C, Sha S et al. Mol Neurobiol 2015. Simvastatin (SV) has been reported to improve cognitive deficits in Alzheimer's disease. Here, we show that chronic administration of SV (20 mg/kg) for 30 days in adult mice (SV mice) enhanced spatial cognitive performance as assessed by Morris water maze and Y-maze. To explore mechanisms underlying SV-enhanced spatial cognition, we further examined synaptic properties and long-term potentiation (LTP) in hippocampal CA1, hippocampal alpha7nAChR expression, and Akt and ERK2 phosphorylation. In comparison with controls, the SV administration caused increase in presynaptic glutamate release and amplitude of NMDAr-dependent LTP (LTP-augmentation), and decrease in threshold of NMDAr-independent LTP induction (LTP-facilitation). The supplement of isoprenoid farnesyl pyrophosphate (FP) by applying farnesol (FOH) could abolish the spatial cognitive potentiation, increased glutamate release, and LTP-augmentation/facilitation in SV mice. Expression of alpha7nAChR, but not alpha4beta2nAChR, was increased in hippocampal pyramidal cells of SV mice with the reduction of transcription factor AP-2alpha, which were abolished by FOH. Levels of Akt and ERK2 phosphorylation in SV mice were elevated, which were suppressed by FOH or alpha7nAChR antagonist methyl-lycaconitine (MLA). In hippocampal slices obtained from SV mice, acute perfusion of MLA blocked the increased glutamate release, whereas FOH, PI3K inhibitor LY294002, or MEK inhibitor U0126 could not. In the slices of SV mice, the perfusion of MLA or U0126,
but not FOH, abolished the LTP-augmentation and LTP-facilitation. By contrast, LY294002 prevented the LTP-facilitation but failed to affect the LTP-augmentation. The findings indicate that the administration of SV through reducing FPP increases alpha7nAChR expression and alpha7nAChR-related Akt and ERK2 phosphorylation, leading to LTP enhancement and spatial cognitive potentiation.

[19] Neuroprotective effects and dynamic expressions of MMP9 and TIMP1 associated with atorvastatin pretreatment in ischemia-reperfusion rats. Fang X, Tao D, Shen J et al. Neurosci Lett 2015. Atorvastatin has been reported to ameliorate ischemic brain damage after stroke, but the underlying mechanisms are not clear. This study investigated the effect of atorvastatin on dynamic expressions of MMP9 and TIMP1 in rats after cerebral ischemia reperfusion (I/R). Atorvastatin (5 mg.kg-1.d-1) or vehicle was administered orally to rats for 21d before middle cerebral artery occlusion (MCAo) for 2h, with perfusion at 3-, 12-, 24-, 48-, or 96-h thereafter. To evaluate functional outcome, a 5-point behavioral rating scale was performed. Ischemic lesion volume was assessed via triphenyl tetrazolium chloride (TTC) staining. mRNA levels of MMP-9 and TIMP-1 were detected by reverse transcription-PCR, and protein levels of MMP-9 and TIMP-1 were measured by immunohistochemical SABC method. At all reperfusion time points, atorvastatin pretreatment was associated with significantly (P<0.05) improved neurological function and reduced brain infarct sizes compared with vehicle treatment, and MMP9 levels were significantly (P<0.05 lower and TIMP1 levels were significantly (P<0.05) higher in both mRNA and protein levels. In conclusion, Oral administration of atorvastatin before stroke may reduce the severity in I/R injury and improve neurological outcome by lowering MMP9 levels and elevating TIMP1 levels.

[20] A family-specific linkage analysis of blood lipid response to fenofibrate in the Genetics of Lipid Lowering Drug and Diet Network. Hidalgo B, Aslibekyan S, Wiener HW et al. Pharmacogenetics and genomics 2015. Cost-effective identification of novel pharmacogenetic variants remains a pressing need in the field. Using data from the Genetics of Lipid Lowering Drugs and Diet Network, we identified genomic regions of relevance to fenofibrate response in a sample of 173 families. Our approach included a multipoint linkage scan, followed by selection of the families showing evidence of linkage. We identified a strong signal for changes in LDL-cholesterol (LDL-C) on chromosome 7 (peak logarithm of odds score=4.76) in the full sample (n=821). The signal for LDL-C response remained even after adjusting for baseline LDL-C. Restricting analyses only to the families contributing to the linkage signal for LDL-C (N=19), we observed a peak logarithm of odds score of 5.17 for chromosome 7. Two genes under this peak (ABCB4 and CD36) were of biological interest. These results suggest that linked family analyses might be a useful approach to gene discovery in the presence of a complex (e.g. multigenic) phenotype.

