Abstract: Sterol regulatory element-binding proteins (SREBPs) regulate homeostasis of LDL, HDL and triglycerides. This study was aimed to determine if inhibition of lowering measures. Patients with higher levels should be referred to specialists with experience in drug therapy and decreasing the risk of pancreatitis in the case of severe hypertriglyceridemia. The pediatrician should address screening, diagnosis and implementation of lipid-lowering strategies to manage these patients.

Abstract: This document is intended for pediatricians, family, nutritionists and others. It aimed to convey the guidelines for early diagnosis and treatment of acute coronary syndrome practice, where high-dose statins are now widely prescribed and demonstrate a significant benefit of a lipid medication in addition to statins. We explore the strengths and weaknesses of IMPROVE-IT in the context of current-day practice, lead to positive results on the primary endpoint, the clinical benefit translated to real-life practice is only modest at best. However, this is the first major trial to IMPROVE on.

CONCLUSIONS: Long-term combination therapy significantly increased the serum cholesterol levels. We should pay close attention to adverse events during this long-term combination therapy.

Abstract: BACKGROUND: Benefits of plant sterols (PS) for cholesterol lowering are compromised by large variability in efficacy across individuals. High fractional cholesterol synthesis measured by deuterium incorporation has been associated with nonresponse to PS consumption; however, prospective studies that show this association have yet to be conducted. OBJECTIVE: To test whether the lipoprotein-lowering to cholesterol ratio (L:C ratio), a surrogate marker of endogenous cholesterol synthesis, serves as a priori predictor of cholesterol lowering in response to PS consumption. DESIGN: Sixty-three mildly hypercholesterolemic adults who were preselected as possessing either high endogenous cholesterol synthesis (HS; n = 24; L:C = 2.03 +/- 0.39 mmol/mol) or low endogenous cholesterol synthesis (LS; n = 39; L:C = 0.99 +/- 0.28 mmol/mol) on the basis of baseline L:C consumed 2 g PS/d or a placebo for 28 d with the use of a dual-center, single-blind, randomized crossover design. Plasma lipoprotein cholesterol concentrations were measured at the end of each phase. RESULTS: PS consumption lowered total cholesterol (TC: -0.25 +/- 0.05 mmol/L; P < 0.0001) and LDL cholesterol (-0.17 +/- 0.04 mmol/L; P < 0.0001) overall. Specifically, LS individuals responded to PS treatment with a reduction in TC (-0.40 +/- 0.07 mmol/L; P < 0.0001) and LDL cholesterol (-0.29 +/- 0.05 mmol/L; P = 0.0002), whereas HS individuals failed to show cholesterol lowering (TC: -0.09 +/- 0.09 mmol/L; P = 0.2843; LDL cholesterol: -0.05 +/- 0.07 mmol/L; P = 0.4917). The odds of LS participants responding to PS consumption with cholesterol lowering better than the mean cholesterol lowering in all participants were 4.25 (95% CI: 1.242, 14.556; P = 0.0211) for TC and 3.36 (95% CI: 1.112, 10.161; P = 0.0317) for LDL cholesterol, which was higher than for HS participants. CONCLUSIONS: The L:C ratio predicts the extent of reduction in circulating TC and LDL cholesterol in response to PS consumption. Cholesterol synthesis assessment may thus have a use in identifying responders and nonresponders to PS therapy. This trial was registered at clinicaltrials.gov as NCT01131832.


Abstract: OBJECTIVES: The aim of this study was to assess the long-term prognosis, efficacy, and safety of combination therapy using ursodeoxycholic acid (UDCA) and bezafibrate (BF) for primary biliary cirrhosis (PBC) patients exhibiting dyslipidemia. METHODS: We performed a prospective, randomized, controlled, multicenter study to compare the long-term clinical results between combination therapy and UDCA monotherapy for patients refractory to UDCA monotherapy. Twenty-seven consecutive PBC patients were enrolled. RESULTS: The median treatment period in the UDCA and UDCA+BF groups was 107 and 110 months, respectively. The serum alkaline phosphatase (ALP) levels and the Mayo risk score in the combination therapy group (mean 290 IU/L) and 0.91, respectively) were significantly lower than those in the UDCA monotherapy group (mean 461 IU/L and 1.42, respectively) at 8 years after the beginning of the study (P<0.05). The serum creatinine levels in the combination therapy group (mean 0.94 mg/dl) were significantly higher than those in the UDCA monotherapy group (mean 0.56 mg/dl) at 8 years after the beginning of the study (P<0.05). However, the survival rate was not significantly different between the groups. We observed dose reduction or discontinuation of the administration of BF, but not UDCA, due to renal dysfunction or muscle pain. CONCLUSIONS: Long-term combination therapy significantly improved the serum ALP levels and the Mayo risk score. However, the rate of survival was not significantly different between the groups. In addition, long-term combination therapy significantly increased the serum triglyceride levels. We should pay close attention to adverse events during this long-term combination therapy.


