
ABSTRACT
Although low-density lipoprotein cholesterol (LDL-C) is widely accepted as the principal lipid fraction associated with atherosclerosis, emerging evidence suggests a causal relation between lifelong elevations in triglyceride-rich lipoprotein cholesterol (TRL-C) and cardiovascular disease (CVD) in genetic studies. To provide further evidence for the potential relevance of TRL-C and atherosclerosis, we have evaluated the relation between TRL-C and coronary artery calcium (CAC) score. We included 3,845 subjects (49.9 +/- 8.4 years, 54% women) who had no history of CVD, were not using lipid-lowering medications, and underwent CAC evaluation. We assessed the relation between increasing fasting TRL-C and the graded increase in CAC and to what extent TRL-C were independently associated with CAC over and above LDL-C using logistic regression models. Overall, 973 (25%) of the participants had a CAC >0 and 308 (8%) had a CAC >100. The median TRL-C level was 22 mg/dl (IQR 16 to 32). Subjects with CAC >0 had higher TRL-C levels than those with CAC = 0 (p <0.001). Similarly, subjects with CAC >0 had higher levels of LDL-C, non-high-density lipoprotein cholesterol, and lower high-density lipoprotein cholesterol (all p <0.001). After multivariate adjustment, log-transformed TRL-C remained associated with the presence and severity of CAC (all p <0.05). When TRL-C was added to models that contained demographic factors and conventional lipids, it significantly improved the model to predict the presence of CAC >0 (p = 0.01). In conclusion, in a large cohort of asymptomatic subjects, TRL-C was associated with subclinical atherosclerosis supporting a potentially causal role in CVD.


ABSTRACT
Atherosclerotic plaque rupture with subsequent embolic events is a major cause of sudden death from myocardial infarction or stroke. Although smooth muscle cells (SMC) produce and respond to collagens in vitro, there is no direct evidence in vivo that SMC are a crucial source of collagens and that this impacts lesion development or fibrous cap formation. We sought to determine how conditional SMC specific knockout of collagen type XV (COL15A1) in SMC lineage tracing mice affects advanced lesion formation given: 1) we previously identified a Col15a1 sequence variant associated with age related atherosclerosis; 2) COL15A1 is a matrix organizer enhancing tissue structural integrity; and 3) siRNA mediated Col15a1 knockdown increased migration and decreased proliferation of cultured human SMC. We hypothesized that SMC-derived COL15A1 is critical in advanced lesions, specifically in fibrous cap formation. Surprisingly, we demonstrate that SMC specific Col15a1 knockout mice fed a Western diet for 18 weeks failed to form advanced lesions. SMC specific Col15a1 knockout resulted in lesions reduced in size by 78%, with marked reductions in number and proliferating SMC, and lacked a
SMC and ECM-rich lesion or fibrous cap. In vivo RNA-seq analyses on SMC Col15a1 knockout and wild type lesions suggest that a mechanism for these effects is through global repression of multiple pro-atherogenic inflammatory pathways involved in lesion development. These results provide the first direct evidence that a SMC-derived collagen, COL15A1, is critical during lesion pathogenesis but contrary to expectations, its loss resulted in marked attenuation rather than exacerbation of lesion pathogenesis.


**ABSTRACT**
The purpose of the present study is to explore the effects of a lipid-lowering drug atorvastatin, a three-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor, in the treatment of erectile dysfunction (ED) in a rat model of atherosclerosis (AS) and the possible mechanisms underneath. A high-cholesterol diet was administrated to Sprague-Dawley rats in an attempt to induce an ASED model, which was later confirmed by abdominal aorta histopathology and erectile function evaluation. ASED rats were further assigned to non-treatment group, atorvastatin low-dose treatment group (5 mg kg⁻¹ day⁻¹), high-dose group (10 mg kg⁻¹ day⁻¹) and sildenafil (1.5 mg kg⁻¹ day⁻¹) treatment group. Lipid profile, erectile function, oxidative stress biochemical markers, endothelial nitric oxide synthase (eNOS) and extracellular superoxide dismutase (SODEX) mRNA expression were evaluated after 8-week treatment duration. Erectile function was impaired in AS rat model, which was preserved in atorvastatin and sildenafil intervention groups. The oxidative stress biochemical markers were attenuated, while eNOS and SODEX mRNA expression were restored in atorvastatin and sildenafil groups, which were found to be involved in ED pathogenesis. However, the lipid profile remained unaltered in the treatment group, and it was elevated in ASED rats. This kind of lipid-lowering agent, or atorvastatin, has the utilisation potential in ASED treatment, even before lipid profiles altered. This effect on erectile function preservation of atorvastatin was attributed to its preservation of endothelial function, possibly through amelioration of oxidative stress and improvement in eNOS expression.


**ABSTRACT**
OBJECTIVES: Deregulated production of interleukin (IL)-17 and IL-21 contributes to the pathogenesis of autoimmune disorders such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). Production of IL-17 and IL-21 can be regulated by ROCK2, one of the two Rho kinases. Increased ROCK activation was previously observed in an SLE cohort. Here, we evaluated ROCK activity in a new SLE cohort, and an RA cohort, and assessed the ability of distinct inhibitors of the ROCK pathway to suppress production of IL-17 and IL-21 by SLE T cells or human Th17 cells. METHODS: ROCK activity in peripheral blood mononuclear cells (PBMCs) from 29 patients with SLE, 31 patients with RA and 28 healthy controls was determined by
ELISA. SLE T cells or in vitro-differentiated Th17 cells were treated with Y27632 (a pan-ROCK inhibitor), KD025 (a selective ROCK2 inhibitor) or simvastatin (which inhibits RhoA, a major ROCK activator). ROCK activity and IL-17 and IL-21 production were assessed. The transcriptional profile altered by ROCK inhibitors was evaluated by NanoString technology. RESULTS: ROCK activity levels were significantly higher in patients with SLE and RA than healthy controls. Th17 cells exhibited high ROCK activity that was inhibited by Y27632, KD025 or simvastatin; each also decreased IL-17 and IL-21 production by purified SLE T cells or Th17 cells. Immune profiling revealed both overlapping and distinct effects of the different ROCK inhibitors. CONCLUSIONS: ROCK activity is elevated in PBMCs from patients with SLE and RA. Production of IL-17 and IL-21 by SLE T cells or Th17 cells can furthermore be inhibited by targeting the RhoA-ROCK pathway via both non-selective and selective approaches.


