
Abstract: BACKGROUND: The ODYSSEY COMBO I study (http://clinicaltrials.gov/show/NCT01644175) evaluated efficacy and safety of alirocumab as add-on therapy to stable maximally tolerated daily statin with or without other lipid-lowering therapy in high cardiovascular risk patients with suboptimally controlled hypercholesterolemia. METHODS: This multicenter, phase 3, randomized (2:1 alirocumab vs placebo), double-blind, 52-week trial enrolled 316 patients with established coronary heart disease or coronary heart disease risk equivalents and hypercholesterolemia. Alirocumab (75 mg every 2 weeks [Q2W]) or placebo Q2W was self-administered subcutaneously via 1 mL prefilled pen. The alirocumab dose was increased to 150 mg Q2W (also 1 mL) at week 12 if week 8 low-density lipoprotein cholesterol (LDL-C) was >/=70 mg/dL. The primary efficacy end point was percent change in LDL-C from baseline to week 24 (intention-to-treat analysis). RESULTS: At week 24, estimated mean (95% CI) changes in LDL-C from baseline were -48.2% (-52.0% to -44.4%) and -2.3% (-7.6% to 3.1%) for alirocumab and placebo, respectively, an estimated mean (95% CI) difference of -45.9% (-52.5% to -39.3%) (P < .0001). Low-density lipoprotein cholesterol <70 mg/dL was achieved by 75% alirocumab versus 9% placebo patients at week 24. At week 12, 83.2% of evaluable alirocumab-treated patients remained on 75-mg Q2W. Treatment-emergent adverse events were comparable between groups. CONCLUSIONS: Alirocumab treatment achieved a significantly greater reduction in LDL-C and allowed a greater proportion of patients to achieve LDL-C goals, versus placebo after 24 weeks in high cardiovascular risk patients with suboptimally controlled hypercholesterolemia at baseline despite receiving maximally tolerated statin with or without other lipid-lowering therapy. The frequency of treatment-emergent adverse events and study medication discontinuations were generally comparable between treatment groups.


Abstract: Cardiovascular disease (CVD) is a universal problem in modern society. Atherosclerosis is the leading cause of CVD resulting in high rate of mortality in the population. Nutrition science has focused on the role of essential nutrients in preventing deficiencies, at the present time, the nutritional strategies are crucial to promote health and intervene with these global noncommunicable diseases. In many cases, diet is a major driving force, which is much easier to change and follow than other factors. It is important to establish that the first strategy to treat atherosclerosis is to modify lifestyle habits, focusing on the beneficial properties of specific nutrients. In the last decades, epidemiological, clinical and experimental studies have demonstrated that diet plays a central role in the prevention of atherosclerosis. In this review we will focus on the effect of specific foods, nutrients and bioactive compounds, including epidemiological facts, potential mechanisms of action and dietary recommendations to reduce the risk of atherosclerosis. In particular, we include information about fiber, plant sterols and stanoles, niacin, taurine, olive oil, omega 3 fatty acids, antioxidants, minerals, methyl nutrients and soy. In addition, we also show that dysbiosis of the intestinal microbiota associated with a consumption of certain animal foods can generate some metabolites that are involved in the development of atherosclerosis and its consequences on CVD. According to the epidemiological, clinical and experimental studies we suggest for some dietary foods, nutrients and bioactive compounds to support the complementary clinical management of patients with atherosclerosis.


Abstract: OBJECTIVE: Dyslipidemia is implicated in abdominal aortic aneurysms (AAAs) in humans and angiotensin (Ang) II-infused mice. This study determined effects of major lipoprotein classes on AngII-induced AAAs using multiple mouse strains with dietary and pharmacological manipulations. APPROACH AND RESULTS: Western diet had minor effects on plasma cholesterol concentrations and the low incidence of AngII-induced AAAs in C57BL/6J mice. Low incidence of AAAs in this strain was not attributed to protection from high-density lipoprotein, because apolipoprotein (apo) AI deficiency did not increase AngII-induced AAAs. ApoAI deletion also failed to alter AAA occurrence in hypercholesterolemic mice. Low-density lipoprotein receptor-/mice fed normal diet had low incidence of AngII-induced AAAs. Western diet feeding of this strain provoked pronounced hypercholesterolemia because of increased apoB-containing lipoproteins with attendant increases of atherosclerosis in both sexes, but AAAs only in male mice. Apo-deficient mice fed normal diet were modestly hypercholesterolemic, whereas this strain fed Western diet was severely hypercholesterolemic because of increased apoB-containing lipoprotein concentrations. The latter augmented atherosclerosis, but did not change the high incidence of AAAs in this strain. To determine whether reductions in apoB-containing lipoproteins influenced AngII-induced AAAs, ezetimibe was administered at a dose that partially reduced plasma cholesterol concentrations to ApoEI-deficient mice fed Western diet. This decreased atherosclerosis, but not AAAs. This ezetimibe dose in ApoEI-deficient mice fed normal diet significantly decreased plasma apoB-containing lipoprotein concentrations and reduced AngII-induced AAAs. CONCLUSIONS: ApoB-containing lipoproteins contribute to augmentation of AngII-induced AAA in male mice. However, unlike atherosclerosis, AAA occurrence was not correlated with increases in plasma apoB-containing lipoprotein concentrations.


