Literature update week 20 (2016)

[1] Statins Reduce the Risk of Cirrhosis and Its Decompensation in Chronic Hepatitis B Patients: A Nationwide Cohort Study. Huang YW, Lee CL, Yang SS et al. Am J Gastroenterol 2016.OBJECTIVES: The protective effect of statins in cirrhosis and its decompensation in chronic hepatitis B (CHB) patients remains unknown. METHODS: We conducted a population-based cohort study using data from the Taiwanese National Health Insurance Research Database from 1997 to 2009. A total of 298,761 CHB patients were identified. CHB patients using statins (n=6,543; defined as >/=28 cumulative defined daily doses (cDDD)) and a 1:1 ratio propensity score and inception point (the date of first use of statins)-matched non-statins (<28 cDDD) were followed up from the inception point until the development of cirrhosis or its decompensation or until withdrawal from insurance or December 2009. RESULTS: After adjustment for competing mortality, CHB patients using statins had a significantly lower cumulative incidence of cirrhosis (relative risk)=0.433; 95% confidence interval (CI)=0.344-0.515; modified log-rank test, P<0.001) and decompensated cirrhosis (relative risk)=0.468; 95% CI=0.344-0.637; P<0.001) compared with patients not using statins. After adjustment for age, gender, comorbidity index, hypertension, diabetes, hyperlipidemia, hepatocellular carcinoma, obesity, non-alcoholic fatty liver disease, aspirin use, diabetes medication, CHB treatment, non-statin lipid-lowering drugs, and triglyceride lipid-lowering drugs using the Cox proportional hazard model, statins were still an independent protector against cirrhosis (adjusted hazard ratio (AHR)=0.512; 95% CI=0.413-0.634; P<0.001) and its decompensation (AHR=0.534; 95% CI=0.433-0.659; P<0.001). The AHRs for cirrhosis were 0.467 and 0.200, and the AHRs for decompensated cirrhosis were 0.611 and 0.231 with 91-365 and >365 cDDD of statins, respectively. CONCLUSIONS: CHB patients who receive statin therapy have a dose-dependent reduction in the risk of cirrhosis and its decompensation. Am J Gastroenterol advance online publication, 10 May 2016; doi:10.1038/ajg.2016.179. Pubmed ID http://www.ncbi.nlm.nih.gov/pubmed/?term=27166128

[2] Local Administration of Simvastatin Stimulates Healing of an Avascular Meniscus in a Rabbit Model of a Meniscal Defect. Zhang S, Matsushita T, Kuroda R et al. Am J Sports Med 2016.BACKGROUND: Repair of an avascular meniscus is challenging because of its low capacity for healing. Several reports have shown that simvastatin stimulates the anabolic activity of intervertebral fibrochondrocytes, suggesting that simvastatin may be used for the treatment of meniscal defects. PURPOSE: To test whether the local administration of simvastatin stimulates healing of an avascular meniscus in rabbits. STUDY DESIGN: Controlled laboratory study. METHODS: In 30 Japanese White rabbits, a cylindrical defect (1.5-mm diameter) was introduced into the avascular zone of the anterior part of the medial meniscus in bilateral knees. Either a gelatin hydrogel (control group) or simvastatin-conjugated gelatin hydrogel (simvastatin group) was implanted into the defect. Histological assessments were performed using qualitative scoring systems, and immunohistochemical analysis was performed at 12 weeks after surgery. The occupation ratio (OR) and safranin O staining occupation ratio (SOR) were evaluated quantitatively at each time point. Stiffness of the regenerated tissue was analyzed biomechanically at 12 weeks after surgery. Rabbit meniscal cells were cultured in the presence or absence of 0.5 muM simvastatin, and then real-time polymerase chain reaction was performed to evaluate gene expression. RESULTS: The qualitative score was significantly higher in the simvastatin group after 8 and 12 weeks (P = .031 and .035, respectively). The mean OR and SOR were also significantly higher in the simvastatin group (OR at 8 weeks: 0.396 +/- 0.019 [control] vs 0.564 +/- 0.123 [simvastatin], P = .008; OR at 12 weeks: 0.451 +/- 0.864 [control] vs 0.864 +/- 0.035 [simvastatin], P = .001; SOR at 8 weeks: 0.071 +/- 0.211 [control] vs 0.487 +/- 0.430 [simvastatin], P = .009; SOR at 12 weeks: 0.093 +/- 0.088 [control] vs 0.821 +/- 0.051 [simvastatin], P = .006). Immunohistochemical analysis showed that at 12 weeks, the
reparative tissue was more strongly positive for type I collagen (COL1), type II collagen (COL2), bone morphogenetic protein 2 (BMP-2), and BMP-7 in the simvastatin group than in the control group. Biomechanical analysis showed significantly higher stiffness in the simvastatin group (2.417 +/- 1.593 N/ms [control] vs 5.172 +/- 1.078 N/ms [simvastatin]; P = .005). In rabbit meniscal cells, BMP-2 and BMP-7 were upregulated after 4 and 8 hours and after 7 and 14 days, whereas COL1A1 and COL2A1 were significantly upregulated by simvastatin after 7 and 14 days. CONCLUSION: The local administration of simvastatin promotes the regeneration of an avascular meniscus in the rabbit model of a meniscal defect. The mechanism may involve the upregulation of BMPs and the subsequent upregulation of COL1 and COL2. CLINICAL RELEVANCE: This study suggests that simvastatin stimulated intrinsic healing of an avascular meniscus. The local administration of simvastatin is safe and inexpensive and seems to be a promising treatment of meniscal injuries. Pubmed ID http://www.ncbi.nlm.nih.gov/pubmed/?term=27159292

