ABSTRACT
Residual risk, which cannot be prevented by statins alone, must be controlled for inhibiting the onset of coronary events. Omega-3 polyunsaturated fatty acids (PUFAs) play an important role in controlling residual risk. The Japan eicosapentaenoic acid (EPA) Lipid Intervention Study demonstrated the inhibitory effect of high-purity EPA preparations on the residual risk of cardiovascular events. Omega-3 PUFAs inhibit coronary artery disease (CAD) through various actions, including triglyceride-lowering action. Besides lipid metabolism, platelet aggregation inhibition, anti-inflammatory effects, improved vascular endothelium function, and anti-hypertensive action contribute to arteriosclerosis inhibition. Conversely, several recent studies did not demonstrate the efficacy of omega-3 PUFAs for CAD prevention. PUFAs levels may need to exceed a threshold for anti-arteriosclerotic action. The efficacy of EPA might depend on the baseline value of the EPA/arachidonic acid (AA) ratio prior to EPA administration. This baseline EPA/AA ratio value varies according to country and region as well as changes of dietary habits. More global research in this field is needed to identify an optimal omega-3 PUFAs administration strategy.


ABSTRACT
This phase 3, multiregional, randomized, double-blind, placebo-controlled study assessed the efficacy/safety profile of anacetrapib added to ongoing therapy with statin +/- other lipid-modifying therapies in patients with hypercholesterolemia who were not at their low-density lipoprotein (LDL-C) goal (as per the National Cholesterol Education Program Adult Treatment Panel III guidelines) and in those with low high-density lipoprotein cholesterol (HDL-C). Patients on a stable dose of statin +/- other lipid-modifying therapies and with LDL-C >/=70 to <115, >/=100 to <145, >/=130, or >/=160 mg/dl for very high, high, moderate, or low CHD risk or at LDL-C goal (per CHD risk category) with HDL-C </=40 mg/dl were randomized in a ratio of 1:1 to anacetrapib 100 mg (n = 290) or placebo (n = 293) for 24 weeks, followed by a 12-week off-drug phase. The co-primary end points were % change from baseline in LDL-C and HDL-C and the safety profile of anacetrapib. Treatment with anacetrapib reduced LDL-C (BQ) by 37% (95% confidence interval -42.5, -31.0) and increased HDL-C by 118% (95% confidence interval 110.6, 125.7) relative to placebo (p <0.001 for both). Anacetrapib also reduced non-HDL-C, apolipoprotein B, and lipoprotein a and increased apolipoprotein AI versus placebo (p <0.001 for all). There were no clinically meaningful differences between the anacetrapib and placebo groups in the % patients who discontinued drug due to an adverse event or in abnormalities in liver enzymes, creatine kinase, blood pressure, electrolytes, or adjudicated cardiovascular events. Treatment with anacetrapib substantially reduced LDL-C and also increased HDL-C and
was well tolerated over 24 weeks in statin-treated patients with hypercholesterolemia or low HDL-C.


**ABSTRACT**

BACKGROUND: There is vast evidence that the renin-angiotensin system is not the sole determinant of blood pressure (BP) elevation in human renovascular hypertension or the relevant experimental models. This study tested the hypothesis that kidney deficiency of 20-hydroxyeicosatetraenoic acid (20-HETE), a product of cytochrome P450 (CYP)-dependent omega-hydroxylase pathway of arachidonic acid metabolism, is important in the pathophysiology of the maintenance phase of 2-kidney, 1-clip (2K1C) Goldblatt hypertension.

MATERIALS AND METHODS: In 2K1C Goldblatt rats with established hypertension, angiotensin II, angiotensin 1-7, 20-HETE concentrations and gene expression of CYP4A1 enzyme (responsible for 20-HETE formation) of the nonclipped kidney were determined. We examined if 14 days administration of fenofibrate, a lipid-lowering drug, would increase CYP4A1 gene expression and renal 20-HETE formation, and if increased 20-HETE concentrations in the nonclipped kidney would decrease BP (telemetric measurements).

RESULTS: CYP4A1 gene expression, 20-HETE and angiotensin 1-7 concentrations were lower and angiotensin II levels were higher in the nonclipped kidney of 2K1C rats than in sham-operated rats. Fenofibrate increased CYP4A1 gene expression and 20-HETE concentration in the nonclipped kidney and significantly decreased BP in 2K1C rats but did not restore it to normotensive range. The treatment did not change BP in sham-operated rats.

CONCLUSIONS: Our results suggest that alterations in the RAS and CYP-dependent omega-hydroxylase metabolites of arachidonic acid in the nonclipped kidneys are both important in the pathophysiology of the maintenance phase of 2K1C Goldblatt hypertension. Therefore, fenofibrate treatment effectively attenuated hypertension, probably via stimulation of 20-HETE formation in the nonclipped kidney.


**ABSTRACT**

BACKGROUND AND AIMS: The effect of LDLc lowering with PCSK9 antibodies on tendon xanthomas (TX) is unknown. METHODS: TX was measured in 24 heterozygous familial hypercholesterolemia (HeFH) cases and in 24 HeFH controls with or without PCSK9 inhibitors for at least one year. RESULTS: Exposure to PCSK9 inhibitors in cases was 2.96 +/- 1.33 years. LDLc decreased 80.8 +/- 7.66% in cases and 56.9 +/- 11.1% in controls. There was a decrease in maximum (-5.03%) and mean (-5.32%) TX in cases but not in controls (+3.97%, +3.16, respectively, p = 0.01). PCSK9 inhibitor treatment was independently associated with TX reduction. CONCLUSION: Addition of a PCSK9 inhibitor to statin and ezetimibe resulted in a greater decrease in LDLc and TX after 3 years of treatment.
BACKGROUND AND AIMS: Overt atherosclerotic cardiovascular disease (ASCVD) warrants aggressive lipid lowering. Imaging for ambiguous symptoms suggesting ischemia or for clarification of CV risk in asymptomatic individuals often uncovers previously unknown ASCVD. Guidelines do not provide clear recommendations for aggressive lipid lowering in such cases. We explored physicians' perception, as influenced by tests that detect ASCVD, regarding appropriateness of getting to lipid goals and for theoretically accessing proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i). METHODS: A questionnaire was developed including cases of low to high CV risk, chronic kidney disease (CKD) or type 2 diabetes mellitus (T2DM). Each case was considered with or without angina symptoms and, in turn, whether testing identified previously unknown advanced, early/subclinical or no ASCVD. Synthesis of responses was facilitated by using a scale for perceived appropriateness from 1 (lowest) to 9 (highest).

RESULTS: Getting to goal and, if not achieved by statins and/or ezetimibe, accessing PCSK9i was considered appropriate in patients with T2DM with preclinical or advanced ASCVD, patients with moderate or high CV risk and advanced ASCVD, patients with CKD or low CV risk with angina symptoms and advanced ASCVD. For most of the remaining cases adding PCSK9i was considered only possibly appropriate. CONCLUSIONS: Physicians' perception of appropriateness for achieving lipid goals, including access to PCSK9i, is markedly influenced by detection of previously unknown ASCVD. Since these commonly encountered scenarios do not clearly meet current indications for PCSK9i, our data identify pressing areas requiring further research.


ABSTRACT

BACKGROUND & AIMS: Lipoprotein(a) [Lp(a)] is a low-density lipoprotein (LDL)-like particle that associates with major adverse cardiovascular events (MACE). We examined relationships between Lp(a) measurements and changes in coronary atheroma volume following long-term maximally-intensive statin therapy in coronary artery disease patients. METHODS: Study of coronary atheroma by intravascular ultrasound: Effect of Rosuvastatin Versus Atorvastatin (SATURN) used serial intravascular ultrasound measures of coronary atheroma volume in patients treated with rosuvastatin 40 mg or atorvastatin 80 mg for 24 months. Baseline and follow-up Lp(a) levels were measured in 915 of the 1039 SATURN participants, and were correlated with changes in percent atheroma volume (DeltaPAV). RESULTS: Mean age was 57.7 +/- 8.6 years, 74% were men, 96% were Caucasian, with statin use prior to study enrolment occurring in 59.3% of participants. Baseline [median (IQR)] LDL-cholesterol (LDL-C) and measured Lp(a) levels (mg/dL) were 114 (99, 137) and 17.4 (7.6, 52.9) respectively; follow-up measures were 60 (47, 77), and 16.5 (6.7, 57.7) (change from baseline: p < 0.001, p = 0.31


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respectively). At baseline, there were 676 patients with Lp(a) levels <50 mg/dL [median Lp(a) of 10.9 mg/dL], and 239 patients with Lp(a) levels >/= 50 mg/dL [median Lp(a) of 83.2 mg/dL]. Quartiles of baseline and follow-up Lp(a) did not associate with DeltaPAV. Irrespective of the achieved LDL-C (<vs. >/=70 mg/dL), neither baseline nor on-treatment (<vs. >/=median) Lp(a) levels significantly associated with DeltaPAV. No significant differences were observed in DeltaPAV in Lp(a) risers versus non-risers, nor in those patients with baseline or on-treatment Lp(a) levels <vs. > 50 mg/dL. CONCLUSIONS: In coronary artery disease patients prescribed long-term maximally intensive statin therapy with low on-treatment LDL-C levels, measured Lp(a) levels (predominantly below the 50 mg/dL threshold) do not associate with coronary atheroma progression. Alternative biomarkers may thus associate with residual cardiovascular risk in such patients.


ABSTRACT
BACKGROUND AND AIMS: The inflammatory process (with TNFalpha, interleukin-6 and interleukin-10 involvement) plays a key role in the development, progression and destabilization of atherosclerotic plaques. The aim of this study was to assess the importance of double-checked measurements of TNFalpha, interleukin-6 (IL-6) and interleukin-10 (IL-10) serum levels in patients with internal carotid artery (ICA) stenosis to determine the dynamics of changes in the stenosis degree and in the ultrasound plaque morphology. METHODS: The study included 65 patients with ICA stenosis. Ultrasound of the carotid arteries was performed during qualification and every 3 months to identify any progression of stenosis degree and dynamics of changes in plaque morphology. Serum concentrations of TNF-alpha, IL-6 and IL-10 were measured during qualification and at month 6 of the study. Calculations considered cytokine concentrations and their indices determined as relative differences of cytokine levels assessed in the first and in second tests. RESULTS: Patients with increasing degree of ICA stenosis had higher indices of IL-6 and IL-10 than patients without any increase in the stenosis degree. In patients with unfavorable dynamics of changes in plaque morphology, significantly higher levels of interleukin-6 were found in the second test; these patients had higher indices of IL-6 and IL-10 than patients with favorable dynamics of atherosclerotic plaque morphology on ultrasound. CONCLUSIONS: Long-term trends in serum concentrations of IL-6 and IL-10 in patients with ICA stenosis allow to predict the progression of the degree of stenosis and the unfavorable change of atherosclerotic plaque morphology.