Abstract: BACKGROUND: Low plasma levels of high-density lipoprotein-cholesterol (HDL-C) are typical of acute myocardial infarction (MI) and predict risk of recurrent cardiovascular events. The potential relationships between modifications in the molecular composition and the functionality of HDL subpopulations in acute MI however remain indeterminate. METHODS AND RESULTS: In ST segment elevation MI (STEMI) patients were recruited within 24h after diagnosis (n=16) and featured low HDL-C (-31%, p<0.05) and acute-phase inflammation (determined as marked elevations in C-reactive protein, serum amyloid A (SAA) and interleukin-6) as compared to age- and sex-matched controls (n=10). STEMI plasma HDL and its subpopulations (HDL2b, 2a, 3a, 3b, 3c) displayed attenuated cholesterol efflux capacity from THP-1 cells (up to >32%, p<0.05, on a unit phospholipid mass basis) vs. CONTROLS: Plasma HDL and small, dense HDL3b and 3c subpopulations from STEMI patients exhibited reduced anti-oxidative activity (up to -68%, p<0.05, on a unit HDL mass basis). HDL3 subpopulations in STEMI were enriched in two proinflammatory bioactive lipids, lysophosphatidylcholine (up to 3.0-fold, p<0.05) and phosphatidic acid (up to 8.4-fold, p<0.05), depleted in apolipoprotein A-I (up to -23%, p<0.05) and enriched in SAA (up to +10.2-fold, p<0.05); such changes were most marked in the HDL3b subfraction. In vitro HDL enrichment in both lysophosphatidylcholine and phosphatidic acid exerted deleterious effects on HDL functionality. CONCLUSIONS: In the early phase of STEMI, HDL particle subpopulations display marked, concomitant alterations in both lipopide and proteome which are implicated in impaired HDL functionality. Such modifications may act synergistically to confer novel deleterious biological activities to STEMI HDL. SIGNIFICANCE: Our present data highlight complex changes in the molecular composition and functionality of HDL particle subpopulations in the acute phase of STEMI, and for the first time, reveal that concomitant modifications in both the lipopide and proteome contribute to functional deficiencies in cholesterol efflux and antioxidative activities of HDL particles. These findings may provide new biomarkers and new insights in therapeutic strategy to reduce cardiovascular risk in this clinical setting where such net deficiency in HDL function, multiplied by low circulating HDL concentrations, can be expected to contribute to accelerated atherogenesis.

5. Arguello G, Balboa E, Arrese M, Zanlungo S: Recent insights on the role of cholesterol in non-alcoholic fatty liver disease.

Abstract: INTRODUCTION: Oral testosterone was found to reduce plasma levels of HDL cholesterol. No previous study has examined the effect of frabtes, known to increase HDL cholesterol, in patients with low testosterone levels requiring testosterone replacement. AIM: The study included three age-, weight- and lipid-matched groups of patients with atherogenic dyslipidemia and late-onset hypogonadism, treated with oral testosterone undecanoate (120 mg daily, n=15), micronized fenofibrate (200 mg daily, n=15) or testosterone plus fenofibrate (n=18). Plasma lipids, glucose homeostasis markers, as well as plasma levels of androgens, uric acid, high-sensitivity C-reactive protein (hsCRP), homocysteine and fibrinogen were assessed before and after 16 weeks of therapy. RESULTS: Apart from an increase in plasma testosterone and a reduction in HDL cholesterol, testosterone undecanoate tended to decrease hsCRP and to improve insulin sensitivity. Fenofibrate administered alone increased HDL cholesterol, reduced triglycerides, decreased insulin resistance, reduced circulating levels of uric acid, hsCRP and fibrinogen, as well as increased plasma levels of homocysteine. The strongest effect on testosterone, HOMA-1IR, uric acid, hsCRP and fibrinogen was observed if fenofibrate was administered together with testosterone. Testosterone-fenofibrate combination therapy was also devoid of unfavorable effect on HDL cholesterol and homocysteine. CONCLUSIONS: Our study shows that fenofibrate produces a stronger effect on cardiometabolic risk factors in men with late-onset hypogonadism and atherogenic dyslipidemia than oral testosterone undecanoate. The obtained results suggest that this group of patients may benefit the most from the combined treatment with oral testosterone undecanoate and micronized fenofibrate. This article is protected by copyright.


Abstract: Two accurate, reliable, and highly sensitive spectrofluorimetric methods were developed for simultaneous determination of the binary mixture of Atorvastatin and Ezetimibe without prior separation steps. The first method is based on double scan synchronous fluorescence spectrometry. Each of Atorvastatin and Ezetimibe can be determined independent of the other when scanned at Deltalambda=100 nm and 40 nm, respectively. The relative fluorescence intensity-concentration plots at two wavelengths, 272 (Deltalambda=100 nm) and 266 nm (Deltalambda=40 nm) were rectilinear over the range of 0.4-8 microg/mL (for Atorvastatin) and 0.6-8 microg/mL (for Ezetimibe), respectively. The second method is based on the technique of simultaneous equations (Vierodt’s method), in which two equations are solved simultaneously after using a single excitation wavelength of 273 nm and lambdaEm1=380 nm of Atorvastatin and lambdaEm2=301 nm of Ezetimibe. Under the optimum conditions, linear relationships were found between the relative fluorescence intensity and the concentrations of the investigated drugs in the range of 0.4-8 microg/mL (for Atorvastatin) 0.6-8 microg/mL (for Ezetimibe). The different experimental parameters affecting the fluorescence intensities of the two drugs were carefully studied and optimized. The proposed methods were successfully applied for the determination of the investigated drugs in pure form, dosage form and in synthetic mixtures with good recovery and the results obtained were favorably compared to those obtained with a reference method


Abstract: This paper focuses on the development and physicochemical characterization of a self-microemulsiying drug delivery system (SMEDDS) containing a fixed-dose combination of atorvastatin (A) and ezetimibe (EZT). The solubility of both drugs was determined in excipient screening studies. Ternary-phase diagrams were drawn for 27 systems composed of different surfactants, cosurfactants, and oils at different surfactant-to-cosurfactant (S/CoS) ratios, and the system exhibiting the largest percentage area of the self-microemulsifying region was selected. The optimum oil ratio in the SMEDDS was selected by evaluating the mean droplet size of the resultant microemulsions. The underlying mechanism of the lower ATR loading capacity compared with EZT was elucidated by measurement of the zeta potential and UV absorption analysis. The results implied that ATR was located exclusively in the surfactant-cosurfactant layer, whereas EZT was located both in the microemulsion core and the surfactant-cosurfactant layer. In vitro dissolution studies showed that the SMEDDS had higher initial dissolution rates for both drugs when compared with marketed products. More importantly, EZT had a significantly increased dissolution profile in distilled water and pH 4.0 acetate buffer, implying enhanced bioavailability.