[3] Estimating the future burden of cardiovascular disease and the value of lipid and blood pressure control therapies in China. Stevens W, Peneva D, Li JZ et al. BMC Health Serv Res 2016; 16:175.BACKGROUND: Lifestyle and dietary changes reflect an ongoing epidemiological transition in China, with cardiovascular disease (CVD) playing an ever-increasing role in China’s disease burden. This study assessed the burden of CVD and the potential value of lipid and blood pressure control strategies in China. METHODS: We estimated the likely burden of CVD between 2016 and 2030 and how expanded use of lipid lowering and blood pressure control medication would impact that burden in the next 15 years. Accounting for the costs of drug use, we assessed the net social value of a policy that expands the utilization of lipid and blood pressure lowering therapies in China. RESULTS: Rises in prevalence of CVD risk and population aging would likely increase the incidence of acute myocardial infarctions (AMIs) by 75 million and strokes by 118 million, while the number of CVD deaths would rise by 39 million in total between 2016 and 2030. Universal treatment of hypertension and dyslipidemia patients with lipid and blood pressure lowering therapies could avert between 10 and 20 million AMIs, between 8 and 30 million strokes, and between 3 and 10 million CVD deaths during the 2016-2030 period, producing a positive social value net of health care costs as high as $932 billion. CONCLUSIONS: In light of its aging population and epidemiological transition, China faces near-certain increases in CVD morbidity and mortality. Preventative measures such as effective lipid and blood pressure management may reduce CVD burden substantially and provide large social value. While the Chinese government is implementing more systematic approaches to health care delivery, prevention of CVD should be high on the agenda. Pubmed ID http://www.ncbi.nlm.nih.gov/pubmed/?term=27165638


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Embase) was performed. Human clinical trials assessing treatment strategies, published in the last 5 yr, were included based on full-text analysis. Study data were extracted using tables depicting study type, sample size, and outcome variables. We identified 49 studies meeting our inclusion criteria. Clazosentan, magnesium, and simvastatin have been tested in large high-quality trials but failed to show a beneficial effect. Cilostazol, eicosapentaenoic acid, erythropoietin, heparin, and methylprednisolone yield promising results in smaller, non-randomized or retrospective studies and warrant further investigation. Topical application of nicardipine via implants after clipping has been shown to reduce clinical and angiographic vasospasm. Methods to improve subarachnoid blood clearance have been established, but their effect on outcome remains unclear. Haemodynamic management of DCI is evolving towards euvoalaemic hypertension. Endovascular rescue therapies, such as percutaneous transluminal balloon angioplasty and intra-arterial spasmolysis, are able to resolve angiographic vasospasm, but their effect on outcome needs to be proved. Many novel therapies for preventing and treating DCI after aneurysmal subarachnoid haemorrhage have been assessed, with variable results. Limitations of the study designs often preclude definite statements. Current evidence does not support prophylactic use of clazosentan, magnesium, or simvastatin. Many strategies remain to be tested in larger randomized controlled trials.

CLINICAL TRIAL REGISTRATION: This systematic review was registered in the international prospective register of systematic reviews. PROSPERO: CRD42015019817. PubMed ID: http://www.ncbi.nlm.nih.gov/pubmed/?term=27160932

[7] Additional therapy for cholesterol lowering in ezetimibe-treated, statin-intolerant patients in clinical practice: results from an internal audit of a university lipid clinic. Cicero AF, Morbini M, Bove M et al. Current medical research and opinion 2016:1-21. OBJECTIVE: The aim of our study was to evaluate the tolerability and efficacy of alternative approaches to improve cholesterolemia control in patients with statin-related myalgia treated with ezetimibe. RESEARCH DESIGN AND METHODS: We retrospectively evaluated 3534 Clinical Report Forms (CRFs) filled in the period June 2012-June 2015 for first visits to the lipid clinic of the University of Bologna. For this study, we selected 252 CRFs based on the following criteria: statin-related myalgia, previous failed treatment with at least two low-dosed statins, well-tolerated treatment with ezetimibe. Then, the following lipid-lowering treatments were added in order to improve the ezetimibe Low Density Lipoprotein Cholesterol (LDL-C)-lowering efficacy, based on clinical judgment: fenofibrate 145 mg, rosuvastatin 5 mg 1 tablet/week, rosuvastatin 5 mg 2 tablets/week, red yeast rice (standardized in Monacolin K 3 mg) + berberine 500 mg, berberine 500 mg b.i.d., phytosterols 900 mg + psyllium fiber 3.5 g b.i.d. Patients continuing to claim a tolerable myalgia were then treated with coenzyme Q10 nanoemulsions 200 mg/day. RESULTS: The treatment with standard lipid-lowering diet plus ezetimibe alone was associated with a mean LDL-C reduction of 17+-2%. The additive LDL-lowering effect with the various tested treatment was: -16/-2% with fenofibrate 145 mg/day, -13/-1% with rosuvastatin 5 mg 1 tablet/week, -17/-3% with rosuvastatin 5 mg 2 tablets/week, -19/-4% with red yeast rice + berberine, -17/-4% with berberine b.i.d. and -10/-3% with phytosterols + psyllium b.i.d. 11% of the patients treated with fenofibrate required treatment modification because of myalgia recurrence, while the percentage was negligible for the other tested treatments. In patients with residual tolerable myalgia, treatment with coenzyme Q10 for 8 weeks was associated with a mean improvement of the graduated myalgia score from 4.8+-1.9 to 2.9+-1.3 (p=0.013). CONCLUSIONS: Some alternative treatments seems to be effective and well tolerated, thus improving the ezetimibe effect on cholesterolemia. PubMed ID: http://www.ncbi.nlm.nih.gov/pubmed/?term=27175514
[8] STATINS IN STROKE PREVENTION: PRESENT AND FUTURE. Castilla-Guerra L, Del Carmen Fernandez-Moreno M, Colmenero-Camacho MA. Current pharmaceutical design 2016.BACKGROUND: Over the last decades, the reduction of the mortality and morbidity of stroke has been a high-priority objective worldwide. Statins, or 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, have emerged as the predominant preventive strategy to tackle the worldwide stroke burden. Currently, statins are considered the most important advance in stroke prevention since the introduction of aspirin and antihypertensive treatments. METHODS: In this paper we review the current evidence regarding the role of statins in the stroke prevention and future directions in this field. RESULTS: A meta-analysis of randomised trials of statins has shown that each 1 mmol/L (39 mg/dL) decrease in low-density lipoprotein cholesterol, equates to a reduction in relative risk for stroke of 21.1%. Statins are now recommended for the primary prevention of ischemic stroke in patients estimated to have a high 10-year risk for cardiovascular events. Nevertheless, until recently there was little evidence that statin therapy reduced the risk of stroke recurrence. The SPARCL, published in 2006, was the first trial to show the benefits of statin therapy in preventing recurrent stroke. Now we know that statins reduce the risk of stroke recurrence by 12-16% and statins are recommended among patients with ischemic stroke or TIA presumed to be of atherosclerotic origin or with other comorbid atherosclerotic cardiovascular disease. CONCLUSION: Traditionally, there has been no clear data demonstrating that adding other lipid-modifying drugs to statins results in a further decrease in stroke or other cardiovascular event, but now things have changed and future directions include combinations with ezetimibe and new treatments such as PCSK9 inhibitors. Only time will tell the real roll of these new promising non-statin lipid-modifying therapies on stroke prevention. Pubmed ID http://www.ncbi.nlm.nih.gov/pubmed/?term=27160755