ABSTRACT
Rosuvastatin is an HMG-CoA reductase inhibitor widely used for treating hypercholesterolaemia. We investigated whether genetic polymorphisms in solute carrier
organic anion transporter 2B1 (SLCO2B1) affect the lipid-lowering effect of rosvastatin in healthy adults with elevated low-density lipoprotein (LDL). This study included 18 volunteers with LDL levels above 130 mg/dL. Rosuvastatin (20 mg) was administered once a day for 8 weeks. Blood samples were drawn before and after the 8-week treatment to measure changes in lipid levels. The presence of single nucleotide polymorphisms (SNPs) of SLCO2B1 (c.935G>A and c.1457C>T), SLCO1B1 (c.521C>T, c.388A>G, and c.-11187G>A) and ABCG2 (c.421C>A) were determined by genotyping. Responses to rosvastatin were compared between wild-type and variant genotypes using permutation test on each polymorphism. In volunteers with SLCO2B1 c.935G>A (rs12422149) variant, rosvastatin was less effective at lowering LDL (mean % decrease: GG 62.8% GA 50.6% AA 49.3%, p=0.012) and apoprotein B (mean % decrease: GG 52.1% GA 42.8% AA 42.8%, p=0.036). Regarding SLCO2B1 c.1457C>T (rs2306168) SNP, there was no significant difference between wild-type and variant genotypes. This study demonstrated that SLCO2B1 c.935G>A (rs12422149) polymorphism influenced the lipid-lowering effects of rosvastatin in volunteers with hypercholesterolaemia. This article is protected by copyright. All rights reserved.


ABSTRACT

The elevated systemic levels of cytokines in rheumatoid arthritis (RA) can change the expression of metabolic enzymes and transporters. Given that statins are lipid-lowering agents frequently used in RA patients with concurrent cardiovascular diseases, the objective of the present study was to investigate the impacts of RA on the pharmacokinetics of statins of different disposition properties in rats with collagen-induced arthritis (CIA). The expression of metabolic enzymes and transporters in tissues of CIA rats were analyzed by RT-qPCR. Statins were given to CIA rats and controls through different routes, respectively. Blood samples were collected and analyzed by UPLC/MS/MS. Isolated microsomes and hepatocytes were used to determine the metabolic and uptake clearance of statins. The results showed that, compared with controls, the mRNA levels of intestinal Cyp3a1 and hepatic Cyp2c6, Cyp2c7, Cyp3a1, Oatp1a1, Oatp1b2, Oatp1a4, and Mrp2 were markedly decreased in the CIA rats. The maximal metabolic activities of Cyp2c and Cyp3a were reduced in liver microsomes of CIA rats. When given orally or injected through hepatic portal vein, the systemic levels of fluvastatin, simvastatin, and atorvastatin, but not of rosvastatin and pravastatin, were increased in CIA rats. The metabolic clearance of simvastatin and hepatic uptake clearance of fluvastatin and atorvastatin were decreased in CIA rats. These findings suggest that the changes in the expression of enzymes and/or transporters in CIA rats differentially affect the pharmacokinetics of statins.


ABSTRACT
Taking statins MA can cause increase in the level of aspartate and alanine aminotransferase. The aim of this study was to assess the usefulness of melatonin in counteracting the adverse hepatic events from statins. Methods. The research program included 60 patients (aged 47-65 years, 41 women and 19 men) with hyperlipidemia taking atorvastatin or rosuvastatin at a dose of 20-40 mg daily. The patients were randomly allocated in two groups. Group I (n = 30) was recommended to take the same statin at a standardized daily dose of 20 mg together with melatonin at a dose of 2 x 5 mg. Group II (n = 30) patients took statin with placebo at the same dose and time of the day. Follow-up laboratory tests (AST, ALT, GGT, and ALP) were evaluated after 2, 4, and 6 months of treatment. Results. In Group I the levels of all enzymes decreased after 6 months, particularly AST, 97,2 +/- 19,1 U/L versus 52,8 +/- 12,3 U/L (p < 0,001); ALT, 87,4 +/- 15,6 U/L versus 49,8 +/- 14,5 U/L (p < 0,001); and GGT, 84,1 +/- 14,8 U/L versus 59,6 U/L (p < 0,001). Conclusion. Melatonin exerts a hepatoprotective effect in patients taking statins.


ABSTRACT

BACKGROUND: Obesity is associated with numerous metabolic and inflammatory disorders. The current study was aimed to evaluate the effects of vitamin D administration on the markers of oxidative stress and inflammation in the cardiac tissue of high-fat diet induced obese rats.

METHODS: In the beginning of the study, 40 male Wistar rats were divided into two groups: normal diet (ND) and high fat diet (HFD) for 16 weeks; then each group subdivided into two groups including: ND, ND + vitamin D, HFD and HFD + vitamin D. Vitamin D supplementation was done for 5 weeks at 500 IU/kg dosage. Tumor necrosis factor (TNF)-alpha concentration and markers of oxidative stress including glutathione peroxidase (GPx), superoxide dismutase (SOD), malondialdehyde (MDA) and catalase (CAT) concentrations in the cardiac tissue and serum concentrations of lipids in rats were determined using ELISA kits and spectrophotometry methods respectively. RESULTS: According to our results, GPx activity in ND and ND + vitamin D group was significantly higher compared with HFD group. Similarly, SOD activity was also significantly increased in ND + vitamin D group compared with ND and HFD groups. Moreover, vitamin D administration, significantly reduced catalase activity in ND + vitamin D and HFD + vitamin D groups (P < 0.05). TNF-alpha concentration in heart tissue in ND + vitamin D group significantly reduced compared with ND group. Cardiac tissue MDA concentration in baseline or after vitamin D administration did not changed significantly. CONCLUSION: Vitamin D improved cardiac oxidative stress and inflammatory markers in HFD induced obese rats. Further studies in human models are needed to further confirm the use of this nutrient in daily clinical practice.


ABSTRACT
BACKGROUND: Atherogenic dyslipidemia is associated with poor cardiovascular outcomes, yet markers of this condition are often ignored in clinical practice. Here, we address a clear evidence gap by assessing the prevalence and treatment of two markers of atherogenic dyslipidemia: elevated triglyceride levels and low levels of high-density lipoprotein cholesterol.

METHODS: This cross-sectional observational study assessed the prevalence of two atherogenic dyslipidemia markers, high triglyceride levels and low high-density lipoprotein cholesterol levels, in the study population from the European Study on Cardiovascular Risk Prevention and Management in Usual Daily Practice (EURika; N = 7641; of whom 51.6% were female and 95.6% were White/Caucasian). The EURika population included European patients, aged at least 50 years with at least one cardiovascular risk factor but no history of cardiovascular disease.

RESULTS: Over 20% of patients from the EURika population have either triglyceride or high-density lipoprotein cholesterol levels characteristic of atherogenic dyslipidemia. Furthermore, the proportions of patients with one of these markers were higher in subpopulations with type 2 diabetes mellitus or those already calculated to be at high risk of cardiovascular disease. Approximately 55% of the EURika population who have markers of atherogenic dyslipidemia are not receiving lipid-lowering therapy. CONCLUSIONS: A considerable proportion of patients with at least one major cardiovascular risk factor in the primary cardiovascular disease prevention setting have markers of atherogenic dyslipidemia. The majority of these patients are not receiving optimal treatment, as specified in international guidelines, and thus their risk of developing cardiovascular disease is possibly underestimated. TRIAL REGISTRATION: The present study is registered with ClinicalTrials.gov (ID: NCT00882336).


ABSTRACT

INTRODUCTION: The risk of recurrent stroke is high in patients with intracranial atherosclerotic stenosis (ICAS). Statin use has been demonstrated to decrease the incidence of stroke by reducing atherosclerotic plaque burden. However, its effect on the hemodynamic situation and cerebral perfusion status has not yet been validated. With the use of computed tomography perfusion (CTP), we aim to evaluate the impact of Rosuvastatin on cerebral hemodynamic changes, as well as the downstream perfusion. METHOD: Cerebral blood flow evaluation of intensive rosuvastatin therapy in patients with intracranial arterial atherosclerotic stenosis (CEIRIS) is a single-center, prospective, randomized, parallel-group, and open-label trial, and it will include 50 participants as estimated. Patients with moderate to severe (50%-99%) ICAS are randomized 1:1 to 10 mg/day or 20 mg/day Rosuvastatin and followed every 13 weeks until 52 weeks. The primary outcome for the trial is the change in the relative regional cerebral blood flow evaluated by CTP after 52 weeks of Rosuvastatin treatment. The secondary outcomes are cerebral blood volume, change in the degree of stenosis of the target vessel and lipid parameters. CONCLUSION: The CEIRIS trial about the effects of statin on the temporal hemodynamic progression of ICAS may extend our understanding of the basic pathophysiology and mechanisms of stroke in ICAS patients.

PM: [PubMed Link]

**ABSTRACT**

INTRODUCTION: Many studies have highlighted the important role of PCSK9 in the development of cardiometabolic changes and its possible function as a biomarker of myocardial infarction or ischemic heart disease. This study aimed to determine the relationship between circulating PCSK9 levels and subclinical vascular changes in the group of low risk patients without manifest cardiovascular diseases. METHODS: In this study, 120 healthy patients, free of manifest cardiovascular diseases, diabetes mellitus, and without lipid-lowering therapy, were divided into three groups based on BMI: normal weight (N = 50), overweight (N = 30), and obese (N = 40). Biochemical parameters, including basic lipid and non-lipid ones, were analyzed. PCSK9 levels were measured by ELISA, vascular changes were quantified by carotid ultrasound (carotid artery intima-media thickness, cIMT), and arterial stiffness parameters (pulse wave velocity, PWV; augmentation index, AI; stiffness parameter, beta) were measured by an echotracking method. RESULTS: Plasma levels of PCSK9 significantly increased in obese (172.78 +/- 51.67 ng/mL) in comparison with overweight (120.14 +/- 37.64, p < 0.001) and normal weight groups (114.92 +/- 35.87, p < 0.001). Differences between the overweight and normal weight groups were not significant (p = 0.85). The level of PCSK9 significantly correlated with values of BMI (p < 0.001, r = 0.38). In addition to increase in laboratory parameters associated with moderate metabolic changes, significant increase in cIMT and parameters of vascular changes (beta, AI, PWV) were detected in groups with elevated BMI. Significant positive linear correlation of PCSK9 concentrations and cIMT (p < 0.001, r = 0.39), PWV (p < 0.001, r = 0.31), and beta (p < 0.001, r = 0.3) were found. In multivariable regression analysis after adjusting for gender, age, BMI, and LDL, the impact of PCSK9 on cIMT, beta, and PWV remained significant (p = 0.006, 0.03, and 0.002, respectively). CONCLUSION: PCSK9 plasma levels significantly correlated with subclinical vascular changes and their values were significantly elevated in obese subjects. We assume that PCSK9 could be used as a predictor of early vascular involvement, prior to the existence of manifest atherosclerosis. These results also highlight the role of anti-PCSK9 treatment in primary prevention.