ABSTRACT
OBJECTIVE: To report the prevalence of Silent Brain Infarcts (SBI) at MRI before and after surgery for asymptomatic high grade carotid stenosis. DESIGN: Single-center retrospective observational study METHODS: Asymptomatic patients who underwent carotid endarterectomy between October 2012 and October 2014 were included. The preoperative assessment included a Doppler and a CT scan dating less than 3 months. A neurological examination was performed during the anesthesia consultation and in the 15 days before surgery. An MRI-angiography was performed the day before and three days after surgery and analysed by an independent neuroradiologist. Preoperative analysis focused on the presence of ischemic events at MRI. The type of plaque, the supra-aortic trunk (SAT) lesions and the quality of the circle of Willis were analysed using Doppler and CT scanning. Postoperatively, we searched for signs of postoperative ischemic events at MRI. RESULTS: Forty-one patients were included (85.4% of men) and the mean age was 72.4 +/- 8.3 years. We noted 7 (17.1%) contralateral stenoses (> 50%) and 2 (4.9%) contralateral thromboses, 6 (14.6%) vertebral stenoses and 7 (17.1%) abnormalities of the circle of Willis. The morphological analysis described 6 unstable plaques including 4 ulcerated, 1 pseudo-dissection and 1 intraplaque haemorrhage. Preoperatively we noted the presence of 21 (51.2%) ischemic lesions including, 9 (21.9%) multiple lacunar ischemic events and 12 (29.3%) silent arterial territory infarcts (SATI). Eversion was performed for all patients except for 6 (14.6%) for whom a bypass was necessary. No deaths or major complications were observed in the 30 postoperative days. Postoperatively, MRI showed 3 (7.3%) asymptomatic recent ischemic strokes, 1 ipsilateral middle cerebral artery (MCA) stroke and 2 contralateral (cerebellar and MCA) strokes. CONCLUSION: Patients with asymptomatic significant carotid stenosis show many preoperative SBI indicating a significant embolic risk. It is difficult to conclude about intra-operative embolic risk but we hope that more data could demonstrate the importance of MRI for the preoperative evaluation of carotid plaques and brain parenchyma, in order to identify high risk embolic patients.
ABSTRACT

OBJECTIVE: Murine atherosclerosis models do not spontaneously develop atherothrombotic complications. We investigated whether disruption of natural anticoagulation allows preexisting atherosclerotic plaques to progress toward an atherothrombotic phenotype.

APPROACH AND RESULTS: On lowering of plasma protein C levels with small interfering RNA (siProc) in 8-week Western-type diet-fed atherosclerotic apolipoprotein E-deficient mice, one out of 4 mice displayed a large, organized, and fibrin- and leukocyte-rich thrombus on top of an advanced atherosclerotic plaque located in the aortic root. Although again at low incidence (3 in 25), comparable thrombi at the same location were observed during a second independent experiment in 9-week Western-type diet-fed apolipoprotein E-deficient mice. Mice with thrombi on their atherosclerotic plaques did not show other abnormalities and had equally lowered plasma protein C levels as siProc-treated apolipoprotein E-deficient mice without thrombi. Fibrinogen and thrombin-antithrombin concentrations and blood platelet numbers were also comparable, and plaques in siProc mice with thrombi had a similar composition and size as plaques in siProc mice without thrombi. Seven out of 25 siProc mice featured clots in the left atrium of the heart. CONCLUSIONS: Our findings indicate that small interfering RNA-mediated silencing of protein C in apolipoprotein E-deficient mice creates a condition that allows the occurrence of spontaneous atherothrombosis, albeit at a low incidence. Lowering natural anticoagulation in atherosclerosis models may help to discover factors that increase atherothrombotic complications.

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ABSTRACT

There is an urgent need to understand the pathophysiological mechanisms related to anxiety associated with diabetes, seeking more effective alternative treatments to treat it. For that, the effect of a preventive and prolonged treatment with fish oil (FO), a source of omega-3 polyunsaturated fatty acid, was tested in streptozotocin-diabetic (DBT) rats submitted to the anxiety tests. Additionally, an immunohistochemistry for neuronal NO synthase (nNOS) was performed in brain areas related to anxiety, such as lateral amygdala (AMY), hippocampus (HIP) and dorsolateral periaqueductal gray (dIPAG). Lastly, the effect of NO precursor L-arginine (L-Arg) or nNOS inhibitor 7-nitroindazole (7-NI) was tested in DBT animals treated with vehicle (VEH) or FO. Our data demonstrated that vehicle-treated DBT animals exhibited a more pronounced anxiogenic-like response and also presented high nNOS levels in the AMY, HIP and rostral dIPAG, what were both significantly prevented by FO treatment. This treatment was able to prevent the impairment in locomotor activity besides improving the high glycemic levels in DBT rats. Interestingly, while injection of 7-NI or L-Arg in VEH-treated DBT animals induced an anxiogenic-like and anxiolytic-like effect, respectively; the previous treatment with both L-Arg
and 7-NI in FO-DBT animals abolished the anxiolytic-like effect induced by FO treatment. Altogether, our data support the hypothesis that a dysregulation in the NO production in brain areas as AMY, HIP and dIPAG may contribute to the mechanisms that link anxiety and diabetes, and the prevention of nNOS brain expression changes induced by a prolonged treatment with FO may be an important mechanism related to its anxiolytic-like effect.


ABSTRACT

AIM: Epidemiological studies suggest a possible link between osteoporosis and cardiovascular diseases. Mevalonate pathway was pointed to as a part of this link. This study was done to investigate the effects of Alendronate (Al) and Simvastatin (Sim), both act on the mevalonate pathway, on osteoporosis, dyslipidemia and atherosclerotic changes in ovariectomized (OVX) rats fed high fat diet (HFD). MAIN METHODS: 60 female albino rats were equally divided into 5 groups: control sham, OVX-HFD untreated, OVX-HFD treated with Al (3mg/kg/d) or/and Sim (6mg/kg/d). Treatments were taken for 4 weeks by oral gavage and were started 8 weeks after ovariectomy. RESULTS: OVX-HFD untreated group exhibited a significant negative alteration in lipid profile and on different bone markers e.g. alkaline phosphatase, hydroxyproline and osteocalcin. A significant increase in body weights and on serum levels of TNFalpha, iNOS and leptin were also found compared to control sham group. Vascular reactivity studies revealed a significant decrease in effective concentration 50 of phenylephrine and in acetylcholine% of relaxation and a significant increase in maximum contractile response of phenylephrine. The atherosclerotic and osteoporotic changes were further confirmed histopathologically. Treatment of OVX-HFD with Al or/and Sim significantly improved these deleterious effects compared to OVX-HFD untreated group. Comparing the combination therapy versus the monotherapy exhibited a significant improvement in different tested parameters which came in favor of the combination therapy. CONCLUSION: Al and Sim have anti-osteoporotic, anti-dyslipidemic and anti-atherosclerotic beneficial effects. Their combination has more promising effects in treatment of osteoporosis, dyslipidemia and atherosclerosis.