Abstract: BACKGROUND: The American Heart Association (AHA) established recommendations based on 7 ideal health behaviors and factors with the goal of improving cardiovascular health (CVH) and reducing both morbidity and mortality from cardiovascular disease by 20% by 2020. Few studies have investigated their association with subclinical coronary heart disease. We sought to examine whether the 7 AHA CVH metrics were associated with calcified atherosclerotic plaque in the coronary arteries. METHODS: In a cross-sectional design, we studied 1,731 predominantly white men and women from the National Heart, Lung, and Blood Institute Family Heart Study without prevalent coronary heart disease. Diet was assessed by a semiquantitative food frequency questionnaire. Coronary artery calcium (CAC) was calculated by cardiac computed tomography. We defined prevalent CAC using an Agatston score of 100+ and fitted generalized estimating equations to calculate prevalence odds ratios of CAC. RESULTS: Mean age was 56.8 years, and 41% were male. The median number of ideal CVH metrics was 3, and no participant met all 7. There was a strong inverse relationship between number of ideal CVH metrics and prevalent CAC. Odds ratios (95% CI) for CAC of 100+ were 1.0 (reference), 0.37 (0.29-0.45), 0.35 (0.26-0.44), and 0.27 (0.20-0.36) among subjects with 0 to 1, 2, 3, and 4+ ideal CVH metrics, respectively (P < 0.0001), adjusting for sex, age, field center, alcohol, income, education, and energy consumption. CONCLUSIONS: These data demonstrate a strong and graded inverse relationship between AHA ideal CVH metrics and prevalent CAC in adult men and women.
inhibits the transcription of SREBP1c and SREBP2, and decreases levels of microRNA 33a/b hosted in the introns of SREBPs, which leads to reciprocally increase ABCA1 levels. In HepG2 cells, MDP shows the same effects as in THP-1 macrophages. MDP also decreases the gene expressions of HMGCGR, FAS and ACC for cholesterol and fatty acid synthesis. MDP further promotes LDL receptor through reducing the PCSK9 level. Collectively, the study demonstrates that MDP potentially increase HDL cholesterol while reducing LDL cholesterol and triglycerides.


Abstract: OBJECTIVE: To perform clinical and genetic analysis of a family with familial hypobetalipoproteinemia in which the proband had been diagnosed with diabetes mellitus. METHODS: Direct sequencing was performed on candidate genes such as APOB, PCSK9, and ANGPTL3. The effect of the mutant gene on lipid profile was investigated using biochemical methods. RESULTS: A novel mutation Y344S in ANGPTL3 was identified but no variants were found in PCSK9 or APOB. Lipid profiles showed the levels of TG, TC, and LDL-C to be significantly lower than in non-carriers in this family. The levels of HDL-C and plasma concentrations of ANGPTL3 showed no significant differences. Western blot analysis revealed that the mutant ANGPTL3 proteins could not be secreted into the medium. CONCLUSION: A novel mutation Y344S was found in ANGPTL3 gene in two diabetic patients with familial hypobetalipoproteinemia. The family study and genetic analysis suggest that this set of gene mutation may be a genetic basis for the lipid phenotypes, and may be a vascular protective factor in the probands with high risk of atherosclerosis.