PM: [PubMed Link]

**ABSTRACT**

We have previously shown that the combination of pravastatin and sarpogrelate is synergistically beneficial for atherosclerosis. In this study, we investigated whether the pravastatin-sarpogrelate combination was sufficient for treatment in an old mouse model of atherosclerosis or if additional intervention would be needed to address the newly included aging factor and its complex pathophysiological impact on the atherosclerogenic state. We added an anti-TNF biologic to the combination treatment cocktail because of the known pathologic roles of TNF in the aging process. Sixty-week-old low-density lipoprotein receptor knockout mice were fed a high-fat, high-cholesterol diet and treated with the sarpogrelate and
pravastatin combination, etanercept alone, or the triple combination. Although, etanercept alone did not significantly reduce aortic root and atherosclerotic plaque areas, the pravastatin-sarpregrelate combination and pravastatin-sarpregrelate-etanercept triple therapy significantly reduced the plaque areas. Surprisingly, TNF-inhibition was critically required to reduce the plaque areas of aortic roots and the expression of ICAM-1, MOMA-2, and TNF. More importantly, a lipid-lowering effect by pravastatin was observed only in the triple therapy group and not in the pravastatin and sarpregrelate combination group. These results suggest that TNF-inhibitory intervention should be added to the conventional therapy as a novel strategy for treating the elderly patients with atherosclerosis. This article is protected by copyright. All rights reserved.


ABSTRACT

AIM: To characterize the single-dose pharmacokinetics (PK) and pharmacodynamics (PD) of bococizumab, a monoclonal antibody inhibiting proprotein convertase subtilisin/kexin type 9 (PCSK9), administered subcutaneously (s.c.) to the abdomen, thigh, or upper arm (NCT02043301). METHODS: Seventy-five adults with low-density lipoprotein cholesterol (LDL-C) >/=130 mg/dL and not on background lipid-lowering therapy were randomized (1:1:1) to a single 150-mg s.c. dose of bococizumab administered to the abdomen, thigh, or upper arm. Blood samples for bococizumab and lipids were collected for 12 weeks post-dose. RESULTS: Plasma bococizumab concentration-time profiles and PK parameters were generally similar across injection sites. Mean maximum observed concentration (Cmax) ranged from 8.14 to 11.9 mug/mL and area under the concentration-time curve (AUCinf) ranged from 160.3 to 198.9 mug*day/mL. The median time to Cmax (Tmax) ranged from 4.25 to 6.93 days. Similar LDL-C concentration-time profiles were observed across injection sites, with mean (% coefficient of variation) maximum reductions in LDL-C of -57.5% (15.8), -57.0% (25.9), and -55.0% (24.1) for the abdomen, thigh, and upper arm, respectively. Adverse events (AEs) were mostly mild and generally similar across injection sites. Commonly reported AEs were upper respiratory tract infection (9.3%), headache (6.7%), and injection-site reaction (6.7%). One serious AE was reported (ischemic colitis), which was not considered related to study drug.

CONCLUSIONS: Similar PK profiles and robust LDL-C reductions were observed following single 150-mg s.c. injections of bococizumab administered to the abdomen, thigh, or upper arm in untreated subjects with LDL-C >/=130 mg/dL. Bococizumab was generally well-tolerated following a single 150-mg s.c. administration in this subject population. ClinicalTrials.gov identifier: NCT02043301.


ABSTRACT
Atorvastatin and ticagrelor combination is a widely accepted therapy for secondary prevention of ischaemic heart disease. However, rhabdomyolysis is a well-known rare side effect of statins which should be considered when treatments are combined with cytochrome P450 3A4 enzyme inhibitors. We report a case of atorvastatin and ticagrelor associated severe rhabdomyolysis that progressed to multiorgan failure requiring renal replacement therapy, inotropes, intubation, and mechanical ventilation. Despite withdrawal of the precipitating cause and the supportive measures including renal replacement therapy, creatinine kinase increased due to ongoing rhabdomyolysis rapidly progressing to upper and lower limbs weakness. A muscle biopsy was performed to exclude myositis which confirmed extensive myonecrosis, consistent with statin associated rhabdomyolysis. After a prolonged ventilatory course in the intensive care unit, patient's condition improved with recovery from renal and liver dysfunction. The patient slowly regained her upper and lower limb function; she was successfully weaned off the ventilator and was discharged for rehabilitation. To our knowledge, this is a second case of statin associated rhabdomyolysis due to interaction between atorvastatin and ticagrelor. However, our case differed in that the patient was also on amlodipine, which is considered to be a weak cytochrome P450 3A4 inhibitor and may have further potentiated myotoxicity.


**ABSTRACT**

Rationale: Inflammation is a key contributor to atherosclerosis. MicroRNA-146a (miR-146a) has been identified as a critical brake on pro-inflammatory NF-kappaB signalling in several cell types, including endothelial cells and bone marrow-derived cells. Importantly, miR-146a expression is elevated in human atherosclerotic plaques, and polymorphisms in the miR-146a pre-cursor have been associated with risk of coronary artery disease. Objective: To define the role of endogenous miR-146a during atherogenesis. Methods and Results: Paradoxically, Low-density lipoprotein receptor (Ldlr)-/- mice deficient in miR-146a develop less atherosclerosis, despite having highly elevated levels of circulating pro-inflammatory cytokines. In contrast, cytokine levels are normalized in Ldlr-/-;miR-146a/-/- mice receiving wild-type bone marrow transplantation, and these mice have enhanced endothelial cell activation and elevated atherosclerotic plaque burden compared to Ldlr-/- mice receiving wild-type bone marrow; demonstrating the atheroprotective role of miR-146a in the endothelium. We find that deficiency of miR-146a in bone marrow-derived cells precipitates defects in hematopoietic stem cell function, contributing to extramedullary hematopoiesis, splenomegaly, bone marrow failure and decreased levels of circulating pro-atherogenic cells in mice fed an atherogenic diet. These hematopoietic phenotypes appear to be driven by unrestrained inflammatory signalling that leads to the expansion and eventual exhaustion of hematopoietic cells, and this occurs in the face of lower levels of circulating LDL cholesterol in mice lacking miR-146a in bone marrow-derived cells. Furthermore, we identify Sort1, a known regulator of circulating LDL levels in humans, as a novel target of miR-146a. Conclusions: Our study reveals that miR-146a regulates cholesterol metabolism and tempers chronic inflammatory responses to atherogenic diet by restraining pro-inflammatory signalling in endothelial cells and bone marrow-derived cells.
Higher in PAH group compared to that in Ctr group, and this effect was suppressed by Ator.

Independent relaxations (EDiRs) were determined. Four weeks after MCT injection, mPAP was hypertrophy index (RVHI%), endothelium by MCT injection (40 mg/kg, i.p.). Mean pulmonary artery pressure (mPAP), right ventricular hypertrophy index (RVH%) endothelium-dependent relaxations (EDdRs), and endothelium-independent relaxations (EDiRs) were determined. Four weeks after MCT injection, mPAP was higher in PAH group compared to that in Ctr group, and this effect was suppressed by Ator.
treatment (PAH: 32.19 +/- 0.91 mm Hg vs. LAtor: 19.13 +/- 1.01 mm Hg, HAtor: 17.55 +/- 0.20 mm Hg, p < 0.05). Similar trend of changes in RVHI% was found in the same way. EDDRs of SPA rings in PAH group were markedly decreased 2 and 4 weeks after MCT injection, while in Ator treated groups, the impairment can only be detected 4 weeks after MCT injection. There were no differences in EDIRs among all groups 1 week after MCT injection. However, 2 weeks and 4 weeks after MCT injection, EDIRs were significantly impaired, while in HAtor and LAtor groups, EDIR was only impaired 4 weeks but not 2 weeks after MCT injection. Preventive treatment with atorvastatin for 2 weeks ameliorated endothelium-dependent and endothelium-independent vasodilative dysfunction in small pulmonary artery rings of MCT-induced PAH rats. It suggests that MCT-induced damage of endothelial function was progressing, and Ator was only beneficial in the early stage of MCT-induced PAH.


ABSTRACT

OBJECTIVE: Circulation inflammation markers such as high-sensitive C-reactive protein (hsCRP) and lipoprotein-associated phospholipase A2 (Lp-PLA2) are considered as predictors of cerebral and cardiac vascular diseases. However, the role of hsCRP and Lp-PLA2 in the anterior circulation cerebral infarction (ACI) is to be elaborated. PATIENTS AND METHODS: We included 100 patients with acute anterior circulation cerebral infarction (AaCI group) and 50 non-infarction subjects (control group). Carotid artery was detected by color Doppler ultrasound. Subjects were grouped based on carotid intima-media thickness (IMT) and degree of stability of carotid atherosclerotic plaque. The levels of hsCRP and Lp-PLA2 were measured in corresponding groups and the association was analyzed. RESULTS: hsCRP and Lp-PLA2 levels were the risk factors for AaCI. With the increment of carotid IMT and degree of plaque instability, the level of hsCRP and Lp-PLA2 showed an elevating tendency. hsCRP and Lp-PLA2 levels were significantly higher in plaque formation group than in IMT normal group (P=0.002 and P=0.001, respectively). hsCRP and Lp-PLA2 levels were significantly higher in vulnerable plaque group than in mixed plaque group and stable plaque group (P=0.003, P<0.001 for hsCRP and P<0.001, P<0.001 for Lp-PLA2). Lp-PLA2 was finally included in the atherosclerotic plaque model (OR=1.019, 95% confidence interval (CI): 1.003-1.035, P=0.020) and vulnerable plaque model (OR=1.041, 95%CI: 1.017-1.065, P=0.001) by performing multivariate logistic regression analysis. The area under the ROC curve (AUC) of Lp-PLA2 levels for atherosclerotic plaque was 0.746 (95% CI: 0.628-0.865, P<0.001). The optimal cut-off value for Lp-PLA2 level was 267.5ng/ml, and its sensitivity and specificity for diagnosis of atherosclerotic plaque were 70.8% and 67.1%, respectively. CONCLUSIONS: The current study demonstrates that hsCRP and Lp-PLA2 are among the risk factors for AaCI. Elevated hsCRP and Lp-PLA2 are associated with carotid plaque formation. Univariate and multivariate logistic regression analysis suggests that elevated Lp-PLA2 is the independent risk factor for carotid plaque and its vulnerability.

ABSTRACT
BACKGROUND: Atherosclerotic plaque rupture is the culprit event which underpins most acute vascular syndromes such as acute myocardial infarction. Novel biomarkers of plaque rupture could improve biological understanding and clinical management of patients presenting with possible acute vascular syndromes but such biomarker(s) remain elusive. Investigation of biomarkers in the context of de novo plaque rupture in humans is confounded by the inability to attribute the plaque rupture as the source of biomarker release, as plaque ruptures are typically associated with prompt down-stream events of myocardial necrosis and systemic inflammation. METHODS: We developed a novel approach to identify potential biomarkers of plaque rupture by integrating plaque imaging, using optical coherence tomography, with both plaque and plasma proteomic analysis in a human model of angioplasty-induced plaque disruption. RESULTS: We compared two pairs of coronary plaque debris, captured by a FilterWire Device, and their corresponding control samples and found matrix metalloproteinase 9 (MMP9) to be significantly enriched in plaque. Plaque contents, as defined by optical coherence tomography, affect the systemic changes of MMP9. Disruption of lipid-rich plaque led to prompt elevation of plasma MMP9, whereas disruption of non-lipid-rich plaque resulted in delayed elevation of plasma MMP9. Systemic MMP9 elevation is independent of the associated myocardial necrosis and systemic inflammation (measured by Troponin I and C-reactive protein, respectively). This information guided the selection of a subset of subjects of for further label free proteomics analysis by liquid chromatography tandem mass spectrometry (LC-MS/MS). We discovered five novel, plaque-enriched proteins (lipopolysaccharide binding protein, Annexin A5, eukaryotic translocation initiation factor, syntaxin 11, cytochrome B5 reductase 3) to be significantly elevated in systemic circulation at 5 min after plaque disruption. CONCLUSION: This novel approach for biomarker discovery in human coronary artery plaque disruption can identify new biomarkers related to human coronary artery plaque composition and disruption.