[9] Novel Aspects in the Management of Cholestatic Liver Diseases. Chazouilleres O. Dig Dis 2016; 34:340-346.BACKGROUND: There is a great need for risk stratification in patients with chronic cholestatic diseases in order to allow for more personalized care and adapted management as well as for well-designed therapeutic trials. Novel tools for monitoring primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC) patients have been recently proposed. In addition, major insight has been gained into bile acid (BA) physiology during the last decade including the role of BAs as metabolic modulators and the gut-liver axis. As a consequence, alongside drugs targeting immune response or fibrotic processes, a number of novel anti-cholestatic agents have undergone pre-clinical and clinical evaluation and have shown promising results although none has been approved yet. KEY MESSAGES: Biochemical non-response to ursodeoxycholic acid (UDCA) (mainly defined by bilirubin and alkaline phosphatase levels at 1 year) is a strong prognostic factor in PBC whereas present biochemical surrogates are far from robust in PSC. By contrast, liver stiffness measurement by vibration-controlled transient elastography (VCTE) is a very promising tool in both PBC and PSC. Novel therapeutic approaches include (i) agonists of nuclear receptors, especially farnesoid X receptor (FXR), pregnane X receptor (PXR), glucocorticoid receptor (GR) and peroxisome proliferator-activated receptor alpha (PPARalpha) that are transcriptional modifiers of bile formation; (ii) agonists of TGR5, a BA membrane receptor expressed in various tissues; (iii) inhibitors of the ileal apical sodium BA transporter; (iv) derivatives of the FXR-induced fibroblast growth factor 19 from the ileum that suppresses hepatic BA synthesis and (v) norUDCA, a side chain shortened UDCA derivative with specific physicochemical and therapeutic properties. The most advanced clinical evaluation (PBC patients) relates to agonists for PPARalpha, FXR and GR/PXR most often in combination with UDCA, namely fibrates, obeticholic acid (OCA) and budesonide, respectively. Existing results look promising even though some side effects are
worrisome such as pruritus in OCA-treated patients. Results of large well-designed studies are eagerly awaited. CONCLUSIONS: Major advances in the management of cholestatic liver diseases are in progress and promising times for these patients seem likely in the near future.Pubmed ID http://www.ncbi.nlm.nih.gov/pubmed/?term=27170387

[10] [ESTIMATING THE EFFECTIVENESS OF HYPOLIPIDEMIC THERAPY WITH ROSUVASTATIN IN PATIENTS WITH CORONARY HEART DISEASE DEPENDING ON THE GENOTYPE OF LIPOPROTEIN LIPASE]. Zvyagina MV, Mal GS, Bushueva OY et al. Eksperimental'naia i klinicheskaia farmakologiiia 2016; 79:15-19. Taking into account the genetic heterogeneity of hyperlipidemias, polymorphic genes involved in the regulation of lipid metabolism may explain differences in the efficacy of hypolipidemic therapy. In the present prospective and randomized study, we have investigated the efficacy of rosuvastatin (10 mg/day) in the therapy of atherogenic hyperlipidemias in a group of 62 patients with coronary heart disease (CHD), depending on the genotype of lipoprotein lipase (LPL). The pharmacological correction was carried out during one year under control of lipid metabolism parameters (total cholesterol, LDL-C, HDL-C, HDL-unrelated cholesterol, triglycerides, atherogenic index) at the baseline and on 4th, 8th, 24th and 48th week. The HindIII polymorphism (+495T > G, rs320) of the LPL gene was genotyped in all patients studied through a real-time PCR TaqMan assay. Rosuvastatin produced a significant hypolipidemic effect with respect to all investigated lipid metabolism parameters for 24 weeks of treatment. Changes in the parameters of lipid metabolism upon rosuvastatin treatment differed in patients with genotype +495GG as compared to the rest LPL genotypes. In comparison to the +495TT and TG genotypes, the genotype +495GG showed a greater reduction in total cholesterol on 8th week, and in LDL-C, HDL-unrelated cholesterol, and atherogenic index on the 48th week of rosuvastatin therapy (p < 0.01). It can be suggested that the pronounced hypolipidemic effect of rosuvastatin in homozygotes +495GG of the LPL gene is associated with modulation of the LPL activity, as it has been previously reported for other statin drugs.Pubmed ID http://www.ncbi.nlm.nih.gov/pubmed/?term=27159952

[11] Cholesteryl ester transfer protein inhibitors: challenges and perspectives. Filippatos TD, Klouras E, Barkas F, ElisaF M. Expert review of cardiovascular therapy 2016. INTRODUCTION: Cholesterol ester transfer protein (CETP) inhibitors substantially increase the concentration of high-density lipoprotein cholesterol (HDL-C), which may have a possible beneficial effect for cardiovascular risk reduction. Areas covered: Current data regarding the effects of CETP inhibitors on cardiovascular risk and possible mechanisms for their effects and safety are presented in this review. Expert commentary: The first CETP inhibitor, torcetrapib, was discontinued because of increased off-target adverse effects (increased aldosterone and blood pressure). The development program of dalcetrapib and evacetrapib, which were not associated with increased blood pressure, was terminated due to futility (insufficient efficacy) concerning cardiovascular outcomes. Although the failure of torcetrapib has been attributed to specific off-target effects, there are some common characteristics between CETP inhibitors pointing to the possibility that certain adverse effects may be class-specific. The newer CETP inhibitors anacetrapib and TA-8995 have promising effects on lipid profile and metabolism (increase of HDL-C and reduction of both low-density lipoprotein cholesterol and lipoprotein (a) levels), but their cardiovascular effects and safety profile have not yet been confirmed in large outcome trials.Pubmed ID http://www.ncbi.nlm.nih.gov/pubmed/?term=27171534