Abstract: 3-Hydroxy-3-methylglutaryl-CoA reductase inhibitor, atorvastatin (ATO), is a highly effective drug used for the treatment of hypercholesterolemia and hypertriglyceridemia. Its application is restricted now-a-days due to several acute and chronic side effects. ATO induced anti hypercholesterolemia and hepatic toxicity has been reported to follow different mechanisms. The present study has been carried out to investigate the protective role of arjunic acid (AA) against ATO induced oxidative impairment and cell death in hepatic and renal tissue in mice. Administration of ATO (at a dose 30 mg/kg/day for 8 weeks) enhanced serum markers, increased reactive oxygen species (ROS) production and altered the pro oxidant-antioxidant status of liver and kidney tissues. Our experimental evidence suggests that ATO exposure induces apoptotic cell death by the activation of caspase-3 and reciprocal regulation of Bcl-2/Bax with the concomitant reduction of mitochondrial membrane potential and increased level of cytosolic cytochrome C(Apop), caspase-9. Besides, ATO markedly increased the phosphorylation of MAPKs, enhanced caspase-12 and calpain level. Histological studies and DNA fragmentation analysis also support the toxic effect of ATO in these organs pathophysiology. Post treatment with AA (at a dose of 20 mg/kg body weight for 4 days), however, reduced ATO-induced oxidative stress and suppressed all these apoptotic events. Results suggest that AA could effectively and extensively counteract these adverse effects and might protect liver and kidney from ATO-induced severe tissue toxicity.

11. [Renoprotective effects of statins under the conditions of acute renal failure, caused by rhabdomyolysis]. *Biofizika* 2014, 59:1027-1030.

Abstract: The experiment on white rats was targeted at the examination of influence of statins (atorvastatin, lovastatin, simvastatin) under the conditions of acute renal failure, caused by rhabdomyolysis. Renoprotective effects of statins were demonstrated by reduction of hyperazotemia and proteinuria in remnant excretor function, which correlated with antioxidant properties of drugs.


Abstract: An improved understanding of the pathogenesis of acute coronary syndromes and its relationship to atherosclerotic plaque rupture and thrombosis has contributed to the investigation of novel therapies for prevention and treatment. New data ascribe an increasingly important role of active inflammation in contributing to thinning of the atherosclerotic fibrous cap and plaque instability. Despite this understanding, there are currently no therapeutic approaches to specifically target the unstable plaque. Multiple randomized trials investigating treatment strategies have recently been completed or are currently being conducted, using anti-inflammatory medications such as methotrexate, colchicine, darapladib, varespladib, losmapimod and canakinumab, to reduce the incidence of cardiovascular events including acute coronary syndromes. These anti-inflammatory medications differ in their mechanism of action from having widespread targets (as is the case for methotrexate and colchicine) to having specific targets (as is the case for darapladib, varespladib, losmapimod and canakinumab). The trials investigating the efficacy of darapladib in reducing cardiovascular events revealed no significant benefit when compared to the current standard of care. The varespladib studies were terminated early due to adverse outcomes. However, the outcomes of the remaining drug studies may still contribute to novel therapeutic approaches in the treatment of patients with unstable coronary artery disease.


Abstract: BACKGROUND/AIMS: Many patients with chronic kidney disease (CKD) do not receive lipid-lowering therapy despite their high cardiovascular risk. The reasons for this are unknown. METHODS: We have conducted a retrospective cohort study of discontinuation of lipid-lowering drugs in patients with CKD stage 3 and higher treated in practices affiliated with two academic medical centers between 2000 and 2010. Information on medication discontinuation and its reasons was obtained from electronic medical records, including natural language processing of electronic notes using previously validated software. RESULTS: Out of 14,034 patients in the study cohort, 10,072 (71.8%) stopped their lipid-lowering drugs at least once, and 2,444 (17.4%) stopped them for at least 1 month. Patients who had a comorbidity associated with higher cardiovascular risk were less likely to stop lipid-lowering drugs. Insurance request was the most common explicitly documented reason for discontinuation, and adverse reactions were the most common reason for long-term discontinuation. In a multivariable analysis, patients were more likely to stop a lipid-lowering drug because of an insurance request if they had government insurance and they were also more likely to stop a lipid-lowering drug because of adverse reactions if they had a history of multiple adverse reactions to other medications. There was no significant relationship between CKD stage and the reason for discontinuation of lipid-lowering drugs. CONCLUSIONS: Patients with CKD frequently stop lipid-lowering drugs. Insurance requests and adverse reactions are common reasons for the discontinuation. Further research is needed to ensure appropriate lipid-lowering therapy for these individuals at high cardiovascular risk.