ABSTRACT
PURPOSE OF REVIEW: Monoclonal antibodies that inhibit proprotein convertase subtilisin/kexin type 9 (PCSK9) have emerged as a novel approach to low-density lipoprotein cholesterol (LDL-C) lowering. The potential role of PCSK9 inhibitors in clinical practice will be reviewed. RECENT FINDINGS: Clinical trials have demonstrated that PCSK9 inhibitors produce robust LDL-C lowering when administered either as monotherapy or in combination with statins. This provides the opportunity to achieve effective lipid lowering in familial hypercholesterolemia, patients with either established atherosclerotic cardiovascular disease or high risk primary prevention and an important opportunity to treat patients with statin intolerance. The findings from plaque imaging and patients with established atherosclerotic cardiovascular disease
suggest that PCSK9 inhibition has favorable outcomes beyond improving lipid profiles, which has the opportunity to expand their use. PCSK9 inhibitors represent a new approach to achieving effective cardiovascular risk reduction in a broader number of patients. How these agents will be taken up in clinical practice remains to be determined.


ABSTRACT

PURPOSE OF THE REVIEW: Community-acquired pneumonia (CAP) is still associated with a large burden and causes significant morbidity and mortality. Besides universal vaccination and antibiotic treatment, statins as adjunctive therapy may also have a beneficial role in the prevention and treatment of CAP. Our goal from this review is to discuss the epidemiology of CAP, and role of statins as adjunctive therapy in the development of CAP. RECENT FINDINGS: Statins are lipid-lowering medications characterized by their ability to control hypercholesterolemia in addition to other pleiotropic effects that could explain their role in the pathogenesis of CAP. While most observational studies have shown that statins reduce risk of pneumonia in the general population, patients with diabetes, and recently in patients with myocardial infarction, no randomized controlled trial (RCT) to date has been conducted to assess the efficacy of statins to prevent development of CAP. Given the paucity of robust randomized evidence to assess statin use and the development of CAP, and considering conflicting results of the observational studies, we are not in favor of initiation of statins for either the prevention or treatment of CAP.


ABSTRACT

A defective mucosal barrier function is the principal cause of the uncontrolled onset and progression of a number of human inflammatory gut diseases, most of which are characterized by chronic intermittent immune and inflammatory responses leading to structural intestinal damage, which can represent a potential risk for colorectal cancer development. During the active disease phase the production of pro-inflammatory cytokines and chemokines, and the induction of oxidative reactions by activated leukocytes and epithelial cells represent the main event in intestinal inflammation. Oxidative stress plays a key role in the development of intestinal damage. Indeed reactive oxygen species and their oxidized by-products regulate redox-sensitive signaling pathways and transcription factors, which sustain inflammation within the intestinal layer. Polysaturated fatty acids and cholesterol are the principal targets of oxidative modifications. These lipids, which are cell membrane constituents or are present in food, readily undergo non-enzymatic oxidation to form chemically-reactive species that can induce a wide range of biological effects including inflammation, programmed cell death, and proliferation. In this review we summarize the current knowledge on the role of lipid oxidation products in regulating redox pathways involved in the pathogenesis of inflammation-related gut diseases. In particular, lipid peroxidation end products, such as isoprostanes and aldehydes, and
cholesterol oxidation-derived oxysterols are taken into consideration. We also discuss the hypothesis that controlling oxidative damage and consequently tissue local over-production of lipid oxidation products by using specific antioxidant and anti-inflammatory molecules in the diet may have clinical and therapeutic benefits.


ABSTRACT
OPINION STATEMENT: Atherosclerotic cardiovascular disease (ASCVD) remains the number one killer in the western world. Low-density lipoprotein cholesterol (LDL-C) reduction with statins and ezetimibe has been shown to reduce the risk of cardiovascular events. Now, proprotein convertase subtilisin/kexin type 9 (PCSK9) monoclonal antibodies (mabs) are available for high-risk individuals with ASCVD or familial hypercholesterolemia on maximally tolerated statin therapy but requiring greater LDL-C reduction. PCSK9 mab outcome trial results from the Further Cardiovascular Outcomes Research with PCSK9 Inhibitions in Subjects with Elevated Risk (FOURIER) study, which was presented at the American College of Cardiology in March 2017, which demonstrated a decrease of 15% in primary and 20% secondary end points over a 2-year period [1**]. These results firmly demonstrated additional benefit beyond maximally tolerated statin therapy in high-risk individuals. Thus, management of LDL-C will soon become more complex, as a new class of medication is added to our standard armamentarium. This review explores the discovery of PCSK9, its biology and physiology, and the development of the PCSK9 mabs.


ABSTRACT
SYNOPSIS: Acarbose delays digestion of complex carbohydrates and disaccharides to absorbable monosaccharides, by reversibly inhibiting alpha-glucosidases within the intestinal brush border, thereby attenuating postprandial blood glucose peaks. Clinical trials have demonstrated that acarbose generally improves glycaemic control in patients with non-insulin-dependent diabetes mellitus (NIDDM) managed with diet alone, or with other antidiabetic therapy, as evidenced by decreased postprandial plasma glucose and glycosylated haemoglobin levels. It does not appear to directly alter insulin resistance, but may lower postprandial plasma insulin levels. Fasting plasma glucose, triglyceride and/or cholesterol levels may also be decreased. Acarbose also improved metabolic control in patients with insulin-dependent diabetes mellitus (IDDM), frequently decreasing insulin requirements, although further studies are required in this indication. Improved metabolic control appears to delay or prevent long term vascular complications of diabetes, and indeed, acarbose appeared to inhibit development of such complications in preliminary animal studies, but this finding requires confirmation in clinical studies. While acarbose seldom causes systemic adverse effects, it is associated with a high incidence of gastrointestinal disturbances such as flatulence, abdominal
distension, borborygmus and diarrhoea, caused by fermentation of unabsorbed carbohydrates. However, these symptoms tend to subside with continued treatment and adherence to an appropriate diet. Thus, acarbose appears to be a worthwhile adjunctive therapeutic option for patients with NIDDM inadequately managed by diet alone, or with pharmacological therapy, and possibly also for patients with IDDM. However, further long term efficacy and tolerability data are required, particularly in the latter indication. PHARMACOLOGICAL PROPERTIES: Acarbose is an oligosaccharide which reversibly inhibits intestinal alpha-glucosidase enzymes responsible for digestion of complex carbohydrates and disaccharides to absorbable monosaccharides. Thus, acarbose delays postprandial absorption of glucose, resulting in attenuation of postprandial plasma glucose, insulin and triglyceride peaks in healthy volunteers. The beneficial effects of acarbose on postprandial glucose levels have been confirmed in patients with insulin-dependent or non-insulin-dependent diabetes mellitus (IDDM or NIDDM), whereas postprandial insulin and triglyceride levels were only occasionally lowered. Pooled data from several clinical trials indicate that acarbose lowers postprandial and fasting blood glucose levels in patients with NIDDM by approximately 20 and 10%, respectively, the latter presumably by an indirect mechanism. Acarbose does not appear to exert any direct effect on insulin resistance in humans. By decreasing the hyperglycaemic stimulus to insulin secretion, acarbose attenuates the blood glucose nadir and associated clinical symptoms which occur after carbohydrate ingestion in patients with reactive hypoglycaemia. Delayed carbohydrate digestion increases the amount of fermentable carbohydrate in the bowel, which does not appear to cause calorie loss, because of metabolism to other absorbable nutrients by colonic microflora, but can induce gastrointestinal adverse effects such as flatulence and borborygmi. Acarbose decreases the postprandial gastric inhibitory polypeptide response, while increasing the enteroglucagon response, and also decreases intestinal absorption of iron. It does not generally appear to lower bodyweight in humans, although this effect has consistently been demonstrated in animal models. Acarbose decreases serum triglycerides, cholesterol and free fatty acid levels in animal models of diabetes and/or hyperlipidaemia, but in human studies in diabetic and nondiabetic individuals, does not consistently lower fasting plasma triglycerides and produces only occasional decreases in fasting plasma cholesterol. The Diabetes Control and Complications Trial (DCCT) has demonstrated that optimal control of blood glucose levels can retard long term complications of diabetes. Indeed, acarbose decreases levels of glycosylated haemoglobin in patients with diabetes, and glycosylation of other body proteins in preliminary animal studies. Moreover, acarbose appeared to inhibit development of renal, cardiovascular, retinal, and neurological complications in various animal models of diabetes and/or hyperlipidaemia. The latter findings await confirmation in clinical studies. Consistent with its intestinal site of action, acarbose is minimally (<2%) absorbed in unchanged form following oral administration to healthy volunteers. However, it is rapidly and extensively metabolised by intestinal digestive enzymes, and absorption of metabolites formed in the gut yields a biphasic pattern of absorption in studies with radiolabelled acarbose, with separate peaks at 1 to 2 and 6 to 24 hours. Administration of acarbose 300mg 3 times daily for 90 days to healthy volunteers did not result in accumulation. Acarbose has a small volume of distribution (0.32 L/kg) and was minimally bound to animal plasma proteins at concentrations >/= 1 mug/L, and 98% bound at 0.008 mug/L. Acarbose and/or its metabolites were secreted into breast milk and penetrated across the placental barrier in rats. Approximately 35% of an orally administered dose of
Acarbose is excreted in the urine, virtually all in metabolised form, and approximately 50% in the faeces. The total body clearance of acarbose was around 600 L/h and values of up to 39.5 hours have been reported for the terminal elimination half-life. THERAPEUTIC USE: In noncomparative and placebo-controlled studies of 2 to 12 months' duration, acarbose generally improved metabolic control in patients with NIDDM, whether used with diet alone, or with other antidiabetic agents, including sulphonylureas, biguanides or insulin. Postprandial plasma glucose levels were lowered by approximately 2 to 3 mmol/L and glycosylated haemoglobin levels were also decreased. Fasting plasma glucose and triglyceride levels, and insulin requirements, were also occasionally decreased. Acarbose was not effective in some patients, possibly reflecting low dosages used and/or severe carbohydrate restrictions in some instances, or lack of sensitivity of intestinal alpha-amylases to acarbose. Acarbose tended to be slightly less effective than sulphonylureas and biguanides, particularly with regard to effects on fasting plasma glucose, but was at least as effective as guar gum in 1 study. Acarbose has been less well studied in patients with IDDM, but improved glycaemic control, as evidenced by improved daily blood glucose profiles and decreased glycosylated haemoglobin levels, and frequently, decreased insulin requirements. It may also lower the risk of late hypoglycaemic episodes (those occurring several hours after a meal) in patients with IDDM. Data from preliminary studies indicated that acarbose might be useful in patients with reactive hypoglycaemia, dumping syndrome and types IIb or IV hyperlipidaemia, but to date no large-scale studies appear to have been performed in these indications. TOLERABILITY: Gastrointestinal disturbances such as flatulence, abdominal distension, diarrhoea and borborygmus, caused by fermentation of unabsorbed carbohydrate in the bowel, are the most common adverse effects associated with acarbose therapy and may occur in up to two-thirds of patients. These symptoms generally improve with continued treatment, and may be minimised by initiating therapy at a low dosage and adherence to diet. The tolerability of acarbose in children aged 5 to 16 years is similar to that in adults. Systemic adverse effects are rare during acarbose therapy. However, analysis of data from phase III US studies indicated that anaemia and elevated transaminase levels were significantly more common in acarbose, than in placebo recipients, occurring in 3.8 and 1.1% of patients, respectively. Acarbose was reported to decrease both peak concentrations and area under the concentration-time curve of metformin by 35% when the 2 drugs were given concurrently to healthy volunteers. DOSAGE AND ADMINISTRATION: The recommended starting dose of acarbose for patients with NIDDM is 50mg 3 times daily, taken before meals, which may be increased to 100mg 3 times daily after 6 to 8 weeks if necessary, and subsequently to a maximum of 200mg 3 times daily if required. Dosages used in patients with IDDM in clinical trials were similar to those used in NIDDM. Patients receiving the maximum dose should be monitored closely for elevation of serum transaminase levels, preferably at monthly intervals, for the first 6 months of treatment. Contraindications to acarbose use include inflammatory bowel disease, partial intestinal obstruction or predisposition to intestinal obstruction, chronic intestinal disease associated with marked disorders of absorption or digestion, conditions which might be exacerbated by increased intestinal gas formation (such as hernias), and impaired hepatic function. Additionally, acarbose has not been studied in patients with severe renal impairment. As acarbose may potentiate the hypoglycaemic effects of insulin and sulphonylureas, dosages of these agents may require adjustment when acarbose is administered concurrently. If
hypoglycaemia occurs, patients should take glucose rather than carbohydrate foods. The effects of acarbose may be reduced by concomitant administration of intestinal adsorbents such as charcoal, and digestive enzyme preparations such as amylase or pancreatin, and enhanced by concomitant administration of neomycin or cholestyramine.