**Italian Society of Hypertension** 2016.

**INTRODUCTION:** Impaired baroreflex function is associated with a shift in autonomic balance towards sympathetic dominance, which may play important role in the development of arterial hypertension and consequent target organ damage. **AIM:** To determine the effect of treatment on the cardiovascular autonomic modulation expressed by baroreflex sensitivity (BRS) in hypertensives. **METHODS:** A total of one hundred fourteen hypertensive patients (58 male/56 female, 65 +/- 13 years of age, BMI 30 +/- 3.4 kg/m2) were enrolled. Control group of 20 subjects with normal blood pressure (BP) (ten male/ten female, 59 +/- 8 years of age, body mass index 28.3 +/- 2.5 kg/m2) without any treatment was also studied. BRS and BRSf were determined by the sequence and spectral method: a 5-min on-invasive beat-to-beat recording of blood pressure and R-R interval with use of Collin CBM-7000 monitor, controlled breathing at a frequency of 0.1 Hz. **RESULTS:** Significant negative correlation between spontaneous BRS and BP was present in hypertensives (r = -0.52, p < 0.001). All cohort of hypertensive patients had significantly lower BRS than subjects with normal blood pressure (p < 0.05). The greatest decline in BRS values was in hypertensive patients with metabolic syndrome, who had BRS values <5 ms/mmHg. Hypertensives with hypercholesterolaemia on low dose statin therapy (atorvastatin 20 mg) had higher BRS/BRSf values than statin free patients (p < 0.05). Only BRSf not BRS was significantly increased in hypertensives with beta-blockers. **CONCLUSION:** An inverse correlation between blood pressure and BRS is present in hypertensives. BRS and BRSf is higher in low dose statin-treated patients with essential hypertension.

**Impact of statin use on cancer recurrence and mortality in breast cancer: A systematic review and meta-analysis.** Manthravadi S, Shrestha A, Madhusudhana S. *International journal of cancer* 2016. Statins have shown antineoplastic properties in preclinical studies with breast cancer cells. They inhibit the enzyme 'HMG CoA reductase' and the expression of this enzyme in cancer cells has been implicated as a favorable prognostic factor in patients with breast cancer. After a search of MEDLINE and Embase from inception through November 2015, 817 abstracts were reviewed to identify studies that described an association between statin use and outcomes in breast cancer. A total of 14 studies which included 75,684 women were identified. In a meta-analysis of 10 studies, statin use was associated with improved recurrence-free survival (RFS) (HR 0.64; 95% CI 0.53-0.79, I2 = 44%). Furthermore, this RFS benefit appeared to be confined to use of lipophilic statins (HR 0.72; 95% CI 0.59-0.89) as hydrophilic statin use was not associated with improvement in RFS (HR 0.80; 95% CI 0.44-1.46). Statin users similarly showed improved overall survival in a meta-analysis with substantial heterogeneity (8 studies, HR 0.66; 95% CI 0.44-0.99, I2 = 89%). Statin users also had improved cancer-specific survival, although this relationship was measured with less precision (6 studies, HR 0.70; 95% CI 0.46-1.06, I2 = 86%). In conclusion, breast cancer patients who use statins, or specifically, lipophilic statins show improved recurrence-free survival. Statin users also had improved overall survival and cancer-specific survival. These findings should be assessed in a prospective randomized cohort and the choice of statin, dose and biomarkers that may predict the efficacy of these drugs should be identified. This article is protected by copyright. All rights reserved. Pubmed ID http://www.ncbi.nlm.nih.gov/pubmed/?term=27160718

**Neuroprotective effect of systemic and/or intravitreal rosvastatin administration in rat glaucoma model.** Unlu M, Aktas Z, Gocun PU et al. *International journal of ophthalmology* 2016; 9:340-347. **AIM:** To evaluate the neuroprotective effect of rosvastatin, in a rat experimental glaucoma model. **METHODS:** Ocular hypertension was induced in right eyes of Long-Evans rats (n=30) by cauterization of three episcleral veins. Left eyes were defined as controls. Rats were divided into five groups: oral...
rosuvastatin, intravitreal rosuvastatin, oral+intravitreal rosuvastatin, intravitreal sham and glaucoma without intervention. Rats were sacrificed at day 14. Retinal ganglion cell (RGC) number was assessed by histopathological analysis. Terminal deoxynucleotidyl transferase-mediated dUTP-nick end-labeling (TUNEL) staining and the expression of glial fibrillary acidic protein (GFAP) in RGC layer was also examined. RESULTS: A significant intraocular pressure (IOP) elevation was seen (P=0.002). Elevated IOP (TUNEL) staining and the expression of glial fibrillary acidic protein (GFAP) in RGC layer was also observed. Terminal deoxynucleotidyl transferase-mediated dUTP-nick end-labeling (TUNEL) staining was also assessed. Retinal ganglion cell (RGC) number was assessed by histopathological analysis. Terminal deoxynucleotidyl transferase-mediated dUTP-nick end-labeling (TUNEL) staining and the expression of glial fibrillary acidic protein (GFAP) in RGC layer was also examined. RESULTS: A significant increase in number of RGCs in group 5 (70.33+/−8.2 cells/mm(2)) when compared with controls (92.50+/−13.72 cells/mm(2); P=0.03). The RGC number in group 1 (92.4+/−7.3 cells/mm(2)) was significantly higher than group 5 (P=0.03). The numbers of RGC in groups 2, 3 (57.3+/−8.2 cells/mm(2), 60.5+/−12.9 cells/mm(2)) were comparable with that of group 5 (P=0.18 and P=0.31). The apoptosis rates with TUNEL staining were also parallel to RGC number. Animals with experimentally induced glaucoma showed an increase in retinal GFAP immunoreactivity. CONCLUSION: Decrease in RGC loss and apoptosis suggest the neuroprotective potential of oral rosuvastatin treatment in a rat model of ocular hypertension. However intravitreal rosuvastatin showed a contrary effect and further studies are required.
[16] MTP Gene Variants and Response to Lomitapide in Patients with Homozygous Familial Hypercholesterolemia. Kolovou GD, Kolovou V, Papadopoulou A, Watts GF. *Journal of atherosclerosis and thrombus* 2016. Homozygous familial hypercholesterolemia (HoFH) is a rare genetic disorder, which leads to premature cardiovascular diseases. Microsomal triglyceride transport protein (MTP) inhibitors, such as lomitapide, offer a new therapeutic approach for treating these patients. We evaluated the lipid lowering (LL) efficacy of lomitapide according to several gene variants in MTP. Four clinically and/or molecularly defined HoFH patients were treated with lomitapide in addition to conventional high intensity LL therapy and regular lipoprotein apheresis. Two patients responded to the therapy, with a significant reduction of LDL cholesterol (LDL-C50%, hyper-responders). Sequencing of all exonic and intronic flanking regions of the MTP gene in all patients revealed 36 different variants. The hyper-responders to lomitapide shared six common variants: rs17533489, rs79194015, rs745075, rs41275715, rs1491246, and rs17533517, which were not seen in hypo-responders (reduction in LDL-C50%). We suggest that in HoFH variants in the MTP gene may impact on the therapeutic response to lomitapide, but this requires further investigation. Pubmed ID http://www.ncbi.nlm.nih.gov/pubmed/?term=27170061