Abstract: Background:The aim of this study was to examine the effects of different statins on the clinical outcomes of Japanese patients with coronary stent implants.Methods and Results:This study included 5,801 consecutive patients (males, 4,160; age, 69.7±11.1 years, mean+/SD) who underwent stent implantation between April 2008 and March 2011. They were treated with a strong statin (n=3,042, 52%, atorvastatin, pitavastatin, or rosuvastatin), a regular statin (n=1,082, 19%, pravastatin, simvastatin, or fluvastatin) or no statin (n=1,677, 29%). The patients with chronic kidney disease (CKD) were divided into mild-to-moderate CKD (0<eGFR<60, n=1,956) and severe CKD (eGFR <30, n=559). Primary endpoints included cardiovascular death and nonfatal myocardial infarction, including stent thrombosis and ischemic stroke. The clinical outcome for the primary endpoint in mild-to-moderate CKD patients treated with a strong statin (hazard ratio 0.50, 95% confidence interval 0.31-0.81; P=0.005) was significantly lower than in those on no statins, but that in the patients treated with a regular statin was not (P=0.160). The clinical outcome for the primary endpoint in severe CKD patients treated with a strong or regular statin was no different than on statin therapy.
Conclusion: In patients with mild-to-moderate CKD, only strong statins were associated with lower risk compared with no statin, but regular statins were not. It is possible that taking a strong statin from the early stage of CKD is useful for suppression of cardiovascular events.

15. Lewandowski J, Symonides B, Gaciog Z, Sinski M: The effect of statins on sympathetic activity: a meta-analysis. Clin.Autor.Res. 2015. Abstract: OBJECTIVE: Beyond lipid-lowering properties, statins decrease sympathetic nervous activity. Due to the limited number of studies and included participants, a meta-analysis of randomized, placebo-controlled studies using microneurography (MSNA) was performed to assess sympatholystic effect of statins. METHODS: We conducted a comprehensive search of online databases (Cochrane, Embase, and EBSCO) for published human studies up to April 2014. Randomized controlled trials (parallel and crossover design) were eligible for inclusion if results of statins versus placebo treatments on sympathetic activity were measured with MSNA. RESULTS: Data from five studies with a total number of subjects n = 82 were included into the meta-analysis. MSNA expressed as bursts/min and as bursts/100 heartbeats was lower in the statin group than in the placebo group with a mean difference of p<0.0013 and p = 0.85 95% CI (-7.56; 4.13), p < 0.001, respectively. No significant publication bias was observed. Meta-regression revealed no significant effect of baseline total cholesterol or dose of statin. No change in blood pressure and heart rate was observed. CONCLUSIONS: Published data show that regardless of type and dose, statins reduce sympathetic activity measured by microneurography. The role of decreased sympatholystic outflow during statin therapy on clinical end points needs to be clarified.

16. Kucera M, Balaz D, Kuzliah P, Ciccioppo R, Oravec S, Rodrigo L, Zulil A, Hirnerova E, Sabaka P, Komornikova A, Sabo J, Slebak P, Gaspar L: The effects of atorvastatin treatment on the mean platelet volume and red cell distribution width in patients with dyslipoproteinaemia and comparison with plasma atherogenicity indicators - a pilot study. Clin.Biochem. 2015. Abstract: OBJECTIVES: The mean platelet volume (MPV) and red cell distribution width (RDW) have recently arisen interest because of their association with an increased cardiovascular risk. The aim of this study was, therefore, to determine whether an association exists between MPV, RDW and lipoprotein sub-fractions, and to show the importance of statin therapy on these new possible biomarkers of atherosclerotic risk. Design and Methods: A cohort of 40 patients with hypercholesterolemia (29 females, mean age 62.69±9 years), without previous hypolipidaemic treatment were enrolled. The patients were treated with atorvastatin 40mg/day for 12 weeks. Total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), high density cholesterol (HDL-C), triglycerides (TG), LDL-C sub-fractions [large LDL-C 1-2 and small dense (sd)-LDL-C 3-7], apolipoproteins (apoA1, apoB, apoB/apoA1 ratio, atherogenic index of plasma (AIp), haematological parameters (including MPV, RDW and safety parameters, renal, hepatic) were measured before and after 12 weeks of atorvastatin treatment. RESULTS: At baseline, a strong correlation was observed between TG, sd-LDL-C, apoB, apoB/apoA1, AIP with MPV (r=-0.56, p<0.001; r=0.7, p<0.001; r=0.73, p<0.001; r=0.41, p<0.05; r=-0.52, p<0.001; r=0.61, p<0.001, respectively) and RDW (r=-0.49, p<0.001; r=-0.67, p<0.001; r=0.41, p<0.05; r=0.65, p<0.001, respectively) was found. After 12 weeks of treatment with atorvastatin, MPV and RDW values underwent significant modification only in those patients displaying the strongest lipid-lowering effect. CONCLUSIONS: Values of MPV and RDW seem to reflect a pro-atherogenic lipoprotein profile mainly represented by the presence of sd-LDL-C.