ABSTRACT

The leading cause of death worldwide is cardiovascular disease. Among the conditions related to the term, the most prominent one is the development of atherosclerotic plaques in the walls of arteries. The situation gets even worse with the fact that the plaque development may stay asymptomatic for a prolonged period of time. When it manifests as a cardiovascular disorder, it is already too late: the unfortunate individual is prescribed with a plethora of synthetic drugs, which are of debatable efficacy in the prevention of atherosclerotic lesions and safety. Cell models could be useful for the purpose of screening substances potentially effective against
atherosclerosis progression and effective in reduction of already present plaques. In this overview, we present studies making use of in vitro and ex vivo models of atherosclerosis development that can prove valuable for clinical applications.


**ABSTRACT**
A 50-year-old male UK resident with a history of hypertension and hypercholesterolaemia presented to the emergency department with a 48-hour history of sudden onset bilateral thigh swelling and pain unrelieved by regular analgesia. 3 days prior to presentation, he performed a vigorous workout in the gym. His medications included ramipril 5 mg once daily and atorvastatin 20 mg at night time. He was a non-smoker and did not consume alcohol. He reported no known drug allergies. Physical examination confirmed bilateral swollen thighs, with no overlying skin changes, clinically suggestive of compartment syndrome. His creatine kinase was >50 000 IU with normal renal and liver function tests. Further investigation with MRI-identified prominent swelling of the vastus intermedius and medialis muscles, more marked on the left, with extensive diffuse short tau inversion recovery (STIR) signal hyperintensity and isointensity on T1 sequences, suggestive of rhabdomyolysis. He underwent bilateral fasciotomies of his thighs and aggressive intravenous fluid resuscitation with close monitoring of his electrolytes. Intraoperatively his muscle was healthy, with no evidence of haematoma or necrosis. His medication atorvastatin was stopped due to his rhabdomyolysis. 48 hours later, he returned to theatre and review of his fasciotomy wounds was unremarkable. 4 days later, he was discharged uneventfully. His postoperative recovery was complicated by a serous discharge from his left medial thigh wound. Further investigation with an ultrasound confirmed a 4x1x1cm multiloculated collection within the superficial tissue directly underlying the wound. An aspirate was performed and cultures revealed no growth. He remains under review in the department of plastic surgery. This case report discusses the aetiological spectrum, clinical presentation, pathophysiology, differential diagnosis, investigations, management and complications of rhabdomyolysis.


**ABSTRACT**
Plant-derived foods rich in polyphenols are associated with several cardiometabolic health benefits, such as reduced postprandial hyperglycaemia. However, their impact on whole-body insulin sensitivity using the hyperinsulinaemic-euglycaemic clamp technique remains understudied. We aimed to determine the effects of strawberry and cranberry polyphenols (SCP) on insulin sensitivity, glucose tolerance, insulin secretion, lipid profile, inflammation and oxidative stress markers in free-living insulin-resistant overweight or obese human subjects (n 41) in a parallel, double-blind, controlled and randomised clinical trial. The experimental group consumed an SCP beverage (333 mg SCP) daily for 6 weeks, whereas the Control group received
a flavour-matched Control beverage that contained 0 mg SCP. At the beginning and at the end of the experimental period, insulin sensitivity was assessed by a hyperinsulinaemic-euglycaemic clamp, and glucose tolerance and insulin secretion by a 2-h oral glucose tolerance test (OGTT). Insulin sensitivity increased in the SCP group as compared with the Control group (+0.9 (sem 0.5)x10-3 v. -0.5 (sem 0.5)x10-3 mg/kg per min per pmol, respectively, P=0.03). Compared with the Control group, the SCP group had a lower first-phase insulin secretion response as measured by C-peptide levels during the first 30 min of the OGTT (P=0.002). No differences were detected between the two groups for lipids and markers of inflammation and oxidative stress. A 6-week dietary intervention with 333 mg of polyphenols from strawberries and cranberries improved insulin sensitivity in overweight and obese non-diabetic, insulin-resistant human subjects but was not effective in improving other cardiometabolic risk factors.


ABSTRACT
The objective of this study was to study the functional changes of left atrium after radiofrequency ablation treatment for atrial fibrillation and the therapeutic effect of Atorvastatin. 58 patients undergoing radiofrequency ablation for atrial fibrillation were randomly divided into non-Atorvastatin group and Atorvastatin group. Patients in Atorvastatin group were treated with Atorvastatin 20mg po per night in addition to the conventional treatment of atrial fibrillation; patients in non-Atorvastatin group received conventional treatment of atrial fibrillation only. Echocardiography was performed before radiofrequency ablation operation, one week, two weeks, three weeks and four weeks after operation. Two-dimensional ultrasound speckle tracking imaging system was used to measure the structural indexes of left atrium. Results indicated that there was no significant change for indexes representing the structural status of left atrium within a month after radiofrequency ablation (P>0.05); however, there were significant changes for indexes representing the functional status of left atrium. There were also significant changes in indexes reflecting left atrial strain status: the S and SRs of Atorvastatin group were higher than those of non-Atorvastatin group (P<0.05). In summary, atorvastatin could improve left atrial function and shorten the duration of atrial stunning after radiofrequency ablation of atrial fibrillation.