Abstract: Background: Statins have immunomodulatory properties that may provide beneficial effects in the treatment of COPD. We investigated whether a statin improves the IL-17/IL-10 imbalance in patients with COPD as has previously been demonstrated in patients with asthma. Methods: Thirty patients with stable COPD were recruited to a double-blind randomized controlled crossover trial comparing the effect of oral simvastatin 20 mg daily with that of a matched placebo on sputum inflammatory markers and airway inflammation. Each treatment was administered for 4 weeks separated by a 4-week washout period. The primary outcome was Th17 cytokines and indoleamine 2,3 dioxygenase (IDO) in induced sputum. Secondary outcomes included sputum inflammatory cells, FEV1 and symptoms using the COPD assessment test (CAT). Results: At 4 weeks there was a significant reduction in sputum IL-17A, IL-22, IL-6, and CXCL8 concentrations (mean difference -16.4 pg/mL, p=0.01; -48.6 pg/mL, p<0.001; -45.3 pg/mL, p=0.002 and -190.9 pg/mL, p=0.007, respectively), whereas IL-10 concentrations, IDO mRNA expression (fold change) and IDO activity (kynurenine/tryptophan ratio) were markedly increased during simvastatin treatment compared with placebo treatment periods (mean difference 24.7 pg/mL, p<0.001; 1.02, p<0.001 and 0.47, p<0.001, respectively). The absolute sputum macrophage count, proportion of macrophages and CAT score
was reduced after simvastatin compared with placebo (mean difference -0.16 ± 0.04; p=0.004; -14.1%, p<0.001 and -3.2%, p=0.02, respectively).

Results for other clinical outcomes were similar between the simvastatin and placebo treatments. Conclusion: Simvastatin reversed the IL-17A/IL-10 imbalance in the airways and reduced sputum macrophage but not neutrophil counts in patients with COPD.


Abstract: Over the past years, genetic studies on lipid traits have substantially extended our understanding of the relationship between lipid metabolism and coronary artery disease (CAD). Thereby, novel pathways and interactions in lipid metabolism unraveled by genetic studies have led to promising novel treatment strategies that are currently evaluated for prevention and treatment of CAD, such as low-density lipoprotein cholesterol (LDL-C) lowering by inhibition of proprotein convertase subtilisin/kexin type 9 (PCSK9). This review article discusses findings from recent genetic studies and their implications for the understanding of the relation between lipid metabolism and CAD as well as the development of novel therapeutic strategies supported by these studies.


Abstract: Diabetes is a global epidemic, associated with a high burden of complications and 4.6 million deaths annually worldwide. As a result of decreasing levels of physical activity and increasing rates of obesity, diabetes is shifting from a disease affecting the elderly to one that affects younger patients or even children. Thus, aggressive treatment and optimal control of risk factors is the key to improve outcomes in those patients. Accumulating evidence of the cardiovascular and lipid effects of glucose-lowering medications suggest that treatment efficacy in diabetes can be further improved. This review provides an overview of the lipid effects and cardiovascular disease risk of current anti-diabetic medications and highlights opportunities and challenges in clinical practice.


Abstract: Cardiovascular disease is the major cause of death in women in developed countries. Dyslipidemia is highly prevalent in women, particularly after the menopause. Elevated low-density lipoprotein cholesterol (LDL-C) has been identified as the key lipid parameter in both genders whereas HDL-cholesterol and triglycerides have been more closely associated, in some studies, with cardiovascular risk in women. Menopause has been shown to be associated with an increase in total and LDL-cholesterol and a decrease in HDL-cholesterol (predominantly in the HDL2 subtraction). Despite its beneficial effects on the lipid profile, hormone replacement therapy is not recommended for primary or secondary prevention of cardiovascular disease in women. The latest meta-analysis of statin trials with gender-specific outcomes showed a similar benefit in women and men. The addition of ezetimibe to simvastatin in patients with acute coronary syndromes showed a further reduction of the primary endpoint in both genders. While there are no gender-related differences in drug treatment of dyslipidemia, current guidelines, to avoid overtreatment, strongly suggest risk estimation before initiating lipid-lowering treatment in women without manifest cardiovascular disease.