**ABSTRACT**

INTRODUCTION: Patients with partial-onset seizures and comorbid cardiovascular disease may concomitantly receive eslicarbazepine acetate (ESL), an antiepileptic drug, and rosuvastatin, an HMG-CoA reductase inhibitor. This study evaluated the effect of multiple-dose ESL on the pharmacokinetic (PK) parameters of a single dose of rosuvastatin in healthy subjects.

METHODS: This was a Phase I, single-center, fixed-sequence, open-label study. Healthy subjects received two treatments, in sequence. Treatment A: a single 40mg oral dose of rosuvastatin on Day 1, followed by a washout period (Days 1-4); treatment B: titration of ESL (400-800mg once daily) on Days 5-18, followed by ESL 1200mg once daily on Days 19-35, with a single dose of rosuvastatin (40mg) on Day 32. Subjects then entered a 2-week follow-up period. Plasma concentrations of rosuvastatin were quantified for PK analyses. Safety and tolerability were assessed throughout the study.

RESULTS: Thirty-three healthy subjects were enrolled and 30 completed the study. Mean rosuvastatin (standard deviation) t1/2 was similar when rosuvastatin was used concomitantly with ESL and when it was used alone (26.5 [16.3]h, and 22.4 [9.5]h, respectively). The geometric least squares mean ratios (90% confidence intervals) of rosuvastatin exposure levels between rosuvastatin used concomitantly with ESL and rosuvastatin used alone were as follows: Cmax, 64.0% (55.9-73.3%); AUC(0-infinity), 63.0% (57.1-69.4%); and AUC(0-last), 60.9% (55.2-67.1%). Concomitant use of ESL and rosuvastatin was generally well tolerated. CONCLUSIONS: Rosuvastatin exposure was 36-39% lower with steady-state administration of ESL, potentially due to reduced oral bioavailability of rosuvastatin. Consequently, when rosuvastatin is used with ESL, a rosuvastatin dose adjustment may be necessary if a clinically significant change in lipids is noted.


**ABSTRACT**

Aims: Proprotein convertase subtilisin/kexin type 9 (PCSK9) has emerged as a promising therapeutic target for the treatment of hypercholesterolaemia and atherosclerosis. PCSK9 binds to the low density lipoprotein receptor and enhances its degradation, which leads to the reduced clearance of low density lipoprotein cholesterol (LDLc) and a higher risk of atherosclerosis. In this study, the AT04A anti-PCSK9 vaccine was evaluated for its therapeutic potential in ameliorating or even preventing coronary heart disease in the atherogenic APOE*3Leiden.CETP mouse model. Methods and results: Control and AT04A vaccine-treated
mice were fed western-type diet for 18 weeks. Antibody titres, plasma lipids, and inflammatory markers were monitored by ELISA, FPLC, and multiplexed immunoassay, respectively. The progression of atherosclerosis was evaluated by histological analysis of serial cross-sections from the aortic sinus. The AT04A vaccine induced high and persistent antibody levels against PCSK9, causing a significant reduction in plasma total cholesterol (-53%, P < 0.001) and LDLc compared with controls. Plasma inflammatory markers such as serum amyloid A (SAA), macrophage inflammatory protein-1beta (MIP-1beta/CCL4), macrophage-derived chemokine (MDC/CCL22), cytokine stem cell factor (SCF), and vascular endothelial growth factor A (VEGF-A) were significantly diminished in AT04A-treated mice. As a consequence, treatment with the AT04A vaccine resulted in a decrease in atherosclerotic lesion area (-64%, P = 0.004) and aortic inflammation as well as in more lesion-free aortic segments (+119%, P = 0.026), compared with control. Conclusions: AT04A vaccine induces an effective immune response against PCSK9 in APOE*3Leiden.CETP mice, leading to a significant reduction of plasma lipids, systemic and vascular inflammation, and atherosclerotic lesions in the aorta.


ABSTRACT

Familial hypercholesterolaemia is an autosomal dominant inherited disorder characterised by elevated low-density lipoprotein cholesterol levels and consequently an increased risk of atherosclerotic cardiovascular disease (ASCVD). Familial hypercholesterolaemia is relatively common, but is often underdiagnosed and undertreated. Cardiologists are likely to encounter many individuals with familial hypercholesterolaemia; however, patients presenting with premature ASCVD are rarely screened for familial hypercholesterolaemia and fasting lipid levels are infrequently documented. Given that individuals with familial hypercholesterolaemia and ASCVD are at a particularly high risk of subsequent cardiac events, this is a missed opportunity for preventive therapy. Furthermore, because there is a 50% chance that first-degree relatives of individuals with familial hypercholesterolaemia will also be affected by the disorder, the underdiagnosis of familial hypercholesterolaemia among patients with ASCVD is a barrier to cascade screening and the prevention of ASCVD in affected relatives. Targeted screening of patients with ASCVD is an effective strategy to identify new familial hypercholesterolaemia index cases. Statins are the standard treatment for individuals with familial hypercholesterolaemia; however, low-density lipoprotein cholesterol targets are not achieved in a large proportion of patients despite treatment. Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors have been shown to reduce low-density lipoprotein cholesterol levels considerably in individuals with familial hypercholesterolaemia who are concurrently receiving the maximal tolerated statin dose. The clinical benefit of PCSK9 inhibitors must, however, also be considered in terms of their cost-effectiveness. Increased awareness of familial hypercholesterolaemia is required among healthcare professionals, particularly cardiologists and primary care physicians, in order to start early preventive measures and to reduce the mortality and morbidity associated with familial hypercholesterolaemia and ASCVD.
BACKGROUND: To evaluate the efficacy of ezetimibe combined with atorvastatin in treatment of carotid artery plaque in patients with type 2 diabetes mellitus complicated with coronary heart disease (CHD). METHODS: A total of 100 patients with carotid atherosclerosis (CAS) confirmed by ultrasound and diagnosed with type 2 diabetes mellitus and CHD were randomly assigned to atorvastatin group (atorvastatin 20 mg/d) or combined treatment group (ezetimibe 10 mg/d and atorvastatin 20 mg/d). All those patients were followed for 12 months. Serum lipid, ALT, AST, CK were measured before and after treatment. Ultrasonography was used to evaluate the stability of carotid artery plaques. RESULTS: After 12 months of treatment, the level of TC, TG, LDL-C, hs-CRP, FPG and HbA1c decreased in both groups compared with before treatment. TC, TG, LDL-C and hs-CRP in the combined treatment group were much lower than that in the atorvastatin group (P <0.05). The IMT and plaque area in the two groups were lower than that before the treatment (P <0.05). IMT and plaques area in the combined treatment group is much lower than that in the atorvastatin group after treatment. There was no significant difference in two groups on the level of ALT, AST, CK compared with baseline after treatment. CONCLUSIONS: The effect of combined use of atorvastatin and ezetimibe was better than atorvastatin alone, which can effectively reduce the blood lipid levels in diabetic patients with CHD and improve plaque stability. Both treatment regimens were safe and well tolerated.

ABSTRACT


ABSTRACT

AIM: Cardiovascular disease is one of the complications of rheumatoid arthritis (RA). We researched the morbidity and severity of existing carotid atherosclerosis plaque and associated risk factors in patients with RA. METHOD: This study included 413 participants, including 208 patients with RA and 205 age- and sex-matched healthy volunteers. Carotid ultrasound, clinical data collection and assessment of cardiovascular risk factors were performed. Atherosclerotic plaque was defined as an intima-media thickness >/= 1.1 mm. Severity of plaque was assessed by plaque score, defined as the sum of the maximal thickness of all plaques in bilateral carotid arteries. RESULTS: Data were analyzed from 200 patients with RA and 202 controls. Carotid plaque was observed more frequently in patients with RA than controls (47.0 vs. 36.1%, P = 0.027). Moreover, plaque score was significantly higher in RA patients (P = 0.032). In logistic regression analysis, RA represented an independent risk factor for the presence of plaque (adjusted odds ratio, 1.68; 95% confidence interval, 1.03-2.74). Comparing RA patients with and without plaque, anti-cyclic citrullinated peptide (anti-CCP) antibodies titer was significantly higher in patients with plaque (315.8 +/- 454.1 U/mL) than in patients without (165.7 +/- 281.1 U/mL; P = 0.005). Moreover, multiple linear regression analysis clarified that anti-CCP antibody titer was associated with plaque score in patients with RA. CONCLUSION: High prevalence of any carotid plaques and severe carotid plaques were more frequent in patients with RA. High titer of anti-CCP antibodies represented a risk factor for severe carotid atherosclerotic plaque in patients with RA.