17. Kurt B, Soufi M, Sattler A, Schaefer JR: Lipoprotein(a)-clinical aspects and future challenges. Clin.Res.Cardiol.Suppl. 2015. Abstract: Lipoprotein(a) (Lp(a)) was first described by K. Berg and is known for more than 50 years. It is an interesting particle and combines the atherogenic properties of low-density lipoprotein (LDL)-cholesterol as well as the thrombogenic properties of plasminogen inactivation. However, due to technical problems and publication of negative trials the potential role of Lp(a) in atherosclerosis was severely underestimated. In recent years our understanding of the function and importance of Lp(a) improved. Intervventional trials with niacin failed to demonstrate any benefit of lowering Lp(a); however, several studies confirmed the residual cardiovascular disease (CVD) risk of elevated Lp(a). LDL/Lp(a) apheresis is able to lower Lp(a) and some new drugs under development should help us to lower Lp(a) in the near future. It will be important to follow this with hard endpoint trials. Until then, many clinicians recommend the use of an aggressive LDL-lowering approach in patients with high Lp(a). Since most of these patients with high Lp(a) might have manifested atherosclerosis anyway, we would also consider the use of acetylsalicylic acid.

18. Man LC, Kelly E, Duffy D: Targeting Lipoprotein (a): an Evolving Therapeutic Landscape. Curr.Atheroscler.Rep. 2015, 17:S02. Abstract: Robust epidemiologic and genetic studies have solidified the role of lipoprotein (a) [Lp(a)] as an independent and causal factor for cardiovascular disease. The increased cardiovascular risk of Lp(a) is mediated through both proatherogenic and prothrombotic/antithrombinolytic mechanisms. Several societies recommend Lp(a) screening for patients with high cardiovascular risk, although no consensus exists on the management of patients with elevated Lp(a). However, numerous pharmacologic approaches are being evaluated that have the potential to reduce Lp(a) and will be the focus of this review. The majority of these interventions have been developed for other lipid-lowering indications, but also lower Lp(a). There are also novel therapies in development that specifically target Lp(a). The efficacy of these therapies varies, and their role in the evolving therapeutic landscape has yet to be determined. Nevertheless, targeted Lp(a) reduction is certainly intriguing and will likely continue to be an active area of investigation in the future.

19. Laufs U: [Lipid lowering by rosuvastatin: How do statins differ?]. Dtsch.Med.Wochenschr. 2015, 140:313. Abstract: Small vessel disease encompasses lacunar stroke, white matter hyperintensities, lacunes and microbleeds. It causes a quarter of all ischemic strokes, is the commonest cause of vascular dementia, and the cause is incompletely understood. Vascular prophylaxis, as appropriate for large artery disease and cardioembolism, includes antithrombosis, and blood pressure and lipid lowering; however, these strategies may not be effective for small vessel disease, or are already used routinely so precluding further detailed study. Further, intensive antiplatelet therapy is known to be hazardous in small vessel disease through enhanced bleeding. Whether acetylsalicylasesterase inhibitors, which delay the progression of Alzheimer’s dementia, are relevant in small vessel disease remains unclear. Potent prophylactic and treatment strategies might be those that target brain microvascular endothelium and the blood brain barrier, microvascular function and neuroinflammation. Potential interventions include endothelin antagonists, neurotrophins, nitric oxide donors and phosphodiesterase 5 inhibitors, peroxisome proliferator-activated receptor-gamma agonists, and prostacyclin mimics and phosphodiesterase 3 inhibitors. Several drugs that have relevant properties are licensed for other disorders, offering the possibility of drug repurposing. Others are in development. Since influencing multiple targets may be most effective, using multiple agents and/or those that have multiple effects may be preferable. We focus on potential small vessel disease mechanistic targets, summarize drugs that have relevant actions, and review data available from randomized trials on their actions and on the available evidence for their use in lacunar stroke.