ABSTRACT
OBJECTIVES: We describe the characteristics of atherosclerotic plaque in patients with peripheral arterial disease (PAD) using near-infrared spectroscopy-intravascular ultrasound (NIRS-IVUS) BACKGROUND: Imaging and autopsy studies have described atherosclerotic plaque in different vascular beds, including varying degrees of lipid, fibrosis, and calcification. Recently,
NIRS has been validated as an accurate method for detecting lipid-core plaque (LCP) in the coronary circulation. Invasive evaluation of plaque composition using NIRS-IVUS has not been reported in different peripheral arterial circulations. METHODS: We performed invasive angiography and NIRS-IVUS in consecutive PAD patients prior to percutaneous revascularization. Imaging evaluation included parameters from angiography, IVUS, and NIRS. NIRS-IVUS findings were compared among different vascular beds with regard to the presence and extent of calcification and LCP. RESULTS: One hundred and forty-nine lesions in 126 PAD patients were enrolled, including the internal carotid (n = 10), subclavian/axillary (n = 9), renal (n = 14), iliac (n = 35), femoropopliteal (n = 69), and infrapopliteal (n = 12) arteries. Plaque morphology was calcified in 132 lesions (89%) and fibrous in 17 lesions (11%). Calcification varied from 100% of renal artery stenoses to 55% of subclavian/axillary artery stenoses. LCP was present in 48 lesions (32%) and prevalence varied from 60% in carotid artery stenoses to 0% in renal artery stenoses (P < 0.005). LCP was only observed in fibrocalcific plaque, and was longitudinally and circumferentially surrounded by a more extensive degree of calcium. CONCLUSIONS: NIRS-IVUS in stable PAD patients demonstrates a high frequency of calcific plaque and statistically significant differences in the frequency of LCP in different arterial beds. LCP, when present in the peripheral circulation, is always associated with calcified plaque. The strong co-localization of calcified plaque and LCP in severe PAD lesions may provide plaque-stabilizing effects; further studies are needed. (c) 2017 Wiley Periodicals, Inc.


ABSTRACT

Loss or dysfunction of tumor suppressor retinoblastoma (RB) is a common feature in various tumors, and contributes to cancer cell stemness and drug resistance to cancer therapy. However, the strategy to suppress or eliminate RB-deficient tumor cells remains unclear. In the present study, we accidentally found that reduction of DNA replication licensing factor MCM7 induced more apoptosis in RB-deficient tumor cells than in control tumor cells. Moreover, after a drug screening and further studies, we demonstrated that statin drug Simvastatin and Atorvastatin were able to inhibit MCM7 and RB expressions. Further study showed that Simvastatin and Atorvastatin induced more chromosome breaks and gaps of RB-deficient tumor cells than control tumor cells. In vivo results showed that Simvastatin and Atorvastatin significantly suppressed Rb-deficient tumor growth than control in xenograft mouse models. The present work demonstrates that ‘old’ lipid-lowering drugs statins are novel weapons against RB-deficient tumors due to their effects on suppressing MCM7 protein levels.


ABSTRACT
OBJECTIVE: Atherosclerosis is an inflammatory process that results in complex lesions or plaques that protrude into the arterial lumen. Carotid atherosclerotic plaque rupture, with distal atheromatous debris embolization, causes cerebrovascular events. This review aimed to explore research progress on the risk factors and outcomes of human carotid atherosclerotic plaques, and the molecular and cellular mechanisms of human carotid atherosclerotic plaque vulnerability for therapeutic intervention. DATA SOURCES: We searched the PubMed database for recently published research articles up to June 2016, with the key words of "risk factors", "outcomes", "blood components", "molecular mechanisms", "cellular mechanisms", and "human carotid atherosclerotic plaques". STUDY SELECTION: The articles, regarding the latest developments related to the risk factors and outcomes, atherosclerotic plaque composition, blood components, and consequences of human carotid atherosclerotic plaques, and the molecular and cellular mechanisms of human carotid atherosclerotic plaque vulnerability for therapeutic intervention, were selected. RESULTS: This review described the latest researches regarding the interactive effects of both traditional and novel risk factors for human carotid atherosclerotic plaques, novel insights into human carotid atherosclerotic plaque composition and blood components, and consequences of human carotid atherosclerotic plaque. CONCLUSION: Carotid plaque biology and serologic biomarkers of vulnerability can be used to predict the risk of cerebrovascular events. Furthermore, plaque composition, rather than lesion burden, seems to most predict rupture and subsequent thrombosis.


ABSTRACT

Multiple randomized controlled trials (RCTs) have assessed the effects of supplementation with eicosapentaenoic acid plus docosahexaenoic acid (omega-3 polyunsaturated fatty acids, commonly called fish oils) on the occurrence of clinical cardiovascular diseases. Although the effects of supplementation for the primary prevention of clinical cardiovascular events in the general population have not been examined, RCTs have assessed the role of supplementation in secondary prevention among patients with diabetes mellitus and prediabetes, patients at high risk of cardiovascular disease, and those with prevalent coronary heart disease. In this scientific advisory, we take a clinical approach and focus on common indications for omega-3 polyunsaturated fatty acid supplements related to the prevention of clinical cardiovascular events. We limited the scope of our review to large RCTs of supplementation with major clinical cardiovascular disease end points; meta-analyses were considered secondarily. We discuss the features of available RCTs and provide the rationale for our recommendations. We then use existing American Heart Association criteria to assess the strength of the recommendation and the level of evidence. On the basis of our review of the cumulative evidence from RCTs designed to assess the effect of omega-3 polyunsaturated fatty acid supplementation on clinical cardiovascular events, we update prior recommendations for patients with prevalent coronary heart disease, and we offer recommendations, when data are available, for patients with other clinical indications, including patients with diabetes mellitus and prediabetes and those with high risk of cardiovascular disease, stroke, heart failure, and atrial fibrillation.

ABSTRACT
Residual cardiovascular risk persists despite statins, yet outcome studies of lipid-targeted therapies beyond low-density lipoprotein cholesterol (LDL-C) have not demonstrated added benefit. Triglyceride elevation is an independent risk factor for cardiovascular events. High-dose eicosapentaenoic acid (EPA) reduces triglyceride-rich lipoproteins without raising LDL-C. Omega-3s have postulated pleiotropic cardioprotective benefits beyond triglyceride-lowering. To date, no large, multinational, randomized clinical trial has proved that lowering triglycerides on top of statin therapy improves cardiovascular outcomes. The Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial (REDUCE-IT; NCT01492361) is a phase 3b randomized, double-blinded, placebo-controlled trial of icosapent ethyl, a highly purified ethyl ester of EPA, vs placebo. The main objective is to evaluate whether treatment with icosapent ethyl reduces ischemic events in statin-treated patients with high triglycerides at elevated cardiovascular risk. REDUCE-IT enrolled men or women age >/=45 years with established cardiovascular disease or age >/=50 years with diabetes mellitus and 1 additional risk factor. Randomization required fasting triglycerides >/=150 mg/dL and <500 mg/dL and LDL-C >40 mg/dL and </=100 mg/dL with stable statin (+/- ezetimibe) >/=4 weeks prior to qualifying measurements. The primary endpoint is a composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina. The key secondary endpoint is the composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke. Several secondary, tertiary, and exploratory endpoints will be assessed. Approximately 8000 patients have been randomized at approximately 470 centers worldwide. Follow-up will continue in this event-driven trial until approximately 1612 adjudicated primary-efficacy endpoint events have occurred.