[21] Statin therapy and plasma coenzyme Q10 concentrations-A systematic review and meta-analysis of placebo-controlled trials. Banach M, Serban C, Ursoniu S et al. Pharmacological research : the official journal of the Italian Pharmacological Society 2015. Statin therapy may lower plasma coenzyme Q10 (CoQ10) concentrations, but the evidence as to the significance of this effect is unclear. We assessed the impact of statin therapy on plasma CoQ10 concentrations through the meta-analysis of available RCTs. The literature search included selected databases up to April 30, 2015. The meta-analysis was performed using either a fixed-effects or random-effect model according to I2 statistic. Effect sizes were expressed as weighted mean difference (WMD) and 95% confidence interval (CI). The data from 8 placebo-controlled treatment arms suggested a significant reduction in plasma CoQ10 concentrations following treatment with statins (WMD: -0.44mmol/L, 95%CI: -0.52, -0.37, p<0.001). The pooled effect size was robust and remained significant in the leave-one-out sensitivity analysis. Subgroup analysis suggested that the impact of statins on plasma CoQ10 concentrations is significant for all 4 types of statins studied i.e. atorvastatin (WMD: -0.41mmol/L, 95%CI: -0.53, -0.29, p<0.001), simvastatin (WMD: -0.47mmol/L, 95% CI: -0.61, -0.33, p<0.001), rosuvastatin (WMD: -0.49mmol/L, 95%CI: -0.67, -0.31, p<0.001) and pravastatin (WMD: -0.43mmol/L, 95%CI: -0.69, -0.16, p=0.001). Likewise, there was no differential effect of lipophilic (WMD: -0.43mmol/L, 95%CI: -0.53, -0.34, p<0.001) and hydrophilic statins (WMD: -0.47mmol/L, 95%CI: -0.62, -0.32, p<0.001). With respect to treatment duration, a significant effect was observed in both subsets of trials lasting <12 weeks (WMD: -0.51mmol/L, 95%CI: -0.64, -0.39, p<0.001) and >/=12 weeks (WMD: -0.40mmol/L, 95%CI: -0.50, -0.30, p<0.001). The meta-analysis showed a significant reduction in plasma CoQ10 concentrations following treatment with statins. Further well-designed trials are required to confirm our findings and elucidate their clinical relevance.
[22] Aggravating Effect of Atorvastatin on Indomethacin-induced Gastric Injury: Focus on PGE, TNF-alpha, Neutrophils and iNOS. Yildirim Fl, Uyanik O, Ozyogurtcu H et al. Prostaglandins Other Lipid Mediat 2015. Statins are suggested to possess healing properties due to their antioxidant and antiinflammatory effects in animal ulcer models. In contrary, a clinical report indicated the formation of gastric ulcer by the use of atorvastatin. In this study, we aimed to investigate the effects of atorvastatin (0.5, 5 and 50mg/kg, p.o.) after single (acute) and multiple (subchronic, 5 days) applications on indomethacin-induced gastric ulcer in rats. In both acute and subchronic models high dose atorvastatin (50mg/kg), unlike to lower doses (0.5 and 5mg/kg), significantly aggravated ulcer lesions induced by indomethacin (30mg/kg) although, a direct ulcerogenic influence was lacking. Proliferative effect of atorvastatin are likely to be associated with decreased mucosal defense mechanisms (GSH and PGE2), and increased neutrophil infiltration and proinflammatory factors (TNF-a and iNOS) possibly via independently from mevalonate pathway. Thus, atorvastatin therapy should be monitored in patients for an increased risk of gastric ulcer particularly when used concomitantly with NSAIDs.

[23] Efficacy of atorvastatin on hippocampal neuronal damage caused by chronic intermittent hypoxia: involving TLR4 and its downstream signaling pathway. Deng Y, Yuan X, Guo XL et al. Respir Physiol Neurobiol 2015. Hippocampal neuronal damage is critical for the initiation and progression of neurocognitive impairment accompanied obstructive sleep apnea syndrome (OSAS). Toll-like receptor 4(TLR4) plays an important role in the development of several hippocampus-related neural disorders. Atorvastatin was reported beneficially regulates TLR4. Here, we examined the effects of atorvastatin on hippocampal injury caused by chronic intermittent hypoxia (CIH), the most characteristic pathophysiological change of OSAS. Mice were exposed to intermittent hypoxia with or without atorvastatin for 4 weeks. Cell damage, the expressions of TLR4 and its two downstream factors myeloid differentiation factor 88 (MYD88) and TIR-domain-containing adapter-inducing interferon-beta(TRIF), inflammatory agents (tumor necrosis factor alpha and interleukin 1beta), and the oxidative stress(superoxide dismutase and malondialdehyde) were determined. Atorvastatin decreased the neural injury and the elevation of TLR4, MyD88, TRIF, pro-inflammatory cytokines and oxidative stress caused by CIH. Our study suggests that atorvastatin may attenuate CIH induced hippocampal neuronal damage partially via TLR4 and its downstream signaling pathway.

[24] Lipoprotein-apheresis: Austrian consensus on indication and performance of treatment. Derfler K, Steiner S, Sinzinger H. Wien Klin Wochenschr 2015. The prevalence of familial disorders of lipid metabolism in Europe is higher than believed so far. In severely affected patients in whom conventional combined lipid lowering agents are insufficient to achieve target values, patients being intolerant to all the available members of the statin family as well as in patients with elevated lipoprotein(a) (100 mg/dl) and progression of atherosclerotic vascular disease, despite even normal low-density lipoproteins (LDL)-cholesterol values, lipoprotein-apheresis treatment is indicated. The Austrian Apheresis Consensus compares the inclusion criteria for patients to be treated in Austria with those from Italy, Germany, Spain, Japan, UK and the United States. The cut off level of 100 mg/dl for lipoprotein(a) is higher in Austria as compared to the aforementioned countries (50 or 60 mg/dl, respectively). The available clinical data reveal that regular weekly lipoprotein apheresis not only results in a significant lowering of the respective atherogenic lipid and lipoprotein parameters, but also in a significant decrease in clinical events and interventions. The underlying mechanisms such as non-lipid effects, side effects as well as the different available treatment principles are compared. For patients meeting the inclusion criteria, lipoprotein apheresis is a safe and effective therapy significantly reducing vascular events.