Abstract: Organic anion transporting polypeptides (OATP) mediate hepatic drug uptake and serve as the loci of drug-drug interactions (DDI). Consequently, there is a major need to develop animal models and refine in-vivo in-vivo extrapolations. Therefore, the in vivo disposition of a model OATP substrate, [3H]rosuvastatin (RSV), was studied in the cynomolgus monkey and reported for the first time. Following a 3 mg/kg oral dose, mass balance was achieved following bile duct cannulation (mean total recovery of radioactivity of 103.6%). Forty-two % of the RSV dose was recovered in urine and bile, and the elimination pathways were similar to those reported for human subjects; 61.7%, 39.0 and 2.9% of the dose was recovered in the feces, bile and urine, respectively. The high levels of unchanged RSV recovered in urine and bile (26% of the dose), and the relatively low levels of metabolites observed, indicated that RSV was eliminated largely by excretion. Also for the first time, the in vitro inhibitory potential of cyclosporin A (CsA) towards cynomolgus monkey OATPs and sodium-taurocholate co-transporting polypeptide (NTCP) was studied in vitro (primary hepatocytes and transfected transporters). It is concluded that one can study the CsA-RSV DDI in the cynomolgus monkey. For example, in the in vitro IC50 values were within 2-fold (monkey vs. human) and the increase (vs. vehicle control) in RSV AUC0-inf (6.3-fold) and Cmax (10.2-fold) with CsA (100 mg/kg) was similar to that reported for humans. The results further support the use of cynomolgus monkey as a model to assess interactions involving OATP inhibition.


Abstract: BACKGROUND: Present guidelines emphasise the importance of low concentrations of LDL cholesterol (LDL-C) in patients with familial hypercholesterolaemia. In most patients with the disease, however, these concentrations are not achieved with present treatments, so additional treatment is therefore warranted. Inhibition of cholesteryl ester transfer protein has been shown to reduce LDL-C concentrations in addition to regular statin treatment in patients with hypercholesterolaemia or at high risk of cardiovascular disease. We aimed to investigate the safety and efficacy of anacetrapib, a cholesteryl ester transfer protein inhibitor, in patients with heterozygous familial hypercholesterolaemia. METHODS: In this multicentre, randomised, double-blind, placebo-controlled, phase 3 study, patients aged 18-80 years with a genotype-confirmed or clinical diagnosis of heterozygous familial hypercholesterolaemia, on optimum lipid-lowering treatment for at least 6 weeks, and with an LDL-C concentration of 2.59 mmol/L or higher without cardiovascular disease or 1.81 mmol/L or higher with cardiovascular disease from 26 lipid clinics across nine countries were eligible. We randomly allocated participants with a computer-generated allocation schedule (2:1, block size of six; no stratification) to oral anacetrapib 100 mg or placebo for 52 weeks, with a 12 week post-treatment follow-up afterwards. We masked patients, care providers, and those assessing outcomes to treatment groups throughout the study. The primary outcome was percentage change from baseline in LDL-C concentration. We did analysis using a constrained longitudinal repeated measures model. This trial is registered with ClinicalTrials.gov number NCT01524289. FINDINGS: Between Feb 10, 2012, and Feb 12, 2014, we randomly allocated 204 patients to anacetrapib and 102 to placebo. One patient in the anacetrapib group did not receive the drug. At week 52, anacetrapib reduced LDL-C concentration from 3.3 mmol/L (SD 0.8) to 2.1 mmol/L (0.8; percentage change 36.0% [95% CI 39.5 to 32.5] compared with an increase with placebo from 3.4 mmol/L (1.2) to 3.5 mmol/L (1.6; percentage change 3.7% [-1.2 to 8.6]), with a difference in percentage change between anacetrapib and placebo of -39.7% (95% CI -45.7 to -33.7; p<0.0001). The number of cardiovascular events was increased in patients given anacetrapib compared with those given placebo (4 [2%] of 203 vs none [0%] of 102; p=0.1544), but the proportion with adverse events leading to discontinuation was similar (12 [6%] of 203 vs five [5%] of 102). INTERPRETATION: In patients with heterozygous familial hypercholesterolaemia, treatment with anacetrapib for 1 year was well tolerated and resulted in substantial reductions in LDL-C concentration. Whether this change leads to a reduction of cardiovascular events will be answered in an outcome study. FUNDING: Merck & Co, Inc.