ABSTRACT
BACKGROUND AND OBJECTIVES: Febuxostat, a nonpurine xanthine oxidase inhibitor, is widely used to treat hyperuricemia. Although febuxostat-associated rhabdomyolysis was reported in some patients with CKD, the association between CKD and febuxostat-associated myopathy remains uncertain. DESIGN, SETTING, PARTICIPANTS, & MEASUREMENTS: Our retrospective cohort study included 1332 patients using febuxostat in Taipei Medical University-Wanfang Hospital from February of 2014 to January of 2016. The primary predictor was time-averaged eGFR as calculated by the equation proposed by the 2009 Chronic Kidney Disease Epidemiology Collaboration. The outcome was febuxostat-associated myopathy defined as elevated creatine kinase levels during febuxostat use that were not attributed to other muscular injuries.
RESULTS: The median duration of febuxostat use was 224 days (25th, 75th percentiles: 86, 441.5 days). Of 1332 study participants, 1222 (91.7%) had CKD; the median eGFR was 20.8 ml/min per 1.73 m2 (25th, 75th percentiles: 9.0, 35.4 ml/min per 1.73 m2). Forty-one of the
participants had febuxostat-associated myopathy (3.2%). All patients with myopathy had CKD, and the incident rate was 0.013 (95% confidence interval, 0.01 to 0.02) events per 100 patient-days in patients with CKD. Of 41 patients with myopathy, 37 had myositis, and four had rhabdomyolysis. Myopathy resolved in 17 patients who withdrew from treatment and eight patients who continued febuxostat treatment. Among the evaluated predictors, multivariate analysis showed that only the lowest eGFR tertile was significantly associated with myopathy in febuxostat users. The odds ratio of the lowest eGFR tertile to the highest tertile was 4.21 (95% confidence interval, 1.7 to 10.43). This finding remained consistent among subgroups stratified by age, sex, diabetes status, coronary artery disease, and statin or fibrate use. CONCLUSIONS: Patients with severely reduced eGFR had higher risk of myopathy with treatment of febuxostat. Regular monitoring of creatine kinase level is suggested for early detection of febuxostat-associated myopathy, particularly in patients with CKD.


ABSTRACT
Statins are used widely in primary and secondary prevention of cardiovascular disease; a treatment effect that has long been thought to be due to their cholesterol-lowering properties. However, statins also have a wide range of anti-inflammatory effects independent of their lipid-lowering mechanisms. In depression, low-grade inflammation is a replicated finding, and several studies have shown antidepressant properties of diverse anti-inflammatory drugs. Large observational studies have suggested reduced risks of depression amongst those taking statins, an effect that is thought to be explained by the anti-inflammatory properties of this class of drugs. Also, preliminary randomized controlled trials (RCTs) have indicated that statins may have adjunctive antidepressant effects when used as add-on treatment to selective serotonin reuptake inhibitors (SSRIs). However, the RCTs were small and limited by low generalizability, and some early observational studies have pointed towards potential neuropsychiatric adverse effects of statin treatment. Nevertheless, based on the good tolerability and general safety of the statins, researchers are currently investigating the potential antidepressant properties of these agents. The present review aims to give an overview on the potential antidepressant effects of statins based on their anti-inflammatory properties, covering topics such as safety versus treatment effects, potential mechanisms of action and the possibility of targeted treatment (precision medicine).