ABSTRACT

We conducted a post hoc analysis of blood pressure (BP) data from long-term antihypertensive trials to identify predictors of visit-to-visit BP variability (BPV). BPV was defined as the within-subject coefficient of variation in systolic BP from week 12 onward. BP data from the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial, Comparison of Amlodipine Versus Enalapril to Limit Occurrences of Thrombosis, NY92011, and R-0510 trials were pooled and dichotomized into top 25th and bottom 75th percentiles because of positive skew. Significant (P < .001)
predicators of BPV within the top 25th percentile were identified using logistic regression. The baseline characteristics of the pooled cohort (n = 47,558) were similar between patients who received amlodipine (n = 17,499) versus other antihypertensive drugs (n = 29,491). BPV in the top 25th percentile was lower with amlodipine versus other treatments (13.7 +/- 3.2 vs. 14.3 +/- 3.5), with single-study analyses of Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial, and Comparison of Amlodipine Versus Enalapril to Limit Occurrences of Thrombosis all showing BPV was the lowest with amlodipine. Baseline diastolic BP, estimated glomerular filtration rate, and smoking were predictors of BPV, with significant two-way interactions between smoking and both age and body mass index and between systolic BP or diastolic BP and being randomized to treatment other than amlodipine. In conclusion, analysis of BPV required transformation of BP data. After transformation, a number of baseline variables and combinations of variables were predictors of BPV.


ABSTRACT

Context: Angiopoietin-like 3 (ANGPTL3) deficiency in plasma due to loss-of-function (LOF) gene mutations causes familial combined hypobetalipoproteinemia (FHBL) type 2 in homozygotes. However, the lipid phenotype in heterozygotes is much milder and does not appear to relate directly to ANGPTL3 levels. Furthermore, the low LDL phenotype in carriers of ANGPTL3 mutations is unexplained. Objective: To determine whether a reduction below a critical threshold in plasma ANGPTL3 levels is a determinant of lipoprotein metabolism in FHBL2, and to study the whether PCSK9 is involved in determining low LDL levels in this condition. Design: We studied subjects from 19 families with ANGPTL3 mutations, and subjects with FHBL type 1 due to truncated apolipoprotein B (apoB) species. Results: Total cholesterol, HDL-c, triglycerides, and HDL and LDL particle concentration correlated with plasma ANGPTL3 levels, but only when this was below 25% of normal (<60 ng/ml); (ii) VLDL particle concentration strongly correlated with plasma ANGPTL3 when this was below 58% of normal; (iii) both FHBL1 and FHBL2 subjects showed low levels of mature and LDL-bound PCSK9, and higher levels of its furin-cleaved form; and (iv) LDL-bound PCSK9 is protected from cleavage by furin, and binds to the LDL receptor more strongly compared to apoB-free PCSK9. Conclusion: Our studies suggest that the hypolipidemic effects of ANGPTL3 mutations in FHBL2 are dependent on threshold plasma ANGPTL3 levels, with differential effects on various lipoprotein particles. The increased inactivation of PCSK9 by furin in FHBL1 and FHBL2 is likely to cause increased LDL clearance and suggests novel therapeutic avenues.


ABSTRACT

Epidemiologic and animal studies implicate overconsumption of fructose in the development of nonalcoholic fatty liver disease, but the molecular mechanisms underlying fructose-induced
chronic liver diseases remain largely unknown. Here, we have presented evidence supporting the essential function of the lipogenic transcription factor carbohydrate response element-binding protein (ChREBP) in mediating adaptive responses to fructose and protecting against fructose-induced hepatotoxicity. In WT mice, a high-fructose diet (HFrD) activated hepatic lipogenesis in a ChREBP-dependent manner; however, in Chrebp-KO mice, a HFrD induced steatohepatitis. In Chrebp-KO mouse livers, a HFrD reduced levels of molecular chaperones and activated the C/EBP homologous protein-dependent (CHOP-dependent) unfolded protein response, whereas administration of a chemical chaperone or Chop shRNA rescued liver injury. Elevated expression levels of cholesterol biosynthesis genes in HFrD-fed Chrebp-KO livers were paralleled by an increased nuclear abundance of sterol regulatory element-binding protein 2 (SREBP2). Atorvastatin-mediated inhibition of hepatic cholesterol biosynthesis or depletion of hepatic Srebp2 reversed fructose-induced liver injury in Chrebp-KO mice. Mechanistically, we determined that ChREBP binds to nuclear SREBP2 to promote its ubiquitination and destabilization in cultured cells. Therefore, our findings demonstrate that ChREBP provides hepatoprotection against a HFrD by preventing overactivation of cholesterol biosynthesis and the subsequent CHOP-mediated, proapoptotic unfolded protein response. Our findings also identified a role for ChREBP in regulating SREBP2-dependent cholesterol metabolism.


ABSTRACT
AIM: Compare the safety and efficacy of intermittent fenofibrate versus simvastatin in chronic hemodialysis patients. PATIENTS & METHODS: Sixty patients received either fenofibrate 100 mg or simvastatin 20 mg after their dialysis session (parallel study). The safety and efficacy of drugs on lipid profile, oxidized low-density lipoprotein (Ox-LDL), glutathione peroxidase and C-reactive protein were compared before and after 16-week treatment. RESULTS: After treatment, significant increase in glutathione peroxidase, significant decrease in total cholesterol, triglycerides, low density lipoprotein (LDL) and ox-LDL (p < 0.05) and no significant changes in C-reactive protein (p > 0.05) were observed in both groups. Both drugs were well tolerated with no serious side effects reported by the patients. CONCLUSION: Both drugs have comparable efficacy and safety when used as intermittent low dose regimen in hemodialysis. Larger studies with longer follow-up periods are needed to confirm our new findings.


ABSTRACT
OBJECTIVE: To investigate the effect of simvastatin on lipid accumulation and the expression of CXCL16 and Nephrin in murine podocytes induced by oxidized LDL (OxLDL) in order to explore the mechanism of protection. METHODS: Murine podocytes (MPC5) were incubated with OxLDL (80 mug/ml) at different concentrations of simvastatin (0, 1.0, and 2.0 mug/ml) for 48
hours. Oil red O staining was used for the assessment of lipid accumulation in podocytes, and colorimetric cholesterol detection kit was used for the quantitative measurement. CXCL16 and Nephrin expression were detected by using Western blot. RESULTS: OxLDL-treated MPC5 cells exhibited significantly higher intracellular lipid accumulations compared with the untreated group. Colorimetric detection found that total cholesterol was 90.3 +/- 30.1 µg/ml in untreated cells and 226.5 +/- 21.6 µg/ml in OxLDL-treated cells. The difference was statistically significant (p < .01). While cells were treated with both OxLDL and simvastatin, we observed little lipid accumulation. Total cholesterol in OxLDL + simvastatin cells were 151.8 +/- 6.8 µg/ml and 135.5 +/- 26.9 µg/ml under 1.0 µg/ml or 2.0 µg/ml of simvastatin treatment, respectively. Both were statistically significantly lower than that of the OxLDL treated cells (p < .05). Western blot analysis showed that CXCL16 expression was significantly increased (p < .05) in OxLDL-treated cells compared with the untreated cells, and was significantly inhibited by application of simvastatin (p < .05). The analysis of nephrin expression showed that there were no changes in group simvastatin compared with that of control group (p > .05). Nephrin expression was significantly reduced by treatment with OxLDL (p < .01), and was significantly increased by application of simvastatin (p < .05). CONCLUSION: Simvastatin treatment could significantly decrease lipid accumulation in murine podocytes and this protective effect was realized through inhibition of the expression of CXCL16 and increase in the expression of nephrin.


ABSTRACT
Sterol regulatory element-binding protein-2 (SREBP-2) activates transcription of all genes needed for cholesterol biosynthesis. To study SREBP-2 function in intestine, we generated a mouse model (Vil-BP2/-/-) in which Cre recombinase ablates SREBP-2 in intestinal epithelia. Intestines of Vil-BP2/-/- mice had reduced expression of genes required for sterol synthesis, in vivo sterol synthesis rates, and epithelial cholesterol contents. On a cholesterol-free diet, they displayed chronic enteropathy with histological abnormalities of both villi and crypts, growth restriction, and reduced survival that was prevented by supplementation of cholesterol in the diet. Likewise, SREBP-2-deficient enteroids required exogenous cholesterol for growth. Blockade of luminal cholesterol uptake into enterocytes with ezetimibe precipitated acutely lethal intestinal damage in Vil-BP2/-/- mice, highlighting the critical interplay in the small intestine of sterol absorption via NPC1L1 and sterol synthesis via SREBP-2 in sustaining the intestinal mucosa. These data show that small intestine requires SREBP-2 to drive cholesterol synthesis that sustains the intestinal epithelia when uptake of cholesterol from the gut lumen is not available, and provide a unique example of cholesterol auxotrophy expressed in an intact, adult mammal.

**ABSTRACT**

AIMS: Methods for integrating external costs into clinical databases are not well-characterized. The purpose of this research was to describe and implement methods for estimating the cost of hospitalizations, prescriptions, and general practitioner and specialist visits used to manage hyperlipidemia patients experiencing cardiovascular (CV) events in the United Kingdom (UK).

METHODS: This study was a retrospective cohort study using the Clinical Practice Research Datalink and Hospital Episode Statistics data. Costs were incorporated based on reference costs from the National Health Service and labor costs from the Personal Social Services Research Unit. The study population included patients seen by general practitioners in the UK from 2006 to 2012. Patients ≥/≤ 18 years were selected at the time of their first CV-related hospitalization defined as myocardial infarction, ischemic stroke, heart failure, transient ischemic attack, unstable angina, or revascularization. To be included, patients must have received ≥/≤ 2 lipid-lowering therapies. Outcome measures included healthcare utilization and direct medical costs for hospitalizations, medications, general practitioner visits, and specialist visits during the 6-month acute period, starting with the CV hospitalization, and during the subsequent 30-month long-term period.

RESULTS: There were 24,093 patients with a CV hospitalization included in the cohort. We identified and costed 69,240 hospitalizations, 673,069 GP visits, 32,942 specialist visits, and 2,572,792 prescriptions representing 855 unique drug and dose combinations. The mean acute period and mean annualized long-term period costs (2014 pound) were pound4060 and pound1433 for hospitalizations, pound377 and pound518 for GP visits, pound59 and pound103 for specialist visits, and pound98 and pound209 for medications.

CONCLUSIONS: Hospital costs represent the largest portion of acute and long-term costs in this population. Detailed costing using utilization data is feasible and representative of UK clinical practice, but is labor intensive. The availability of a standardized coding system in the UK drug costing data would greatly facilitate drug costing.