Abstract: **BACKGROUND:** Although the effectiveness of treatment with ursodeoxycholic acid (UDCA) and fenofibrate for primary biliary cirrhosis (PBC) has been suggested by small trials, a systematic review to summarize the evidence has not yet been carried out. **METHODS:** A meta-analysis of all long-term randomized controlled trials comparing the combination of UDCA and fenofibrate with UDCA monotherapy was performed via electronic searches. **RESULTS:** Six trials, which included 84 patients, were assessed. Combination therapy with UDCA and fenofibrate was more effective than UDCA monotherapy in improving alkaline phosphatase (mean difference [MD]: -90.44 IU/L; 95% confidence interval [CI]: [-119.95 to -60.92; P=0.00001]), gamma-glutamyl transferase (MD: -61.58 IU/L; 95% CI: [-122.80 to -0.35; P=0.05]), immunoglobulin M (MD: -38.45 mg/dL; 95% CI: [-64.38 to -12.51; P=0.004]), and triglycerides (MD: -0.41 mg/dL; 95% CI: [-0.82 to -0.01; P=0.05]). However, their effects on pruriitis (odds ratio [OR]: 0.39; 95% CI: 0.09-1.78; P=0.23), total bilirubin (MD: -0.05 mg/dL; 95% CI: -0.21 to 0.12; P=0.58), and alanine aminotransferase (MD: -3.31 IU/L; 95% CI: -14.60 to 7.97; P=0.56) did not differ significantly. **CONCLUSION:** In this meta-analysis, combination therapy with UDCA and fenofibrate was more effective in reducing alkaline phosphatase than UDCA monotherapy, but it did not improve clinical symptoms. There did not appear to be an increase in adverse events with combination therapy.


Abstract: Familial hypercholesterolemia (FH) is an oligogenic disorder characterized by markedly elevated low-density lipoprotein cholesterol (LDLC) levels. Variants in four genes have been reported to cause the classical autosomal-dominant form of the disease. FH is largely under-diagnosed in European countries. As FH increases the risk for coronary artery disease (CAD) and myocardial infarction (MI), it might be specifically overlooked in the large number of such patients. Here, we systematically examined the frequency of potential FH-causing variants by exome sequencing in 250 German patients with premature MI and a positive family history for CAD. We further performed co-segregation analyses in an average of 5.5 family members per MI patient. In total, we identified 11 potential disease-causing variants that co-segregate within the families, that is, 5% of patients with premature MI and positive CAD family history had FH. Eight variants were previously reported as disease-causing and three are novel (LDLR.c.610G>A (p.(D204N)) and STAP1.c.139A>G (p.(T47A))). Co-segregation analyses identified multiple additional family members per MI patient. In total, we identified 11 potential disease-causing variants that co-segregate within the families, that is, 5% of patients with premature MI and positive CAD family history had FH. Eight variants were previously reported as disease-causing and three are novel (LDLR.c.610G>A (p.(D204N)) and STAP1.c.139A>G (p.(T47A))). Co-segregation analyses identified multiple additional family members carrying one of these FH variants and the clinical phenotype of either FH (n=2) or FH and premature CAD (n=15). However, exome sequencing also revealed that some variants in FH genes, which have been reported to cause FH, do not co-segregate with FH. The data reveal that a large proportion of FH patients escape the diagnosis, even when they have premature MI. Hence, systematic molecular-genetic screening for FH in such patients may reveal a substantial number of cases and thereby allow a timely LDL-C-lowering in both FH/MI patients as well as their variant-carrying family members.

European Journal of Human Genetics advance online publication, 3 June 2015; doi:10.1038/ejhg.2015.100.


Abstract: **INTRODUCTION:** The prevalence of chronic kidney disease (CKD), a risk factor for cardiovascular disease (CVD), is increasing worldwide. Statin treatment, the cornerstone of prevention or treatment of CVD, might have beneficial effects on urine protein excretion and renal function as determined by the glomerular filtration rate, whereas it might protect from acute kidney injury (AKI), mainly due to contrast-induced AKI. These beneficial effects on CKD may not be drug class effects; specific statins at specific doses may help prevent CKD deterioration and reduce CVD risk. We analysed all statin studies that had renal and CVD endpoints as main outcome measures. MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials were searched up to February 2015. Areas covered: We consider the effects of statins on microalbuminuria, proteinuria, glomerular filtration rate, AKI associated with angiography or percutaneous coronary intervention and on CVD event rates in patients with CKD.
Expert opinion: Current evidence points towards the need to prescribe high-potency statins in patients with CKD, before a major decline in kidney function occurs. This may reduce CVD risk and delay the progress of CKD. Administration of either atorvastatin or rosuvastatin can prevent contrast-induced AKI before angiography or percutaneous coronary intervention. The combination of simvastatin + ezetimibe may decrease vascular events in patients with advanced CKD.


Abstract: Fasting and postprandial hypertriglyceridemia appear to be causally related to athero-sclerotic cardiovascular disease, and plasma triglyceride (TG) concentrations above 10 mmol/l increase susceptibility to acute pancreatitis. Exclusion of secondary causes of hypertriglyceridemia and implementation of lifestyle measures are the initial treatment in all types of hypertriglyceridemia. Current evidence regarding the benefit of adding non-statin agents, i.e. fibrate and n-3 polyunsaturated fatty acids, to statins in patients with hypertriglyceridemia (plasma 2.3 < TG <= 5.7 mmol/l) is insufficient. Therefore, the clinical use of non-statin agents in this context requires a careful trade-off between anticipated benefits and potential adverse events within the context of a clinical consultation. It is reasonable to consider adding fenofibrate to a maximally tolerated dose of a statin with or without ezetimibe in higher risk patients with metabolic syndrome or established athero-sclerotic cardiovascular disease with persistent, residual elevation in TG > 2 mmol/l. Patients with very high fasting plasma TG levels (>10 mmol/l) need immediate expert review to offset pancreatitis and, along with strict dietary control and triglyceride-lowering pharmacotherapy, may need lipoprotein apheresis or plasma exchange.