ABSTRACT
BACKGROUND: The current paradigm for cardiovascular disease (CVD) emphasises absolute risk assessment to guide treatment decisions in primary prevention. Although the derivation and validation of multivariable risk assessment tools, or CVD risk scores, have attracted considerable attention, their effect on clinical outcomes is uncertain. OBJECTIVES: To assess the effects of evaluating and providing CVD risk scores in adults without prevalent CVD on
cardiovascular outcomes, risk factor levels, preventive medication prescribing, and health behaviours. SEARCH METHODS: We searched the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library (2016, Issue 2), MEDLINE Ovid (1946 to March week 1 2016), Embase (embase.com) (1974 to 15 March 2016), and Conference Proceedings Citation Index-Science (CPCI-S) (1990 to 15 March 2016). We imposed no language restrictions. We searched clinical trial registers in March 2016 and handsearched reference lists of primary studies to identify additional reports. SELECTION CRITERIA: We included randomised and quasi-randomised trials comparing the systematic provision of CVD risk scores by a clinician, healthcare professional, or healthcare system compared with usual care (i.e. no systematic provision of CVD risk scores) in adults without CVD. DATA COLLECTION AND ANALYSIS: Three review authors independently selected studies, extracted data, and evaluated study quality. We used the Cochrane 'Risk of bias' tool to assess study limitations. The primary outcomes were: CVD events, change in CVD risk factor levels (total cholesterol, systolic blood pressure, and multivariable CVD risk), and adverse events. Secondary outcomes included: lipid-lowering and antihypertensive medication prescribing in higher-risk people. We calculated risk ratios (RR) for dichotomous data and mean differences (MD) or standardised mean differences (SMD) for continuous data using 95% confidence intervals. We used a fixed-effects model when heterogeneity (I²) was at least 50% and a random-effects model for substantial heterogeneity (I² > 50%). We evaluated the quality of evidence using the GRADE framework. MAIN RESULTS: We identified 41 randomised controlled trials (RCTs) involving 194,035 participants from 6422 reports. We assessed studies as having high or unclear risk of bias across multiple domains. Low-quality evidence evidence suggests that providing CVD risk scores may have little or no effect on CVD events compared with usual care (5.4% versus 5.3%; RR 1.01, 95% confidence interval (CI) 0.95 to 1.08; I² = 25%; 3 trials, N = 99,070). Providing CVD risk scores may reduce CVD risk factor levels by a small amount compared with usual care. Providing CVD risk scores reduced total cholesterol (MD -0.10 mmol/L, 95% CI -0.20 to 0.00; I² = 94%; 12 trials, N = 20,437, low-quality evidence), systolic blood pressure (MD -2.77 mmHg, 95% CI -4.16 to -1.38; I² = 93%; 16 trials, N = 32,954, low-quality evidence), and multivariable CVD risk (SMD -0.21, 95% CI -0.39 to -0.02; I² = 94%; 9 trials, N = 9549, low-quality evidence). Providing CVD risk scores may reduce adverse events compared with usual care, but results were imprecise (1.9% versus 2.7%; RR 0.72, 95% CI 0.49 to 1.04; I² = 0%; 4 trials, N = 4630, low-quality evidence). Compared with usual care, providing CVD risk scores may increase new or intensified lipid-lowering medications (15.7% versus 10.7%; RR 1.47, 95% CI 1.15 to 1.87; I² = 40%; 11 trials, N = 14,175, low-quality evidence) and increase new or increased antihypertensive medications (17.2% versus 11.4%; RR 1.51, 95% CI 1.08 to 2.11; I² = 53%; 8 trials, N = 13,255, low-quality evidence). AUTHORS' CONCLUSIONS: There is uncertainty whether current strategies for providing CVD risk scores affect CVD events. Providing CVD risk scores may slightly reduce CVD risk factor levels and may increase preventive medication prescribing in higher-risk people without evidence of harm. There were multiple study limitations in the identified studies and substantial heterogeneity in the interventions, outcomes, and analyses, so readers should interpret results with caution. New models for implementing and evaluating CVD risk scores in adequately powered studies are needed to define the role of applying CVD risk scores in primary CVD prevention.
Rosuvastatin is a frequently used probe in transporter-mediated drug-drug interaction (DDI) studies. This report describes the development of a physiologically based pharmacokinetic (PBPK) model of rosuvastatin for prediction of pharmacokinetic (PK) DDIs. The rosuvastatin model predicted the observed single (i.v. and oral) and multiple dose PK profiles, as well as the impact of coadministration with transporter inhibitors. The predicted effects of rifampin and cyclosporine (6.58-fold and 5.07-fold increase in rosuvastatin area under the curve (AUC), respectively) were mediated primarily via inhibition of hepatic organic anion-transporting polypeptide (OATP)1B1 (Inhibition constant (Ki) approximately 1.1 and 0.014 microM, respectively) and OATP1B3 (Ki approximately 0.3 and 0.007 microM, respectively), with cyclosporine also inhibiting intestinal breast cancer resistance protein (BCRP; Ki approximately 0.07 microM). The predicted effects of gemfibrozil and its metabolite were moderate (1.88-fold increase in rosuvastatin AUC) and mediated primarily via inhibition of hepatic OATP1B1 and renal organic cation transporter 3. This model of rosuvastatin will be useful in prospectively predicting transporter-mediated DDIs with novel pharmaceutical agents in development.


ABSTRACT
BACKGROUND: The prevalence of premature atherosclerosis and cardiovascular disease (CVD) is constantly increasing worldwide. It has been proved that LDL-cholesterol (LDL-C) plays causal role in the development of coronary atherosclerosis. The fact that atherosclerosis is a chronic and progressive disease which onsets during the first three decades of life bores questions what to do to maintain LDL-C at low levels throughout life and thus to delay and/or prevent the progress this disease. Currently, most of public health expenses are spared on treatment, but not on prophylaxis. METHODS: This is a review article summarizing novel reports concerning the efficacy of sterols/stanols as lipid-lowering agents, assessing their influence on cardiovascular risk and safety. RESULTS: It has been suggested that sterols and stanols are effective in the lowering of low-density cholesterol levels and diminishing cardiovascular risk. However, the results of other studies suggest that phytosterols may not exert positive effects during atherogenesis. Firstly, patients with phytosterolaemia (genetic disease in which high plant sterol plasma concentrations are observed) develop malignant premature atherosclerosis. Moreover, several epidemiological studies demonstrated the association between upper normal plasma concentrations of plant sterols and increased risk of cardiovascular events. Finally, the supplementation with plant stanols and plant sterols may be not beneficial due to their incorporation in various tissues and potentially resulting in adverse effects. CONCLUSION: Despite the worldwide promotion of sterols as health improving supplements, it seems that in some people responding with relatively high phytosterol serum levels after its consumption such additives may turn out to be as good as it has been believed.
ABSTRACT
Various clinical studies have revealed that cardiovascular diseases (CVD) are associated with bone loss diseases such as osteoporosis and periodontitis, especially in older population. As one of the best-established risk factors of CVD, hyperlipidemia is also reported to interfere with the metabolism, function and regeneration of mineralized tissues. Derived from postnatal tissue reservoirs, mesenchymal stem cells (MSCs) are considered promising cell sources for mesenchymal and non-mesenchymal tissue regeneration based on their capacities for self-renewal and multi-lineage differentiation as well as potent immunosuppressive effects, secretion of cytokines and regulation of vascularization. MSCs could home to the injury sites from peripheral circulation, proliferate and differentiate into bone-forming cells, therefore significantly enhancing bone regeneration. However, elevated blood lipid levels affect the physiological behaviors of MSCs, as well as the performance of transplanted MSCs. This review aims to summarize the effects of hyperlipidemia and CVD on the proliferation, osteogenic differentiation and homing of MSCs. The principal observations of the underlying cellular and molecular mechanisms as well as the effects of lipid-lowering therapy on MSCs are also discussed.

ABSTRACT
The aim of this study was to investigate properties of atelocollagen/gelatin complexes (AC/Gel) and their characteristics of sustained statin release, to assess the utility of AC/Gel. AC/Gel were prepared by changing the mixing ratio of AC (0 to 40% of AC). Analysis of spectra of fluvastatin (Flu), gelatin (Gel), and Flu with Gel complex using a Fourier transform-infrared spectrometer indicates that Flu was bound to Gel through a bond involving the carboxyl and amino groups. Evaluation of characteristics of sustained release of Flu from the AC/Gel using an ultraviolet-visible spectrophotometer showed that the release rate of Flu decreased with increasing the AC content. The histological evaluation using of Sprague-Dawley rats suggest that, unlike the pure Gel sponge, the AC/Gel was not absorbed in an early stage. Therefore, the present study showed that sustained Flu release can be controlled by using an AC/Gel, suggesting the utility of this composite material.