[18] Novel Genetic Loci Associated with the Plasma Triglyceride Response to an Omega-3 Fatty Acid Supplementation. Vallee Marcotte B, Cormier H, Guenard F et al. *Journal of nutrigenetics and nutrigenomics* 2016; 9:1-11. BACKGROUND: A recent genome-wide association study (GWAS) by our group identified 13 loci associated with the plasma triglyceride (TG) response to omega-3 (n-3) fatty acid (FA) supplementation. This study aimed to test whether single-nucleotide polymorphisms (SNPs) within the IQCJ, NXPH1, PHF17 and MYB genes are associated with the plasma TG response to an n-3 FA supplementation. METHODS: A total of 208 subjects followed a 6-week n-3 FA supplementation of 5 g/day of fish oil (1.9-2.2 g of eicosapentaenoic acid and 1.1 g of docosahexaenoic acid). Measurements of plasma lipids were made before and after the supplementation. Sixty-seven tagged SNPs were selected to increase the density of markers near GWAS hits. RESULTS: In a repeated model, independent effects of the genotype and the gene-supplementation interaction were associated with plasma TG. Genotype effects were observed with two SNPs of NXPH1, and gene-diet interactions were observed with ten SNPs of IQCJ, four SNPs of NXPH1 and three SNPs of MYB. Positive and negative responders showed different genotype frequencies with nine SNPs of IQCJ, two SNPs of NXPH1 and two SNPs of MYB. CONCLUSION: Fine mapping in GWAS-associated loci allowed the identification of SNPs partly explaining the large interindividual variability observed in plasma TG levels in response to an n-3 FA supplementation. Pubmed ID http://www.ncbi.nlm.nih.gov/pubmed/?term=27160456

[19] Atorvastatin attenuates contrast-induced nephropathy by modulating inflammatory responses through the regulation of JNK/p38/Hsp27 expression. He X, Li L, Tan H et al. *Journal of pharmacological sciences* 2016. This study aimed to investigate whether atorvastatin reduce the contrast-induced nephropathy inflammatory response and apoptosis of renal tubular epithelial cells and the relationship with MAPK signaling pathway. We utilized the iopamidol-induced contrast-induced nephropathy (CIN) rat model which was induced by a single dose of iopamidol (2.9 g iodine/kg) and a cell model in which
human embryonic proximal tubular (HK2) cells were treated with iopamidol. The rats were divided into five groups: (1) control rats (CR); (2) atorvastatin (CA); (3) iopamidol (CM); (4) iopamidol and atorvastatin (20 mg/kg d) (CMA2); (5) iopamidol and atorvastatin (40 mg/kg d) (CMA4). On days 1, 2 and 6 after iopamidol injection, the urea nitrogen and cystatin C increased in CM compared with CR but decreased in CMA compared with CM. Inflammatory parameters and the percentage of apoptotic cells were increased in CM compared with CR and CA, but they were decreased in CMA compared with CM. We also found that atorvastatin ameliorated the renal tubular necrosis, apoptosis, and the deterioration of renal function in a dose dependent manner (P < 0.05). Furthermore, in vivo, both of SP600125 (JNK inhibitor) and SB203580 (p38 inhibitor) could decrease the expression of Bax and caspase-3, but increase Bcl-2 levels in HK2 cells treated with iopamidol. Our study demonstrates that high-dosage atorvastatin treatment attenuates both the inflammatory processes and apoptosis in contrast-induced acute kidney injury, and that the JNK/p38 MAPK pathway participates in the contrast-induced apoptosis of renal tubular cells. Finally, atorvastatin reduces CIN by suppression of apoptosis, which may be through inhibition of JNK/p38 MAPK pathways.


[20] Short-term rosuvastatin therapy prevents contrast-induced acute kidney injury in female patients with diabetes and chronic kidney disease: a subgroup analysis of the TRACK-D study. Li J, Li Y, Xu B et al. J Thorac Dis 2016; 8:1000-1006.BACKGROUND: Female patients are at higher risk of contrast-induced acute kidney injury (CIAKI) compared to males. In the multicenter, prospective, TRACK-D study, short-term rosuvastatin has proven effectively reduce CIAKI in patients with type 2 diabetes mellitus and stage 2-3 chronic kidney disease (CKD). This study aimed to explore the efficacy of rosuvastatin in the female TRACK-D population. METHODS: This study was a gender-based analysis of 2,998 patients (1,044 females) enrolled in the TRACK-D study and were randomized to short-term (2 days before and 3 days after procedure) rosuvastatin therapy or standard of care. The primary outcome was the incidence of CIAKI and the secondary outcome was a composite of death, dialysis/hemofiltration or worsening heart failure at 30 days. RESULTS: CIAKI incidence was comparable between male and female patients in the overall study population (2.5% vs. 3.4%, P=0.165) and in the rosuvastatin group (2.4% vs. 2.1%, P=0.72), while it was higher in females than in males in the control group (3.1% vs. 5.3%, P=0.04). Female gender was an independent risk factor of CIAKI [odds ratio (OR) = 1.65; 95% confidence interval (CI), 1.03-2.63; P=0.036]. Rosuvastatin treatment vs. control lowered CIAKI rate in females [2.1% vs. 5.3%; relative risk (RR) = 0.39; 95% CI, 0.19-0.77; number needed to treat (NNT) = 31], particularly among those with CKD stage 2 (1.2% vs. 4.1%, P=0.011). Secondary outcome incidence was similar for females in the rosvastatin and control groups (3.7% vs. 4.9%, P=0.37). CONCLUSIONS: Compared to males, untreated females with diabetes mellitus and CKD had a higher risk of CIAKI, which can be reduced by short-term rosvastatin treatment. Pubmed ID http://www.ncbi.nlm.nih.gov/pubmed/?term=27162677