Abstract: Proprotein convertase subtilisin/kexin type 9 (PCSK9), belongs to a family of proprotein convertases (PCs), encodes a neural apoptosis-regulated convertase 1. However, the precise role of PCSK9 during glioma cells apoptosis has not been reported. Therefore, we examined the effects of knockdown and overexpression of PCSK9 on apoptosis of human neuroglioma U251 cells, and investigated the underlying mechanisms of apoptosis. We found that PCSK9 regulated cells proliferation as determined by CCK-8 and Hoechst staining analysis. In addition, western blot results showed that PCSK9 siRNA promote apoptosis via activation of caspase-3 and down-regulation of the anti-apoptotic proteins, XIAP and p-Akt, while PCSK9 overexpression inhibited apoptosis. Moreover, PCSK9 siRNA improved the ratio of Bax/Bcl-2 which leads to the release of cytochrome c, while PCSK9 overexpression decreased it. Taken together, these data demonstrate that PCSK9 may regulate apoptosis through mitochondrial pathway and is expected to be a promising therapeutic strategy for the malignant glioma.


Abstract: Proprotein convertase subtilisin/kexin 9 (PCSK9) is the ninth member of the proprotein convertase family. It is an important regulator of cholesterol metabolism. PCSK9 can bind to low-density lipoprotein receptors (LDLRs) and induce the degradation of these receptors through the endosome/lysosome pathway, thus decreasing the LDLR levels on the cell surface of hepatocytes, resulting in increased serum low-density lipoprotein cholesterol (LDL-C) concentrations. Recent studies have found that gene polymorphisms of PCSK9 are associated with hypercholesterolemia, risk of atherosclerosis, and ischemic stroke. Furthermore, monoclonal antibodies, peptide mimetics, small molecule inhibitors and gene silencing agents that are associated with PCSK9 are some of the newer pharmaceutical therapeutic strategies and approaches for lowering serum LDL-C levels. In this review, we will discuss recent advances in PCSK9 research, which show that PCSK9 is correlated with lipid metabolism, atherosclerosis, and, in particular, ischemic stroke. We will also discuss the current state of PCSK9 therapeutics and their potential in modulating these diseases.


Abstract: RATIONALE: Prior intracerebral haemorrhage and cerebral microbleeds may increase the risk of haemorrhagic stroke. However, the optimal long-term antiplatelet therapy and lipid management in these patients remain unclear. AIM: Prevention of Cardiovascular events in Ischemic Stroke patients with high risk of cerebral hemorrhage was designed to compare cilostazol and aspirin and to assess the effect of adding probucol, a lipid-lowering and anti-oxidative agent, in patients with high intracerebral haemorrhage stroke. SAMPLE SIZE ESTIMATE: The projected sample size is 1600 patients with at least 12 months of follow-up. METHODS AND DESIGN: Prevention of Cardiovascular events in ischemic stroke patients with high risk of cerebral hemorrhage is a randomized trial involving 67 institutes from 3 countries. Patients with non-cardioembolic ischemic stroke or transient ischemic attack within 180 days and with prior intracerebral haemorrhage or multiple cerebral microbleeds on gradient echo imaging are eligible. Enrolled patients are simultaneously randomized in a 2 x 2 factorial design: double-blind for cilostazol 200 mg/day vs. aspirin 100 mg/day, and an open-label, blind end-point evaluation for probucol 500 mg/day vs. non-probucol. STUDY OUTCOMES: The co-primary end-points are the safety end-point of haemorrhagic stroke and the efficacy end-point of a composite of stroke, myocardial infarction, or vascular death. Time-to-event will be analyzed separately for each intervention: superiority testing for the safety of cilostazol aspirin as well as the efficacy of probucol over non-probucol, and non-inferiority testing for the efficacy of cilostazol to aspirin. DISCUSSION: Prevention of Cardiovascular events in ischemic Stroke patients with high risk of cerebral hemorrhage is the largest secondary stroke prevention trial for informing antiplatelet therapy and lipid management in patients at high risk of haemorrhagic stroke.


Abstract: BACKGROUND: Glycoprotein VI (GPVI) is the essential platelet collagen receptor in atherothrombosis, but its inhibition causes only a mild bleeding tendency. Thus, targeting this receptor has selective antithrombotic potential. OBJECTIVES: This study sought to compare compounds interfering with platelet GPVI-atherosclerotic plaque interaction to improve current antiatherothrombotic therapy. METHODS: Human atherosclerotic plaque-induced platelet aggregation was measured in anticoagulated blood under static and arterial flow conditions (550/s, 1,100/s, and 1,500/s). Inhibition by dimeric GPVI fragment crystallizable region of IgG (Fc) masking GPVI binding sites on collagen was compared with that of 3 anti-GPVI antibodies: BLO8-1, a human domain antibody; 5C4, a fragment antigen-binding (Fab fragment) of monoclonal rat immunoglobulin G; and Fab-F, a human recombinant sFab against GPVI dimers. RESULTS: GPVI-Fc reduced plaque-triggered platelet aggregation in static blood by 51%, BLO8-1 by 88%, and 5C4 by 93%. Under arterial flow conditions, BLO8-1 and 5C4 almost completely inhibited platelet aggregation while preserving platelet adhesion on plaque. Inhibition by GPVI-Fc, even at high concentrations, was less marked but increased with shear rate. Advanced optical imaging revealed rapid persistent GPVI-Fc binding to collagen under low and high shear flow, upstream and downstream of plaque fragments. At low shear particularly, platelets adhered in plaque flow niches to GPVI-Fc-free segments of collagen fibers and recruited other platelets onto aggregates via ADP and Txa2 release. CONCLUSIONS: Anti-GPVI antibodies inhibit atherosclerotic plaque-induced platelet aggregation under static and flow conditions more effectively than GPVI-Fc. However, potent platelet inhibition by GPVI-Fc at a higher shear rate (1,500/s) suggests localized antithrombotic efficacy at denuded or fissured stenotic high-risk lesions without systemic bleeding. The compound-specific differences have
relevance for clinical trials targeting GPVI-collagen interaction combined with established antiplatelet therapies in patients with spontaneous plaque rupture or intervention-associated plaque injury