ABSTRACT


ABSTRACT

AIMS: Occurrence of metabolic syndrome (MetS) in the United Arab Emirates (UAE) is rising steadily, with subsequent increase in the prevalence of type 2 diabetes and cardiovascular disease (CVD). Recent studies have shown that PCSK9 plays a substantial role in atherogenic dyslipidemia. Hence, the aim of this study was to assess level of PCSK9 and its relationship with MetS components among young adult females. METHODS: This study was carried out on 137 adult females over 18 years of age residing in the UAE. Subjects were categorized into two groups according to waist circumferences (WC): normal (<80cm; n=41) and large (>/=80cm; n=96). Anthropometric and biochemical parameters in the fasting state (glucose, insulin, lipid profile, and PCSK9) were determined using conventional techniques. Homeostasis model assessment of insulin resistance (HOMA-IR) and MetS scores were calculated as appropriate. RESULTS: PCSK9 was lower in subjects with large WC compared to normal WC (p=0.016). PCSK9 correlated negatively with measures of obesity (p<0.05), and positively with IR (r=0.425, p<0.001). Multiple linear regression analysis revealed that the strongest predictor of PCSK9 was IR (B=6.213; p<0.001), followed by WC (B=-2.488; p<0.001) and triglycerides (B=0.897; p=0.013). CONCLUSION: Results from this study demonstrate that PCSK9 correlates with some components of metabolic syndrome and central obesity in young females. Such findings support the suggestion of using PCSK9 inhibitors in the management of MetS to modify risk for development of CVD.


ABSTRACT

Bile acids are amphipathic water-soluble steroid-based molecules best known for their important lipid-solubilizing role in the assimilation of fat. Recently, bile acids have emerged as metabolic integrators with glucose-lowering potential. Among a variety of gluco-metabolic effects, bile acids have been demonstrated to modulate the secretion of the gut-derived incretin hormone glucagon-like peptide-1 (GLP-1), possibly via the transmembrane receptor Takeda G protein-coupled receptor 5 (TGR5) and the nuclear farnesoid X receptor (FXR), in intestinal L cell. The present article critically reviews current evidence connecting established glucose-lowering drugs to bile acid-induced GLP-1 secretion and discusses whether bile acid-induced GLP-1 secretion may constitute a new basis for understanding how metformin, inhibitors of the apical sodium-dependent bile acids transporter, and bile acid sequestrants - old, new and neglected glucose-lowering drugs - improve glucose metabolism.

ABSTRACT
Proteomic-based techniques provide a powerful tool for identifying the full spectrum of protein targets of a drug, elucidating its mechanism(s) of action, and identifying biomarkers of its efficacy and safety. Herein, we outline the technological advancements in the field, and illustrate the contribution of proteomics to the definition of the pharmacological profile of statins, which represent the cornerstone of the prevention and treatment of cardiovascular diseases (CVDs). Statins act by inhibiting 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase, thus reducing cholesterol biosynthesis and consequently enhancing the clearance of low-density lipoproteins from the blood; however, HMG-CoA reductase inhibition can result in a multitude of additional effects beyond lipid lowering, known as 'pleiotropic effects'. The case of statins highlights the unique contribution of proteomics to the target profiling of a drug molecule.

ABSTRACT
The effect of breviscapine injection on the pharmacokinetics of simvastatin and the mRNA expression of hepatic cytochrome P450 (CYP) enzyme was investigated with rats. The rats were pretreated for 8 consecutive days with breviscapine injection (20 mg/kg/day, i. v.), followed by administration of simvastatin through gavage (40 mg/kg). The control rats received the corresponding volume of saline solution for the pretreatment. Blood samples were collected at varied time points after simvastatin administration and the liver was harvested after the last collection of the blood sample for measurement of the CYP3A4 mRNA expression. Pre-treatment with breviscapine injection led to increased plasma concentration of simvastatin, showing 57% increase for AUC0-infinity (P<0.01), 31% increase for C max (P<0.01), and 36% decrease for the total plasma clearance, compared with the control. Pre-treatment with breviscapine injection also inhibited the mRNA expression of the hepatic CYP3A4. These findings indicate that pre-treatment with breviscapine injection could increase the plasma concentration of simvastatin, possibly by inhibiting the expression of the hepatic CYP3A4, and combined use of breviscapine with simvastatin may improve the simvastatin efficacy and reduce its adverse reactions through reduced its dosage.

ABSTRACT
BACKGROUND: Older patients are prone to multimorbidity and polypharmacy, with an inherent risk of adverse events and drug interactions. To the best of our knowledge, available information on the appropriateness of lipid-lowering treatment is extremely limited. AIM: The aim of the present study was to quantify and characterize lipid-lowering drug use in a population of complex in-hospital older patients. METHODS: We analyzed data from 87 units of
internal medicine or geriatric medicine in the REPOSI (Registro Politerapie della Societa Italiana di Medicina Interna) study, with reference to the 2010 and 2012 patient cohorts. Lipid-lowering drug use was closely correlated with the clinical profiles, including multimorbidity markers and polypharmacy. RESULTS: 2171 patients aged >65 years were enrolled (1057 males, 1114 females, mean age 78.6 years). The patients treated with lipid-lowering drugs amounted to 508 subjects (23.4%), with no gender difference. Atorvastatin (39.3%) and simvastatin (34.0%) were the most widely used statin drugs. Likelihood of treatment was associated with polypharmacy (>5 drugs) and with higher Cumulative Illness Rating Scale (CIRS) score. At logistic regression analysis, the presence of coronary heart disease, peripheral vascular disease, and hypertension were significantly correlated with lipid-lowering drug use, whereas age showed an inverse correlation. Diabetes was not associated with drug treatment. CONCLUSIONS: In this in-hospital cohort, the use of lipid-lowering agents was mainly driven by patients' clinical history, most notably the presence of clinically overt manifestations of atherosclerosis. Increasing age seems to be associated with lower prescription rates. This might be indicative of cautious behavior towards a potentially toxic treatment regimen.