[22] Evaluation of Simvastatin and Bone Marrow-Derived Mesenchymal Stem Cell Combination Therapy on Airway Remodeling in a Mouse Asthma Model. Mohammadian M, Sadeghi-Posh H, Kashani IR et al. Lung 2016.INTRODUCTION: The effect of bone marrow-derived mesenchymal stem cells (BMSCs) on asthma treatment was shown in our previous study. Several studies have shown the effect of statins on BMSC preservation and migration to sites of inflammation. In this study, the effects of
simvastatin and BMSC combination therapy in an ovalbumin-induced asthma model in mouse were examined. METHODS: Four groups of BALB/c mice were studied including control group (animals were not sensitized), asthma group (animals were sensitized by ovalbumin), asthma + simvastatin group (asthmatic animals were treated with simvastatin), and asthma + BMSC + simvastatin group (asthmatic animals were treated with simvastatin and BMSCs). BMSCs were isolated, characterized, labeled with BrdU, and transferred into asthmatic mice. BMSC migration, airways histopathology, and total and differential white blood cell (WBC) count in bronchoalveolar lavage (BAL) fluid were evaluated. RESULTS: A significant increase in the number of BrdU-BMSCs was found in the lungs of mice treated with simvastatin + BMSCs compared to mice treated with BMSCs. The histopathological changes, BAL total WBC counts, and the percentage of neutrophils and eosinophils were increased in asthma group compared to the control group. Treatment with simvastatin significantly decreased airway inflammation and inflammatory cell infiltration. Combination therapy improved all measured parameters higher than simvastatin. Goblet cell hyperplasia and subepithelial fibrosis were also decreased in combination therapy group. CONCLUSION: These results indicated that simvastatin and BMSC combination therapy was superior to simvastatin therapy and BMSC therapy alone in reduction of airway remodeling and lung inflammation in the ovalbumin-induced asthma model in mouse. Pubmed ID http://www.ncbi.nlm.nih.gov/pubmed/?term=27161569

[23] Statin Use and Its Impact on Survival in Pancreatic Cancer Patients. Lee HS, Lee SH, Lee HJ et al. *Medicine (Baltimore)* 2016; 95:e3607. Statins are cholesterol-lowering medications that are associated with a number of signaling pathways involved in carcinogenesis. Recent observational studies raised the possibility that the use of statins may reduce overall mortality in various types of cancer. We investigated whether statins used after pancreatic cancer diagnosis are associated with longer survival in pancreatic cancer patients. We retrospectively analyzed data from 1761 patients newly diagnosed with pancreatic adenocarcinoma between January 1, 2006, and December 31, 2014. We used the time-dependent Cox proportional hazards regression model to estimate mortality among pancreatic cancer patients according to statin use. Among the 1761 pancreatic cancer patients, 118 patients had used statins. During the study period, 1176 patients (66.7%) died. After adjusting for age, sex, location of cancer, cancer stage, diabetes mellitus, hypertension, dyslipidemia, smoking, alcohol use, body mass index, and CA 19-9, statin use was associated with a lower risk of cancer death (hazard ratio [HR], 0.780; 95% confidence interval [CI], 0.617-0.986), especially among simvastatin users (HR, 0.554; 95% CI, 0.312-0.982) and atorvastatin users (HR, 0.636; 95% CI, 0.437-0.927). Subgroup analysis showed that overall survival was statistically significantly longer in patients with nonmetastatic pancreatic cancer (log-rank P = 0.024). We found that the use of simvastatin and atorvastatin after cancer diagnosis is associated with longer survival in patients with nonmetastatic pancreatic adenocarcinoma. Pubmed ID http://www.ncbi.nlm.nih.gov/pubmed/?term=27175667

[24] Increased postprandial apolipoprotein B-48 level after a test meal in diabetic patients: A multicenter, cross-sectional study. Park CY, Park JY, Choi J et al. *Metabolism* 2016; 65:843-851. OBJECTIVE: To evaluate plasma apolipoprotein B (ApoB)-48 concentrations among Korean diabetic subjects with normal to moderately high levels of low-density-lipoprotein cholesterol (LDL-C). METHODS: This multicenter, cross-sectional study included subjects with LDL-C levels between 100 and 160mg/dL who had not been treated with a lipid-lowering agent for over 6 weeks prior to baseline. Blood tests to assess lipid-profile parameters were conducted in both fasting and postprandial states. This study compared ApoB-48 and other lipid-profile parameters in diabetic and nondiabetic subjects.
RESULTS: Of the 93 subjects enrolled, 88 (42 diabetic; 46 nondiabetic) completed the study. Significantly higher mean incremental area under curve (0-6h; iAUC0-6h) of postprandial ApoB-48 levels was noted among diabetic subjects than nondiabetic subjects (p=0.0078). The mean postprandial ApoB-48 peak level was higher in diabetic subjects; however, the difference was not statistically significant. The fasting ApoB-48 level was similar in both groups: 5.9 (3.5) in diabetics and 7.3 (5.8) in nondiabetics (p=0.18). The iAUC0-6h of postprandial total cholesterol (TC), triglyceride (TG), LDL-C, non-high-density-lipoprotein cholesterol (non-HDL-C), ApoB-100, and remnant cholesterol was similar in both groups. The ApoB-48 level was moderately correlated with TG and non-HDL-C for both groups (p<0.05).