Abstract: CONTEXT: Despite current standard-of-care, many patients at high cardiovascular disease (CVD) risk still have elevated low-density lipoprotein cholesterol (LDL-C). Alirocumab is a fully human monoclonal antibody to proprotein convertase subtilisin/kexin type 9 (PCSK9).
OBJECTIVE: To compare LDL-C-lowering efficacy of adding alirocumab vs other common lipid-lowering strategies. Design, Patients, Interventions: Patients (n=365) with CVD and LDL-C levels ≥70 mg/dL, or CVD risk factors and LDL-C ≥100 mg/dL, on baseline atorvastatin 20 or 40 mg, were randomized to: (1) add-on alirocumab 75 mg every 2 weeks (Q2W) subcutaneously; (2) add-on ezetimibe 10 mg/day; (3) double atorvastatin dose; (4) for atorvastatin 40 mg regimen only, switch to rosuvastatin 40 mg. For patients not achieving protocol-defined LDL-C goals, alirocumab dose was increased (blinded) at week 12 to 150 mg Q2W. MAIN OUTCOME MEASURE: Primary endpoint was % change in calculated LDL-C from baseline to 24 weeks (intent-to-treat). RESULTS: Among atorvastatin 20 and 40 mg regimens respectively, add-on alirocumab reduced LDL-C levels by 44.1% and 54.0% (p<0.001 vs all comparators); add-on ezetimibe, 20.5% and 22.6%; doubling of atorvastatin dose, 5.0% and 4.8%; and switching atorvastatin 40 mg to rosuvastatin 40 mg, 21.4%. Most alirocumab-treated patients (87.2% and 84.6%) achieved their LDL-C goals. Most alirocumab-treated patients (86%) maintained their 75 mg Q2W regimen. Treatment-emergent adverse events occurred in 65.4% of alirocumab patients, vs 64.4% ezetimibe and 63.8% double atorvastatin switch to rosuvastatin (data pooled). CONCLUSIONS: Adding alirocumab to atorvastatin provided significantly greater LDL-C reductions vs adding ezetimibe, doubling atorvastatin dose, or switching to rosvastatin, and enabled greater LDL-C goal achievement.

Abstract: Diabetic hazard on the myocardium is a complication of diabetes that intensifies its morbidity and increases its mortality. Therefore, alleviation of diabetic cardiomyopathy (DCM) by a reliable drug remains a matter of interest in experimental research. The aim of this study was to explore the structural alterations in the myocardium induced by atorvastatin (ATOR) in DCM, induced by streptozotocin (STZ), along with the associated changes occurring in apoptosis and oxidative stress markers. Thirty-two rats were divided into four groups; group A (control), group B (non-diabetic, received ATOR, orally, 50 mg/kg daily), group C (DMC, received STZ 70 mg/kg, single i.p. injection) and group D (DMC + ATOR). After 6 weeks, left ventricle (LV) specimens were prepared for histological and immunohistochemical study by hematoxylin and eosin, Masson’s trichrome, anti-cleaved caspase-3 stains as well as for assays of oxidative stress markers. All data were measured morphometrically and statistically analyzed. The DCM group showed disorganization of the cardiomyocytes, interstitial edema, numerous fibroblasts, significant increases in the collagen volume fraction (p < 0.001), cleaved caspase-3 expression % area (p < 0.001) and, malondialdehyde blood in blood (p < 0.001), in LV (p < 0.05) compared with DCM + ATOR group. The latter has LV wall thickness, relative heart weight and antioxidant activities nearly similar to the control, independent from ATOR lipid-lowering effect. Therefore, ATOR can preserve myocardial structure in DCM nearly similar to normal. This may be achieved by suppressing apoptosis that parallels the correction of the antioxidant markers, which can be considered as non-lipid lowering benefit of statins.


Abstract: OBJECTIVE: To comprehensively assess the pharmacogenomic evidence of routinely used drugs for clinical utility. METHODS: Between January 2, 2011, and May 31, 2013, we assessed 71 drugs by identifying all drug/genetic variant combinations with published clinical pharmacogenomic evidence. Literature supporting each drug/variant pair was assessed for study design and methods, outcomes, statistical significance, and clinical relevance. Proposed clinical summaries were formally scored using a modified AGREE (Appraisal of Guidelines for Research and Evaluation) II instrument, including recommendation for or against guideline implementation. RESULTS: Positive pharmacogenomic findings were identified for 51 of 71 cardiovascular drugs (71.8%), representing 884 unique drug/variant pairs from 597 publications. After analysis for quality and clinical relevance, 92 drug/variant pairs were proposed for translation into clinical summaries, encompassing 23 drugs (32.4% of drugs reviewed). All were recommended for clinical implementation using AGREE II, with mean +/− SD overall quality scores of 5.18+/−0.91 (of 7.0; range, 3.67-7.0). Drug guidelines had highest mean +/− SD scores in AGRE II domain 1 (Scope) (91.9+/−6.1 of 100) and moderate but still robust mean +/− SD scores in domain 3 (Rigor) (73.1+/−11.1), domain 4 (Clarity) (67.8+/−12.5), and domain 5 (Applicability) (65.8+/−10.0). Clopidogrel (CYP2C19), metoprolol (CYP2D6), simvastatin (rs4149056), dabigatran (rs2244613), hydralazine (rs1799983, rs1799998), and warfarin (CYP2C9/ VKORC1) were distinguished by the highest scores. Seven of the 9 most commonly prescribed drugs warranted translation guidelines summarizing clinical pharmacogenomic information. CONCLUSION: Considerable clinically actionable pharmacogenomic information for cardiovascular drugs exists, supporting the idea that consideration of such information when prescribing is warranted.