**ABSTRACT**

The effects of systemically administered rosuvastatin on alveolar bone loss (ABL), cytokine levels and oxidative status were investigated in rats with ligature-induced periodontitis. Rats were divided randomly into four groups: a non-ligated group (C); a non-ligated+rosuvastatin group (R); a ligated group (P); and a ligated+rosuvastatin group (PR). Ligatures were placed at the maxillary second molars, and rosuvastatin was administered for 14 days. After the rats had been euthanatized, histomorphometric and histological analyses were performed, and the serum levels of interleukin (IL)-1beta, IL-10 and oxidant and antioxidant parameters (malondialdehyde [MDA], superoxide dismutase, glutathione, and glutathione peroxidase) were evaluated by enzyme-linked immunosorbent assay. Rosuvastatin significantly decreased the extent of ABL, inflammatory infiltration and osteoclasts in periodontitis, but increased the numbers of osteoblasts. Although rosuvastatin reduced the levels of IL-1beta, they did not differ significantly between the PR and P groups. In the PR group, not only were IL-10 levels significantly higher but also the ratio of IL-1beta to IL-10 was lower than in the P group.
Although MDA levels were significantly increased in the P group relative to the C group, they did not differ significantly between the PR and C groups. The present data suggest that rosuvastatin decreases ABL in ligation-induced periodontitis, and that its anti-inflammatory effect is more remarkable than its antioxidant effect.


ABSTRACT
OBJECTIVES: To assess the association between biomarkers of thyroid status and 5alpha-stanols in patients with sitosterolemia treated with ezetimibe (EZE). STUDY DESIGN: Eight patients with sitosterolemia (16-56 years of age) were studied during 14 weeks off EZE therapy and 14 weeks on EZE (10 mg/day). Serum thyroid biomarkers (free triiodothyronine [FT3], free thyroxine [FT4], FT3/FT4 ratio, thyroid-stimulating hormone), 5alpha-stanols (sitostanol and cholestanol), and cholestanol precursors (total cholesterol and its synthesis marker lathosterol, and 7alpha-hydroxy-4-cholesten-3-one cholestenol) were measured at baseline and during the 14 weeks off EZE and on EZE. RESULTS: EZE increased FT3/FT4 (10% +/- 4%; P = .02). EZE reduced plasma and red blood cells sitostanol (-38% +/- 6% and -20% +/- 4%; all P < .05) and cholestanol (-18% +/- 6% and -13% +/- 3%; all P < .05). The change in plasma cholestanol level on EZE inversely correlated with the change in FT3/FT4 (r = -0.86; P = .01). EZE lowered total cholesterol (P < .0001) and did not affect 7alpha-hydroxy-4-cholesten-3-one cholestenol. EZE increased (P < .0001) lathosterol initially, but the level was not sustained, resulting in similar levels at week 14 off EZE and on EZE. CONCLUSION: In patients with STSL, 5alpha-stanols levels might be associated with thyroid function. EZE reduces circulating 5alpha-stanols while increasing FT3/FT4, implying increased conversion of T4 to T3, thus possibly improving thyroid hormone status. TRIAL REGISTRATION: ClinicalTrials.govNCT01584206.


ABSTRACT
OBJECTIVES: This study sought to determine whether coronary artery calcium (CAC) could be used to optimize statin allocation among individuals for whom trial-based evidence supports efficacy of statin therapy. BACKGROUND: Recently, allocation of statins was proposed for primary prevention of atherosclerotic cardiovascular disease (ASCVD) based on proven efficacy from randomized controlled trials (RCTs) of statin therapy, a so-called trial-based approach. METHODS: The study used data from MESA (Multi-Ethnic Study of Atherosclerosis) with 5,600 men and women, 45 to 84 years of age, and free of clinical ASCVD, lipid-lowering therapy, or missing information for risk factors at baseline examination. RESULTS: During 10 years' follow-up, 354 ASCVD and 219 hard coronary heart disease (CHD) events occurred. Based on enrollment criteria for 7 RCTs of statin therapy in primary prevention, 73% of MESA participants (91% of those >55 years of age) were eligible for statin therapy according to a trial-based approach. Among those individuals, CAC = 0 was common (44%) and was associated with low
rates of ASCVD and CHD (3.9 and 1.7, respectively, per 1,000 person-years). There was a graded increase in event rates with increasing CAC score, and in individuals with CAC >100 (27% of participants) the rates of ASCVD and CHD were 18.9 and 12.7, respectively. Consequently, the estimated number needed to treat (NNT) in 10 years to prevent 1 event varied greatly according to CAC score. For ASCVD events, the NNT was 87 for CAC = 0 and 19 for CAC >100. For CHD events, the NNT was 197 for CAC = 0 and 28 for CAC >100. CONCLUSIONS: Most MESA participants qualified for trial-based primary prevention with statins. Among the individuals for whom trial-based evidence supports efficacy of statin therapy, CAC = 0 and CAC >100 were common and associated with low and high cardiovascular risks, respectively. This information may guide shared decision making aimed at targeting evidence-based statins to those who are likely to benefit the most.


PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=28623954

ABSTRACT

BACKGROUND: Statins are generally well-tolerated and serious side effects are infrequent, but some patients experience adverse events and reduce their statin dose or discontinue treatment altogether. Alirocumab is a highly specific, fully human monoclonal antibody to proprotein convertase subtilisin/kexin type 9 (PCSK9), which can produce substantial and sustained reductions of low-density lipoprotein cholesterol (LDL-C). METHODS: The randomized, double-blind, placebo-controlled, parallel-group, phase 3 ODYSSEY NIPPON study will explore alirocumab 150 mg every 4 weeks (Q4W) in 163 Japanese patients with hypercholesterolemia who are on the lowest-strength dose of atorvastatin (5 mg/day) or are receiving a non-statin lipid-lowering therapy (LLT) (fenofibrate, bezafibrate, ezetimibe, or diet therapy alone). Hypercholesterolemia is defined as LDL-C >/= 100 mg/dL (2.6 mmol/L) in patients with heterozygous familial hypercholesterolemia or non-familial hypercholesterolemia with a history of documented coronary heart disease, or >/=120 mg/dL (3.1 mmol/L) in patients with non-familial hypercholesterolemia classified as primary prevention category III (i.e. high-risk patients). During the 12-week double-blind treatment period, patients will be randomized (1:1:1) to receive alirocumab subcutaneously (SC) 150 mg Q4W alternating with placebo for alirocumab Q4W, or alirocumab 150 mg SC every 2 weeks (Q2W), or SC placebo Q2W. The primary efficacy endpoint is the percentage change in calculated LDL-C from baseline to week 12. The long-term safety and tolerability of alirocumab will also be investigated. DISCUSSION: The ODYSSEY NIPPON study will provide insights into the efficacy and safety of alirocumab 150 mg Q4W or 150 mg Q2W among Japanese patients with hypercholesterolemia who are on the lowest-strength dose of atorvastatin, or are receiving a non-statin LLT (including diet therapy alone). TRIAL REGISTRATION: ClinicalTrials.gov number: NCT02584504.

ABSTRACT
OBJECTIVE: To better understand the pathogenesis of inflammatory-related diseases after menopause, we studied the adiposity-independent association between endogenous sex hormones and C-reactive protein (CRP), a biomarker of inflammation. METHODS: We conducted a secondary, cross-sectional analysis of baseline data from the Alberta Physical Activity and Breast Cancer Prevention Trial (2003-2007), including 319 healthy, postmenopausal women not using hormone therapy. Multivariable linear regression models related serum CRP levels to estrogens, androgens, and sex hormone-binding globulin (SHBG), all on the natural logarithmic scale. Models were adjusted for age, lipids, medication, and former menopausal hormone therapy use, and also for adiposity (body mass index [BMI], per cent body fat [via whole-body dual x-ray absorptiometry], or intra-abdominal fat area [via computed tomography]). RESULTS: Without adiposity adjustment, estrone, total estradiol, and free estradiol were significantly positively associated with CRP, whereas SHBG was significantly inversely associated with CRP. Of all adiposity measures, adjustment for BMI caused the greatest attenuation of CRP-estrogen associations; only free estradiol (beta = 0.24, 95% confidence interval [CI] 0.06, 0.43) and SHBG (beta = -0.37, 95% CI -0.60, -0.13) associations remained significant. Inverse associations between CRP-total testosterone became stronger with BMI adjustment (beta = -0.20, 95% CI -0.40, -0.01). Differential associations across categories of BMI, former hormone therapy use, and years since menopause were suggestive, but not statistically significant (Pheterogeneity > 0.05). CONCLUSIONS: Prospective and systems epidemiological studies are needed to understand whether or not the cross-sectional associations we observed, independent of adiposity, between CRP-SHBG, CRP-total testosterone, and CRP-free estradiol, are causal.


ABSTRACT
BACKGROUND: The aim of this paper is to explore the application and clinical significance of color Doppler ultrasound (CDU) in diagnosing lower extremity vascular disease in type 2 diabetes mellitus (T2DM) patients. METHODS: The lower extremity arteries of 81 patients with T2DM and 50 control patients were examined by CDU for blood vessel diameter, intima-media thickness, plaque on the vessel wall, lumen stenosis and filling defect in blood flow. The occurrence of diabetes mellitus was investigated in additional T2DM patients of various ages. RESULTS: Left popliteal artery, left and right dorsal artery of the foot; the incidence of atherosclerotic plaque, stenosis and occlusion of the lower extremity vascular lumen of T2DM patients was significantly higher than that in the control group. Vascular disease in the lower extremities was mainly small and medium vascular disease (lower than popliteal artery), especially the dorsal artery of the foot, for which the difference was statistically significant (P<0.05). The elder patients had a greater chance of lower extremity arterial disease. CONCLUSIONS: CDU is the examination method of preference for T2DM patients with lower
extremity vascular disease. It has a very important clinical significance for early diagnosis, prevention and treatment.


ABSTRACT
Taking fish oil supplements in the third trimester of pregnancy was associated with significantly less wheezing or asthma in the child at the age of 3-5 years, according to a randomized clinical trial by Bisgaard et al., NEJM 2017. However, the results of this study should be interpreted with caution. The primary end points were modified at a late stage in the study, and two primary end points, eczema in the first 3 years of life and allergic sensitization at 18 months of age, were demoted to secondary end points, and showed no significant effect of treatment. Furthermore, the age range for the published primary end point, persistent wheeze, differed from that in the protocol. Additional concerns include the emphasis on outcomes by omega-3 fatty acid levels in the blood, a post hoc subgroup analysis not included in the protocol. In our opinion, this study does not justify advising routine fish oil supplements in pregnancy.


ABSTRACT
INTRODUCTION: Cocoa has been known for many health benefits, but its lipid-lowering activity still remains unresolved. OBJECTIVES: To investigate effects of varying amounts of defatted cocoa on serum lipids in cholesterol-fed rats. METHODS: Forty-eight male Sprague-Dawley rats were randomly assigned into four cholesterol-free (control) and four cholesterol-supplemented (experimental) diets containing 0, 1, 2 or 3% defatted cocoa (DC) and given ad libitum to the rats for ten weeks. Serum total cholesterol (TC), low- and very low-density lipoprotein cholesterol (LDL-C and VLDL-C), high-density lipoprotein cholesterol (HDL-C) and triglycerides (TG) were quantified, atherogenic index (AI) was calculated, and other biological parameters were assessed. RESULTS: Food intake and body weight did not respond to DC. Compared to 0% DC, 3% DC had the most prominent effect on serum lipids inducing significant fall in LDL-C and TG, and rise in TC/TG in cholesterol-deprived rats, and increase in VLDL-C and AI, and decrease in HDL-C in cholesterol-fed rats. Differences in lipid variables of rats fed on DC diets were less evident. CONCLUSIONS: Results suggest that, in contrast to cholesterol-free situations, defatted cocoa is seemingly incapable of counteracting the atherogenic effect of cholesterol in rats, perhaps in an interaction that is likely to have clinical implications in cardiometabolic conditions.