Abstract: The discovery and elucidation of the role of the low-density lipoprotein receptor (LDL-R) in familial hypercholesterolaemia (FH) ushered in the statin group of drugs. These drugs, in addition to lowering low-density lipoprotein cholesterol (LDL-C), result in a significant reduction in cardiovascular events (CVE) and mortality. Recently, a gain-of-function mutation in another protein, proprotein convertase subtilisin/kexin type 9 (PCSK9), was reported to result in a FH phenotype by promoting degradation of the LDL-R. More importantly, loss-of-function mutations in the same gene resulted in low LDL-C and a reduction in CVE, making this an enticing target for drug development. Numerous strategies have been developed to target PCSK9, the most successful being monoclonal antibodies (mAbs) that bind PCSK9. These mAbs have been shown to reduce LDL-C around 50% as either monotherapy with diet or in combination with statin therapy. In this short perspective, we discuss the biochemistry and biology of PCSK9 in relation to lipid metabolism and the promising studies in humans demonstrating a substantial reduction in LDL-C with relative good short-term safety of PCSK9 mAbs.


Abstract: Metabolic syndrome (MetS) is a disease composed of different risk factors such as obesity, type 2 diabetes or dyslipidemia. The prevalence of this syndrome is increasing worldwide in parallel with the rise in obesity. Nonalcoholic fatty liver disease (NAFLD) is now the most frequent chronic liver disease in western countries, affecting more than 30% of the general population. NAFLD encompasses a spectrum of liver manifestations ranging from simple steatosis to nonalcoholic steatohepatitis (NASH), fibrosis and cirrhosis, which may ultimately progress to hepatocellular carcinoma. There is accumulating evidence supporting an association between NAFLD and MetS. Indeed, NAFLD is recognized as the liver manifestation of MetS. Insulin resistance is increasingly recognized as a key factor linking MetS and NAFLD. Insulin resistance is associated with excessive fat accumulation in ectopic tissues, such as the liver, and increased circulating free fatty acids, which can further promote inflammation and endoplasmic reticulum stress. This in turn aggravates and maintains the insulin resistant state, constituting a vicious cycle. Importantly, evidence shows that most of the patients developing NAFLD present at least one of the MetS traits. This review will define MetS and NAFLD, provide an overview of the common pathophysiological mechanisms linking MetS and NAFLD, and give a perspective regarding treatment of these ever growing metabolic diseases.


Abstract: Breast cancer is the leading cause of cancersassociated mortality in female individuals worldwide. Previous studies have investigated the proapoptotic and antiangiogenic effects of statins, and have demonstrated that simvastatin exhibits antitumor activity and potent chemopreventive effects. However, the mechanism underlying the effects of simvastatin in breast cancer remains to be elucidated. The present study demonstrated that simvastatin inhibited the proliferation of MDAMB231 human breast cancer cells in a dose-dependent manner; decreased the protein expression of B cell lymphoma 2 (Bcl2) and increased the protein expression of Bcl2-associated X protein in time and dosedependent manners. In addition, simvastatin decreased the protein expression of matrix metalloproteinase (MMP)2 and suppressed the activation of nuclear factor (NF)κappaB in the MDAMB231 cells. Taken together, these results demonstrated that the antitumor effect of simvastatin in the human MDAMB231 breast cancer cell line was via the