Abstract: OBJECTIVE: Non-alcoholic fatty liver disease (NAFLD) is a common disorder characterized by excessive hepatic fat accumulation, production of reactive oxygen species (ROS), inflammation and potentially resulting in non-alcoholic steatohepatitis (NASH), cirrhosis and end-stage liver disease. Recently, we have shown that niacin significantly prevented hepatic steatosis and regressed pre-existing steatosis in high-fat fed rat model of NAFLD. To gain further insight into the cellular mechanisms, this study investigated the effect of niacin on human hepatocyte fat accumulation, ROS production, and inflammatory mediator IL-8 secretion. MATERIALS AND METHODS: Human hepatoblastoma cell line HepG2 or human primary hepatocytes were first stimulated with palmitic acid followed by treatment with niacin or control for 24h. RESULTS: The data indicated that niacin (at 0.25 and 0.5mmol/L doses) significantly inhibited palmitic acid-induced fat accumulation in human hepatocytes by 45-62%. This effect was associated with inhibition of diacylglycerol acyltransferase 2 (DGAT2) mRNA expression without affecting the mRNA expression of fatty acid synthase (FAS) and carnitine palmitoyltransferase 1 (CPT1). Niacin attenuated hepatocyte ROS production and it also inhibited NADPH oxidase activity. Niacin reduced palmitic acid-induced IL-8 levels. CONCLUSIONS: These findings suggest that niacin, through inhibiting hepatocyte DGAT2 and NADPH oxidase activity, attenuates hepatic fat accumulation and ROS production respectively. Decreased ROS production, at least in part, may have contributed to the inhibition of pro-inflammatory IL-8 levels. These mechanistic studies may be useful for the clinical development of niacin and niacin-related compounds for the treatment of NAFLD/NASH and its complications.

Abstract: Background Statin therapy reduces low-density lipoprotein (LDL) cholesterol levels and the risk of cardiovascular events, but whether the addition of ezetimibe, a nonstatin drug that reduces intestinal cholesterol absorption, can reduce the rate of cardiovascular events further is not known. Methods We conducted a double-blind, randomized trial involving 18,144 patients who had been hospitalized for an acute coronary syndrome within the preceding 10 days and had LDL cholesterol levels of 50 to 100 mg per deciliter (1.3 to 2.6 mmol per liter) if they were receiving lipid-lowering therapy or 50 to 125 mg per deciliter (1.3 to 3.2 mmol per liter) if they were not receiving lipid-lowering therapy. The combination of simvastatin (40 mg) and ezetimibe (10 mg) (simvastatin-ezetimibe) was compared with simvastatin (40 mg) and placebo (simvastatin monotherapy). The primary end point was a composite of cardiovascular death, nonfatal myocardial infarction, unstable angina requiring rehospitalization, coronary revascularization (>30 days after randomization), or nonfatal stroke. The median follow-up was 6 years. Results The median time-weighted average LDL cholesterol level during the study was 53.7 mg per deciliter (1.4 mmol per liter) in the simvastatin-ezetimibe group, as compared with 69.5 mg per deciliter (1.8 mmol per liter) in the simvastatin-monotherapy group (P<0.001). The Kaplan-Meier event rate for the primary end point at 7 years was 32.7% in the simvastatin-ezetimibe group, as compared with 34.7% in the simvastatin-monotherapy group (absolute risk difference, 2.0 percentage points; hazard ratio, 0.936; 95% confidence interval, 0.89 to 0.99; P=0.016). Rates of prespecified muscle, gallbladder, and hepatic adverse effects and cancer were similar in the two groups. Conclusions When added to statin therapy, ezetimibe resulted in incremental lowering of LDL cholesterol levels and improved cardiovascular outcomes. Moreover, lowering LDL cholesterol to levels below previous targets provided additional benefit. (Funded by Merck; IMPROVE-IT ClinicalTrials.gov number, NCT00202978.)

Abstract: Previous studies have reported an association between a more pro-inflammatory diet profile and various chronic metabolic diseases. The Dietary Inflammatory Index (DII) was used to assess the inflammatory potential of nutrients and foods in the context of a dietary pattern. We prospectively examined the association between the DII and the incidence of cardiovascular disease (CVD: myocardial infarction, stroke or cardiovascular death) in the PREDIMED (Prevencion con Dieta Mediterranea) study including 7216 high-risk participants. The DII was computed based on a validated 137-item food frequency questionnaire. Multivariate-adjusted hazard ratios (HR) and 95% confidence intervals of CVD risk were computed across quartiles of the DII where the lowest (most anti-inflammatory) quartile is the referent. Risk increased across the quartiles (i.e., with increasing inflammatory potential): HRquartile2 = 1.42 (95%CI = 0.97-2.09); HRquartile3 = 1.85 (1.27-2.71); and HRquartile4 = 1.73 (1.15-2.60). When fit as continuous the multiple-adjusted hazard ratio for each additional standard deviation of the DII was 1.22 (1.06-1.40). Our results provide direct prospective evidence that a pro-inflammatory diet is associated with a higher risk of cardiovascular clinical events.