**ABSTRACT**

High insulin levels in obese people are considered as a risk factor to induce breast carcinogenesis. And consumption of fish oils which mainly contain omega-3 fatty acids is associated with a reduced risk of breast cancer. However, whether omega-3 free fatty acids (FFAs) modulate insulin signaling pathway to prevent breast cancer is poorly understood. The current study tested the hypothesis that omega-3 FFAs attenuate insulin-induced breast cancer cell proliferation and regulate insulin signaling pathway. We show here that omega-3 FFAs attenuate MCF-7 cell proliferation and Akt and Erk1/2 phosphorylation levels stimulated by insulin. Knockdown Shp2 by siRNA resulted in significantly elevated omega-3 FFAs-activated Akt phosphorylation but failed to change insulin-stimulated Akt and Erk1/2 phosphorylation. And viable cell number was not affected by either downregulation of Shp2 expression or Erk1/2 inhibitor U0126 treatment. These observations indicated that omega-3 FFAs attenuate insulin-promoted breast cancer cell proliferation and insulin-activated Akt phosphorylation.


**ABSTRACT**

Neuronal Ceroid Lipofuscinosis (NCL), also known as Batten disease, is a group of genetically distinct lysosomal disorders that mainly affect the central nervous system, resulting in progressive motor and cognitive decline primarily in children. Multiple distinct genes involved in the metabolism of lipids have been identified to date with various mutations in this family of diseases. There is no cure for these diseases but some new therapeutic approaches have been tested that offer more hope than the standard palliative care. Many of the therapeutic advances require invasive procedures but some progress in slowing the disease has been found and more options can be expected in the future. We also review the literature on children with disease/conditions other than NCL for the non-invasive use, safety, and tolerability of a lipid-lowering drug, gemfibrozil, as a potential treatment for NCLs. Gemfibrozil has shown efficacy in an animal model of NCL known as CLN2 (late infantile classic juvenile) and has been shown to be safe for lowering lipids in children. Among the 200 non-NCL children found in the published literature who were treated with gemfibrozil for NCL-related problems, only 3 experienced adverse events, including 2 with muscle pain and 1 with localized linear IgA bullous dermatitis. We conclude that gemfibrozil is safe for long-term use in children, causes minimal adverse events, is well tolerated, and may delay the progression of NCLs. Gemfibrozil may potentially be an alternative to more invasive therapeutic approaches currently under investigation and has the potential to be used in combination with other therapeutic approaches.


**ABSTRACT**

This paper aims to discuss the short-term effect of Atorvastatin on lower-extremity function of patients with hypertension and peripheral arterial disease (PAD). 40 patients with hypertension...
and ankle-brachial index (ABI) less than 0.9 were divided into the control group (20 cases) and Atorvastatin group (20 cases) and treated for 6 months. The variation between the 6-min walk and the gait speed of 4-m-walk before and after the treatment were respectively observed. With regard to the two groups, differences of the drop-out values before and after the treatment were adjusted in accordance with gender, ages, body mass index (BMI), difference values of systolic pressure, ABI, difference values of total cholesterol (TC), difference values of low density lipoprotein, triacylglycerol, smoking and drug-taking situation. After the treatment, the 6-min walk had no obvious change between the two groups (P>0.05), but the 4-m normal and rapid walking speed changed obviously (P<0.01). Short-term therapy with atorvastatin can significantly delay the decline of the walking speed in short distance and improve the lower-extremity function of patients with hypertension and PAD.


ABSTRACT
OBJECTIVE: Niacin has been used for seven decades to modulate plasma lipids, but its mechanism of action is still unclear. We sought to determine whether variants in the niacin receptor gene, hydroxyl-carboxylic receptor 2 (HCAR2), are associated with lipid response to treatment. PARTICIPANTS AND METHODS: Coding variants, rs7314976 (p.R311C) and rs2454727 (p.M317I), were genotyped in 2067 participants from the Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides and Impact on Global Health Outcomes (AIM-HIGH) trial. AIM-HIGH was a randomized, placebo-controlled trial that was conducted to assess the effect of extended-release niacin in patients with cardiovascular disease aggressively treated with low-density lipoprotein cholesterol-lowering therapy. RESULTS: There was no association of p.R311C or p.M317I with changes in low-density lipoprotein cholesterol, triglycerides, or high-density lipoprotein cholesterol at 1 year in groups receiving placebo or extended-release niacin. In White patients, the reduction in lipoprotein (a) [Lp(a)] in response to niacin was greater in homozygous carriers of the major 317M allele (-22.7%; P=0.005) compared with minor allele carriers (-15.3%). This was directionally consistent in the Black participants. Upon combining both groups, the reduction in Lp(a) in response to niacin was significantly greater in the homozygous major allele carriers (-23.0%; P=0.003) compared with minor allele carriers (-15.2%). CONCLUSION: Understanding the genetic contribution toward variation in response to niacin therapy, including Lp(a) reduction, could uncover mechanisms by which niacin decreases Lp(a), an important independent risk factor for cardiovascular disease.


ABSTRACT
OBJECTIVE: To investigate the effect of a heart rate (HR) lowering agent (Ivabradine) on features of atherosclerotic plaque vulnerability with magnetic resonance imaging (MRI),
ultrasound imaging, and histology. APPROACH AND RESULTS: Atherosclerosis was induced in the abdominal aorta of 19 rabbits. Nine rabbits were treated with Ivabradine (17 mg/kg/day) during the entire study period. At week 14, imaging was performed. Plaque size was quantified on contrast-enhanced T1-weighted MR images. Microvascular flow, density, and permeability was studied with dynamic contrast-enhanced MRI. Plaque biomechanics was studied by measuring the aortic distension with ultrasound. After, animals were sacrificed and histology was performed. HR was reduced by 16% (p = 0.026) in Ivabradine-treated animals. No differences in absolute and relative vessel wall beat-to-beat distension were found, but due to the reduction in HR, the frequency of the biomechanical load on the plaque was reduced. Plaque size (MR and histology) was similar between groups. Although microvessel density (histology) was similar between groups, AUC and Ktrans, indicative for plaque microvasculature flow, density, and permeability, were decreased by 24% (p = 0.029) and 32% (p = 0.037), respectively. Macrophage content (relative RAM11 positive area) was reduced by 44% (p<0.001) on histology in Ivabradine-treated animals. CONCLUSIONS: HR lowering treatment with Ivabradine in an atherosclerotic rabbit model is associated with a reduction in vulnerable plaque features. The current study suggests that HR reduction may be beneficial for inducing or maintaining a more stable plaque phenotype.


ABSTRACT
Chronic kidney disease (CKD) patients have a high burden of cardiovascular disease. In the general population, lipid metabolism disorders, which cause the initiation and progression of atherosclerotic vascular changes, are major targets for preventive and therapeutic strategies in cardiovascular medicine. However, data from large cohort studies and from clinical trials suggest that the treatment guidelines on cardiovascular disease prevention and therapy cannot uncritically be transferred from individuals with intact renal function to CKD patients. Thus, unlike in the general population, neither plasma levels of HDL-cholesterol, nor the key parameter of HDL-cholesterol function—that is, cholesterol efflux capacity—predicts future cardiovascular events. Therefore, HDL-cholesterol should presently not be considered as therapeutic target in CKD patients. In contrast, lowering of LDL-cholesterol has been shown to reduce cardiovascular events at least among nondialysis CKD patients. The cardiovascular benefit of targeting LDL-cholesterol among dialysis CKD patients is less evident. We strongly believe that at least some subgroups of dialysis patients may profit from such treatment, particularly those with highest baseline LDL-cholesterol. Finally, as CKD patients have been characterized to have rather high intestinal cholesterol absorption, and relatively low hepatic cholesterol synthesis, substituting combined statin/ezetimibe treatment for statin monotherapy may be of particular benefit for nephrologic patients.

**ABSTRACT**

BACKGROUND AND PURPOSE: We investigated whether statin pretreatment can dose dependently reduce periprocedural complications in patients undergoing carotid artery stenting because of symptomatic carotid artery stenosis. METHODS: We enrolled a consecutive series of 397 symptomatic carotid artery stenosis (>/>=50% stenosis on conventional angiography) treated with carotid artery stenting at 2 tertiary university hospitals over a decade. Definition of periprocedural complications included any stroke, myocardial infarction, and death within 1 month after or during the procedure. Statin pretreatment was divided into 3 categories according to the atorvastatin equivalent dose: none (n=158; 39.8%), standard dose (<40 mg of atorvastatin, n=155; 39.0%), and high dose (>/>=40 mg; n=84; 21.2%). A multivariable logistic regression analysis with the generalized estimating equation method was used to investigate independent factors in periprocedural complications. RESULTS: The patients' mean age was 68.7 years (81.6% men). The periprocedural complication rates across the 3 categories of statin use were 12.0%, 4.5%, and 1.2%. After adjustment, a change in the atorvastatin dose category was associated with reduction in the odds of periprocedural complications for each change in dose category (standard-dose statin: odds ratio, 0.24; 95% confidence interval, 0.07-0.81; high-dose statin: odds ratio, 0.11; 95% confidence interval, 0.01-0.96; P for trend=0.01). Administration of antiplatelet drugs was also an independent factor in periprocedural complications (OR, 0.18; 95% CI, 0.05-0.69). CONCLUSIONS: This study shows that statin pretreatment may reduce the incidence of periprocedural complications dose dependently in patients with symptomatic carotid artery stenting.


**ABSTRACT**

Worldwide, the number of patients with type 2 diabetes mellitus (T2DM), obesity, and cardiovascular diseases (CVD) continues to increase steadily. Despite long-term studies of obesity and concomitant diseases, the molecular genetic bases for the development of these pathological conditions have remained the subject of numerous investigations so far. Recent investigations point to the involvement of miRNAs as dynamic modifiers of the pathogenesis of various pathological conditions, including obesity, T2DM, and CVD. MicroRNAs are involved in various biological processes underlying the development of CVDs, including endothelial dysfunction, cell adhesion, and atherosclerotic plaque formation and rupture. Some of them are considered as potential sensitive diagnostic markers of coronary heart disease and acute myocardial infarction. Approximately 1,000 microRNAs are found in the human body. It has been determined that miRNAs regulate 30% of all human genes. Among them there are about 50 circulating miRNAs presumably associated with cardiovascular diseases. This review provides recent data on the participation of some miRNAs in various pathological and physiological states associated with CVD in DM and obesity. An extended and exact understanding of the function of miRNAs in the gene regulatory networks associated with cardiovascular risk in obesity will be able to reveal new mechanisms for the progression of disease, to predict its development, and to elaborate innovative therapeutic strategies.
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