Abstract: Breast cancer is associated with high levels of incidence, morbidity and mortality; therefore, the identification of effective chemopreventive strategies is crucial. The aim is important for clinicians to be able to identify the populations at risk who would benefit from chemoprevention, and the interventions that are effective and safe. The aim of the present study was to investigate the combined effects of simvastatin and exemestane on MCF7 human breast cancer cells. The antiproliferative effects of simvastatin and exemestane, alone and in combination, on the growth of MCF7 human breast cancer cells were assessed by MTT assay. The synergism between the two drugs was determined in vitro using the combination index (CI) analysis. Cell cycle distribution and apoptosis were analyzed by flow cytometry, and alterations to the signaling pathway in MCF7 cells were examined by immunoblotting following treatment with various regimens. The results of the MTT assay indicated that the combined treatment of simvastatin and exemestane significantly decreased the viability of MCF7 estrogen receptorpositive (ER+) human breast cancer cells, as compared with those that were treated with the individual drugs (CI<1). In addition, coadministration of exemestane and simvastatin was shown to result in marked inhibition of tumor cell proliferation, significant cell cycle arrest at G0/G1 phase and induction of apoptosis, as compared with that of the control and individual drugtreated cells. Furthermore, the results of the present study indicated that these synergistic effects may be associated with the Bcell lymphoma 2 (Bcl2)/Bcl2-associated X protein apoptotic pathway and the mitogenactivated protein kinase/mammalian target of rapamycin/p70S6 kinase growth pathway. The combination of exemestane and simvastatin generated synergistic effects on MCF7 ER+ breast cancer cells, indicating that the combination of these drugs may be a potential therapeutic strategy for the treatment of hormone-dependent breast cancer. The combination of the two inhibitors markedly increased the efficacy, as compared with the singleagent treatment, suggesting that combination treatment could become a highly effective approach for breast cancer. The results of the present study suggested that this combination of drugs has therapeutic potential, and requires further mechanistic and biomarker investigations in clinical trials.


Abstract: OBJECTIVE: To observe the effects of different loading doses of atorvastatin calcium on the outcomes of percutaneous coronary intervention (PCI) in elderly patients with coronary heart disease (CHD). METHODS: A total of 120 CHD patients aged over 80 years were randomly assigned into 3 equal groups to receive intensive pretreatment with statin at the doses of 20, 40, or 60 mg prior to PCI performed within 48 to 72 h after admission. The changes of postoperative cardiac biochemical markers including creatine kinase isoenzyme (CKMB), troponin I (cTNI) and high-sensitivity c-reactive protein (hs-CRP) were observed and the incidence of major adverse cardiac events (MACE, including cardiac death, myocardial infarction, and target vessel revascularization) were recorded within 30 days after PCI. RESULTS: Thirty-four patients in 20 mg statin group, 40 in 40 mg statin group, and 38 in 60 mg statin group completed this study. In all the 3 groups, hs-CRP level significantly increased at 12 and 24 h after PCI compared with the preoperative levels (P<0.05). The patients in 60 mg statin group showed significantly lower levels of CKMB, cTNI, and hs-CRP at 24 h after PCI than those in 20 mg statin group (P<0.05), and had also a significantly lower incidence of total MACE within 30 days after PCI (2.6% vs 26.5%, P=0.003) resulting primarily from significantly reduced myocardial infarction associated with PCI (2.6% vs 20.6%, P=0.016). The adverse drug reactions were comparable among the 3 groups (P>0.05). CONCLUSIONS: Intensive pretreatment with 60 mg/day atorvastatin calcium can significantly reduce myocardial infarction related to PCI with good safety in elderly patients with CHD.


Abstract: [This corrects the article DOI: 10.1371/journal.pone.0014232.]


Abstract: INTRODUCTION: High plasma levels of low-density lipoprotein (LDL) cholesterol are a risk factor for the development of premature atherosclerosis. Direct adsorption of lipoproteins (DALI) is an apheresis technique by which LDL cholesterol is selectively removed from whole blood. OBJECTIVE: The present study describes our experience with DALI LDL apheresis in severely hypercholesterolemic patients. METHODS: Three hypercholesterolemic patients suffering from atherosclerotic complications were treated fortightly by DALI apheresis, in a total of 308 sessions between December 2008 and January 2013. All patients were on the highest tolerated dose of statins and other lipid-lowering drugs. RESULTS: The sessions were essentially uneventful, adverse events being recorded in only 3.6% of them. A mean 63.3% acute reduction in LDL cholesterol was obtained. CONCLUSION: DALI apheresis proved to be a simple, safe and efficient method of lipid apheresis in hypercholesterolemic patients refractory to conservative lipid-lowering therapy.