Abstract: Statins are used extensively as anti-hyperlipidemic agents. In addition to curtailing cholesterol synthesis they have been found to have multiple actions unrelated to cholesterol lowering "the pleiotropic effects," which includes inhibition of inflammation. We aimed at investigating the effect of pitavastatin a 3rd generation statin, in suppressing acute inflammation in rat paw edema model. Male Sprague-Dawley rats were randomly assigned to one of five groups (n=8): Control, indomethacin and pitavastatin (0.2mg/kg, 0.4mg/kg, 0.8mg/kg) treated. 1 hour following treatment, inflammation was induced by sub-plantar injection of egg albumin into the hind paw. Anti-inflammatory effect was evaluated by measurement of edema formation every half hour for three hours, assessment of polymorphonuclear leukocyte (PMNL) infiltration and measurement of tissue damage in skin biopsies. Ascending doses of pitavastatin were found to attenuate these parameters. The lowest dose of pitavastatin (0.2mg/kg) was found to significantly reduce edema volume, PMNL infiltration and tissue damage. The efficacy of the smallest dose was found comparable to indomethacin.

Abstract: Purpose: To assess the relationship between total, calcified, and noncalcified coronary plaque burdens throughout the entire coronary vasculature at coronary computed tomographic (CT) angiography in relationship to cardiovascular risk factors in asymptomatic individuals with low-to-moderate risk. Materials and Methods This HIPAA-compliant study had institutional review board approval, and written informed consent was obtained. Two hundred two subjects were recruited to an ongoing prospective study designed to evaluate the effect of HMG-CoA reductase inhibitors on atherosclerosis. Eligible subjects were asymptomatic individuals older than 55 years who were eligible for statin therapy. Coronary CT angiography was performed by using a 320-detector row scanner. Coronary wall thickness and plaque were evaluated in all epicardial coronary arteries greater than 2 mm in diameter. Images were analyzed by using dedicated software involving an adaptive lumen attenuation algorithm. Total plaque index (calcified plus noncalcified plaque) was defined as plaque volume divided by vessel length. Multivariable regression analysis was performed to determine the relationship between risk factors and plaque indexes. Results The mean age of the subjects was 65.5 years +/- 6.9 (standard deviation) (36% women), and the median coronary artery calcium (CAC) score was 73 (interquartile range, 1-434). The total coronary plaque index was higher in men than in women (42.06 mm2 +/- 9.22 vs 34.33 mm2 +/- 8.35; P <.001). In multivariable analysis controlling for all risk factors, total plaque index remained higher in men than in women (by 5.01 mm2; P =.03) and in those with higher simvastatin doses (by 0.44 mm2/10 mg simvastatin dose equivalent; P =.02). Noncalcified plaque index was positively correlated with systolic blood pressure (beta = 0.80 mm2/10 mg Hg; P =.03), diabetes (beta = 4.47 mm2; P =.03), and low-density lipoprotein (LDL) cholesterol level (beta = 0.04 mm2/mg/dL; P =.02); the association with LDL cholesterol level remained significant (P =.02) after additional adjustment for the CAC score. Conclusion LDL cholesterol level, systolic blood pressure, and diabetes were associated with noncalcified plaque burden at coronary CT angiography in asymptomatic individuals with low-to-moderate risk. (c) RSNA, 2015 Online supplemental material is available for this article.

Abstract: PURPOSE: Identify the main pharmacological classes inducing pancreatitis using spontaneous reports recorded in the French pharmacovigilance database (FPVD). METHODS: Cases of pancreatitis recorded in FPVD between January 1st 1985 and December 31st 2013 were selected using the 2001 consensus conference criteria of the French High Health Authority. RESULTS: During this period, 2975 observations were selected with 1151 fulfilling criteria of drug-induced pancreatitis (i.e. 0.22% of total notifications in the FPVD). According to ATC classification, the pharmacological classes most frequently found were antiinflammatory, analgesic, lipid-lowering, immunosuppressive and insulin secreting drugs. For some drugs (metformin, omeprazole, etc.) pancreatitis was "unlabelled" in the summary of product characteristics. CONCLUSIONS: This review allows to identify the main classes currently involved in spontaneous reporting of pancreatitis in France.

Abstract: OBJECTIVE: Kidney ischemia and reperfusion (I/R) injury-associated acute and chronic kidney injury often leads to cardiac dysfunction, which may involve depletion of intracellular NAD(+) (the oxidized form of the nicotinamide adenine dinucleotide coenzyme) and reduction in intracellular adenosine triphosphate (ATP) levels, resulting in mitochondrial dysfunction. We examined whether treatment with niacin, an antioxidant and a component of NAD+, protects cardiac function and improves myocardial mitochondrial metabolism during kidney I/R injury. METHODS: Studies were performed in Sprague-Dawley male rats divided into sham-operated, kidney I/R, and niacin-treated kidney I/R groups. Niacin was administered 3 days before the ischemia through 7 days of reperfusion. Kidney ischemia was conducted by bilateral occlusion of renal pedicles for 45 minutes, followed by releasing the clamps and closing the abdominal incision. After 7 days of reperfusion, we measured the cardiac function using a simultaneous pressure-volume catheter, cardiac biomarker (troponin T; cTnT), and kidney injury marker (creatinine and blood urea nitrogen). Myocardial malondialdehyde level and peroxisome proliferator-activated receptor-gamma coactivator (PGC)-1alpha mRNA expression also were measured. RESULTS: Kidney I/R injury impairs cardiac function, induces myocardial and kidney injury, and markedly increases myocardial PGC-1alpha mRNA expression, suggesting utilizing more free fatty acid for ATP production. Niacin treatment improved cardiac function, reduced oxidative stress, and sustained PGC-1alpha expression (P < .05). CONCLUSIONS: Kidney I/R-associated cardiac dysfunction is likely associated with increases in myocardial lipid peroxidation and utilizing more free fatty acid for ATP production. Niacin improves mitochondrial metabolism and reduced myocardial oxidative stress.