CONCLUSION: Without lipid-lowering treatment, the postprandial increment in ApoB-48 level was significantly higher in Korean diabetic subjects compared with nondiabetic subjects, irrespective of similar LDL-C levels. Pubmed ID http://www.ncbi.nlm.nih.gov/pubmed/?term=27173463

[25] Detection and Quantification of Molecular Calcification by PET/Computed Tomography: A New Paradigm in Assessing Atherosclerosis. Saboury B, Ziai P, Alavi A. PET clinics 2011; 6:409-415. Atherosclerotic plaque rupture is the leading cause of acute coronary syndrome. Molecular calcification represent as one of the early stages of plaque evolution has been hypothesized to play a potential role in atherosclerotic plaque instability and subsequent rupture. Several invasive and non-invasive structural imaging techniques have been utilized to diagnose atherosclerosis, but none of these methods are capable of detecting and quantifying molecular calcification. Fluorine-18-Sodium Fluoride (18F-NaF) positron emission tomography/computed tomography (PET/CT) imaging allows detection and quantification of arterial molecular calcification in heart and across multiple vessels. In this review the authors discuss the feasibility, application and potential future of 18F-NaF-PET/CT in detecting molecular calcification and in defining the future risk of atherosclerotic plaque rupture in the affected vessels. Pubmed ID http://www.ncbi.nlm.nih.gov/pubmed/?term=27156875

[26] The Evaluation of Therapeutic Efficacy and Safety Profile of Simvastatin Prodrug Micelles in a Closed Fracture Mouse Model. Zhang Y, Jia Z, Yuan H et al. Pharm Res 2016. PURPOSE: To evaluate the therapeutic efficiency of a micellar prodrug formulation of simvastatin (SIM/SIM-mPEG) and explore its safety in a closed femoral fracture mouse model. METHODS: The amphiphilic macromolecular prodrug of simvastatin (SIM-mPEG) was synthesized and formulated together with free simvastatin into micelles. It was also labeled with a near infrared dye for in vivo imaging purpose. A closed femoral fracture mouse model was established using a three-points bending device. The mice with established closed femoral fractures were treated with SIM/SIM-mPEG micelles, using free simvastatin and saline as controls. The therapeutic efficacy of the micelles was evaluated using a high-resolution micro-CT. Serum biochemistry and histology analyses were performed to explore the potential toxicity of the micelle formulation. RESULTS: Near Infrared Fluorescence (NIRF) imaging confirmed the passive targeting of SIM/SIM-mPEG micelles to the bone lesion of the mice with closed femoral fractures. The micelle was found to promote fracture healing with an excellent safety profile. In addition, the accelerated healing of the femoral fracture also helped to prevent disuse-associated ipsilateral tibia bone loss. CONCLUSION: SIM/SIM-mPEG micelles were found to be an effective and safe treatment for closed femoral fracture repair in mice. The evidence obtained in this study suggests that it may have the potential to be translated into a novel therapy for clinical management of skeletal fractures and non-union. Pubmed ID http://www.ncbi.nlm.nih.gov/pubmed/?term=27164897

[27] Assessment of pharmacogenetic tests: presenting measures of clinical validity and potential population impact in association studies. Tonk EC, Gurwitz D, Maitland-van der Zee AH, Janssens AC.
The progressing discovery of genetic variants associated with drug-related adverse events has raised expectations for pharmacogenetic tests to improve drug efficacy and safety. To further the use of pharmacogenetics in health care, tests with sufficient potential to improve efficacy and safety, as reflected by good clinical validity and population impact, need to be identified. The potential benefit of pharmacogenetic tests is often concluded from the strength of the association between the variant and the adverse event; measures of clinical validity are generally not reported. This paper describes measures of clinical validity and potential population health impact that can be calculated from association studies. We explain how these measures are influenced by the strength of the association and by the frequencies of the variant and the adverse event. The measures are illustrated using examples of testing for HLA-B*5701 associated with abacavir-induced hypersensitivity and SLCO1B1 c.521T>C (*5) associated with simvastatin-induced adverse events.

We tested the hypothesis that lipopolysaccharide (LPS), the leading cause of death in critically ill patients. While decreased Proprotein Convertase Subtilisin/Kexin type 9 (PCSK9) function improves clinical outcomes in murine and human sepsis, the mechanisms involved have not been fully elucidated. We tested the hypothesis that lipopolysaccharide (LPS), the major Gram-negative bacteria endotoxin, is cleared from the circulation by hepatocyte Low Density Lipoprotein Receptor. In our study, we observed that the HDL associated acute phase protein serum amyloid A (SAA) was significantly increased in AMD patients (p<0.01), whereas all other assessed apolipoproteins including ApoA-I, apoa-II, apoC-II, apoC-III and apoE as well as major HDL associated lipids were not altered. HDL efflux capacity, anti-oxidative capacity and arylesterase activity were not different in AMD patients when compared with the control group. The ability of apoB-depleted serum to inhibit monocyte NF-kappaB expression was significantly improved in AMD patients (mean difference (MD) -5.6, p<0.01). Moreover, lipoprotein-associated phospholipase A2 activity, a marker of vascular inflammation, was decreased in AMD subjects (MD -24.1, p<0.01). CONCLUSIONS: The investigated metrics of HDL composition and HDL function were not associated with exudative AMD in this study, despite an increased content of HDL associated SAA in AMD patients. Unexpectedly, anti-inflammatory activity of apoB-depleted serum was even increased in our study. Our data suggest that the investigated parameters of serum HDL function showed no significant association with exudative AMD. However, we cannot exclude that alterations in locally produced HDL may be part of the AMD pathogenesis.

[28] High-Density Lipoprotein Function in Exudative Age-Related Macular Degeneration. Pertl L, Kern S, Weger M et al. PloS one 2016; 11:e0154397. PURPOSE: High-density lipoproteins (HDL) have long been implicated in the pathogenesis of age-related macular degeneration (AMD). However, conflicting results have been reported with regard to the associations of AMD with HDL-cholesterol levels. The present study is the first to assess HDL composition and metrics of HDL function in patients with exudative AMD and control patients. METHODS: Blood samples were collected from 29 patients with exudative AMD and 26 age-matched control patients. Major HDL associated apolipoproteins were determined in apoB-depleted serum by immunoturbidimetry or ELISA, HDL-associated lipids were quantified enzymatically. To get an integrated measure of HDL quantity and quality, we assessed several metrics of HDL function, including cholesterol efflux capacity, anti-oxidative and anti-inflammatory activities using apoB-depleted serum from study participants. RESULTS: In our study, we observed that the HDL associated acute phase protein serum amyloid A (SAA) was significantly increased in AMD patients (p<0.01), whereas all other assessed apolipoproteins including ApoA-I, apoa-II, apoC-II, apoC-III and apoE as well as major HDL associated lipids were not altered. HDL efflux capacity, anti-oxidative capacity and arylesterase activity were not different in AMD patients when compared with the control group. The ability of apoB-depleted serum to inhibit monocyte NF-kappaB expression was significantly improved in AMD patients (mean difference (MD) -5.6, p<0.01). Moreover, lipoprotein-associated phospholipase A2 activity, a marker of vascular inflammation, was decreased in AMD subjects (MD -24.1, p<0.01). CONCLUSIONS: The investigated metrics of HDL composition and HDL function were not associated with exudative AMD in this study, despite an increased content of HDL associated SAA in AMD patients. Unexpectedly, anti-inflammatory activity of apoB-depleted serum was even increased in our study. Our data suggest that the investigated parameters of serum HDL function showed no significant association with exudative AMD. However, we cannot exclude that alterations in locally produced HDL may be part of the AMD pathogenesis.

[29] Lipopolysaccharide Is Cleared from the Circulation by Hepatocytes via the Low Density Lipoprotein Receptor. Topchiy E, Cirstea M, Kong HJ et al. PloS one 2016; 11:e0155030. Sepsis is the leading cause of death in critically ill patients. While decreased Proprotein Convertase Subtilisin/Kexin type 9 (PCSK9) function improves clinical outcomes in murine and human sepsis, the mechanisms involved have not been fully elucidated. We tested the hypothesis that lipopolysaccharide (LPS), the major Gram-negative bacteria endotoxin, is cleared from the circulation by hepatocyte Low Density Lipoprotein Receptor.
Lipoprotein Receptors (LDLR)-receptors downregulated by PCSK9. We directly visualized LPS uptake and found that LPS is rapidly taken up by hepatocytes into the cell periphery. Over the course of 4 hours LPS is transported towards the cell center. We next found that clearance of injected LPS from the blood was reduced substantially in Ldlr knockout (Ldlr/-) mice compared to wild type controls and, simultaneously, hepatic uptake of LPS was also reduced in Ldlr/- mice. Specifically examining the role of hepatocytes, we further found that primary hepatocytes isolated from Ldlr/- mice had greatly decreased LPS uptake. In the HepG2 immortalized human hepatocyte cell line, LDLR silencing similarly resulted in decreased LPS uptake. PCSK9 treatment reduces LDLR density on hepatocytes and, therefore, was another independent strategy to test our hypothesis. Incubation with PCSK9 reduced LPS uptake by hepatocytes. Taken together, these findings demonstrate that hepatocytes clear LPS from the circulation via the LDLR and PCSK9 regulates LPS clearance from the circulation during sepsis by downregulation of hepatic LDLR.

[30] Microparticles as new markers of cardiovascular risk in diabetes and beyond. Santilli F, Marchisio M, Lanuti P et al. Thrombosis and haemostasis 2016; 116. The term microparticle (MP) identifies a heterogeneous population of vesicles playing a relevant role in the pathogenesis of vascular diseases, cancer and metabolic diseases such as diabetes mellitus. MPs are released by virtually all cell types by shedding during cell growth, proliferation, activation, apoptosis or senescence processes. MPs, in particular platelet- and endothelial-derived MPs (PMPs and EMPs), are increased in a wide range of thrombotic disorders, with an interesting relationship between their levels and disease pathophysiology, activity or progression. EMP plasma levels have been associated with several cardiovascular diseases and risk factors. PMPs are also shown to be involved in the progressive formation of atherosclerotic plaque and development of arterial thrombosis, especially in diabetic patients. Indeed, diabetes is characterised by an increased procoagulant state and by a hyperreactive platelet phenotype, with enhanced adhesion, aggregation, and activation. Elevated MP levels, such as TF+ MPs, have been shown to be one of the procoagulant determinants in patients with type 2 diabetes mellitus. Atherosclerotic plaque constitutes an opulent source of sequestered MPs, called "plaque" MPs. Otherwise, circulating MPs represent a TF reservoir, named "blood-borne" TF, challenging the dogma that TF is a constitutive protein expressed in minute amounts. "Blood-borne" TF is mainly harboured by PMPs, and it can be trapped within the developing thrombus. MP detection and enumeration by polychromatic flow cytometry (PFC) have opened interesting perspectives in clinical settings, particularly for the evaluation of MP numbers and phenotypes as independent marker of cardiovascular risk, disease and outcome in diabetic patients.

[31] Effects of preoperative statin on liver reperfusion injury in major hepatic resection: a pilot study. Sarin S, Kaman L, Dahiya D et al. Updates in surgery 2016. During major liver resection, ischemia reperfusion injury occurs resulting in adverse outcome. Animal studies have demonstrated the beneficial effect of statins on hepatic ischemic injury, but no clinical studies have been performed. Twenty consecutive patients undergoing major hepatic resection were included and were randomized into two groups. The study group (n = 10) patients received oral atorvastatin 40 mg for 3 days prior to surgery, including the day of surgery, and the control group (n = 10) received a placebo. Outcomes were assessed at 4, 24, and 72 h by measurement of serum liver enzymes and cytokines-IL-1, IL-6, CRP, and TNF alpha. The two groups were evenly matched for demographic and perioperative variables. The AST levels were significantly higher in the control group compared with the study group at 4 h (909.60 +/- 222 vs. 362.6 +/- 129 U/L), 24 h (215.30 +/- 86.9 vs. 605.30 +/- 186.1 U/L) and 72 h (84.30 +/- 32.7 vs. 222 +/- 36.2 U/L).
Plasma IL-1 values in the study group showed significantly lower values compared with the control group (p < 0.001) postoperatively. Plasma IL-6 values postoperatively showed significantly lower mean values as compared with the mean of the control population (p < 0.001). TNF alpha values at 4, 24, and 72 h postoperatively comparable in the two groups (p = 0.011) (p = 0.096) and (p = 0.237), respectively. Statins have the potential for pharmacological prevention of IRI. Further studies would be needed to substantiate the role of statins in prevention of IRI during liver resection.