ABSTRACT

BACKGROUND: Patients (pts) scheduled for coronary artery bypass grafting, burdened with high risk of carotid stenosis, are recommended to undergo duplex ultrasonography (DUS) of carotid arteries. PURPOSE: To validate pocket-size imaging device (PSID) equipped with linear probe as an easily accessible tool enabling bedside screening for carotid artery stenosis (CAS). METHODS: A total of 100 pts (60 men, mean age 69+-11 years) with multivessel coronary artery disease underwent bedside DUS of carotid arteries with the use of PSID performed by a cardiology resident trained in DUS. Subsequently, DUS with the use of stationary high-end ultrasound system was performed in all pts to verify findings of PSID examination. RESULTS: Initial diagnosis of atherosclerotic plaque presence obtained with PSID in 59 patients was confirmed by high-end ultrasound system examination in all cases. There was a statistically significant correlation of intima-media thickness measurements between PSID and stationary system (r=.58; 95% CI: 0.48-0.66; P<.0001), but the coefficient of agreement (kappa) between the two methods in classification of intima-media as normal or thickened (>0.9 mm) was only .38 (95% CI: 0.299-0.459). During PSID examination, turbulent flow was observed in 21 pts-CAS was confirmed in all these pts-5 pts were diagnosed with significant CAS, the rest with CAS ranging from 30% to 70%. CONCLUSIONS: Pocket-size imaging device equipped with linear probe allows for identification of patients with atherosclerotic plaques and turbulent flow in carotid arteries; however, the degree of CAS cannot be reliably determined. The measurement accuracy of intima-media thickness is insufficient for a diagnostic purpose.


ABSTRACT
Cardiovascular disease remains the leading cause of morbidity and mortality in developed nations, with elevated low-density lipoprotein-cholesterol (LDL-C) levels being a major modifiable risk factor for coronary atherosclerosis. While lipid-lowering therapies such as statins are effective in lowering LDL-C, a proportion of patients do not achieve target LDL-C goals with statins or are intolerant to statins necessitating other treatment options. Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are a new class of agents that reduce LDL-C beyond the maximum achievable LDL-C reductions with statins, and have been well studied in different patient groups. However, there are concerns regarding their potential adverse effects and cost, given that morbidity and mortality benefits have not yet been demonstrated. This state-of-the-art review provides an overview of the development of PCSK9 inhibitors, the evidence regarding their clinical efficacy in specific target populations, and highlights future trials and challenges that need to be addressed before PCSK9 inhibitors are widely adopted into contemporary clinical practice.


ABSTRACT
AIM: To assess clinical characteristics, use of resources and costs of patients at very high risk (VHR) of cardiovascular (CV) events. Further, to assess how VHR patients are treated with statins (rate of prescription, dosages, adherence). METHODS AND RESULTS: A record linkage analysis was carried out of patient demographics, drug prescriptions, hospital discharge, specialty procedures from the ARNO Observatory, including 2,989,512 subjects of Local Health Units well representing the whole Italian country. Accrual lasted from January 1 to December 31, 2011. Among these subjects, 17,126 (0.56%) experienced a CV event, representing the cohort at VHR. Between VHR patients, 4810 (28.1%) individuals represent the diabetic cohort. Mean age of VHR patients was 77+/−13, females were 43.8%. Statins and/or ezetimibe were prescribed in 59.9% and 68.5% during the first year of follow respectively in VHR and VHR-diabetics. Prescription continuity at 1 year was 64.7% in patients at VHR, and 63.4% in VHR diabetics. At 1 year, at least one re-hospitalization occurred in 55.0% of patients for a total of 17,631 re-hospitalizations. In VHR diabetics, at least one readmission occurred in 59.6% of patients. Average annual cost for a single VHR patient was euro11,644 (drugs: euro1007; hospitalizations: euro10,097; specialty procedures: euro540); the corresponding cost for diabetics was euro13,199 (drugs: euro1394; hospitalizations: euro11,032, specialty procedures euro773). CONCLUSIONS: Atherothrombotic events are a relevant cause of hospitalization in the community setting. Prescription rate and continuity of treatment with statins seem to be at least suboptimal. NHS costs are high, with re-hospitalizations being the main cost-driver.

ABSTRACT
BACKGROUND: Statin combined with ezetimibe demonstrates significant benefit in lowering low density lipid cholesterol (LDL-C) and cardiovascular events abroad, but whether intermediate intensity statins combined with ezetimibe is superior to high-intensity statin monotherapy in Chinese people is unknown. METHODS: A total of 125 patients were randomly assigned to a intermediate intensity rosuvastatin group (rosuvastatin 10mg/d, n=42), high-dose rosuvastatin group (rosuvastatin 20mg/d, n=41) or combination therapy group (ezetimibe 10mg/d and rosuvastatin 10mg/d, n=42) with a 12-week follow-up. The primary end point was the proportion of patients who achieved the 2011 ESC/EAS LDL-C goal <70mg/dL (1.8mmol/L) at week 12. Secondary end points included changes from baseline in lipids, the occurrence of all cardiovascular events, high-sensitivity C-reactive protein and safety markers. RESULTS: The combination therapy group in the primary end point was significantly higher than rosuvastatin (20mg) and rosuvastatin (10mg) at week 12 (81.0% vs 68.3% vs 33.3%, P<0.001). And the similar change was observed in reducing LDL-C levels at week 12 (67.28% vs 52.80% vs 43.89%, P<0.001). The incidence of drug-related adverse events was much higher in the rosuvastatin 20mg group than the rosuvastatin 10mg group and the combination therapy group (17.0% vs 2.4% vs 4.8%, P<0.05). CONCLUSIONS: The combination of rosuvastatin 10mg/ezetimibe 10mg was an effectively alternative therapy superior to rosuvastatin 20mg or 10mg with a greater effect on lowering LDL-C and a lower incidence of drug-related adverse events in Chinese patients.


ABSTRACT
Purpose: The purpose of this study was to investigate the therapeutic effect of omega-3 polyunsaturated fatty acid (omega-3 PUFA) administration in a rat model of anterior ischemic optic neuropathy (rAION). Methods: The level of blood arachidonic acid/eicosapentaenoic acid (AA/EPA) was measured to determine the suggested dosage. The rAION-induced rats were administered fish oil (1 g/day EPA) or phosphate-buffered saline (PBS) by daily gavage for 10 consecutive days to evaluate the neuroprotective effects. Results: Blood fatty acid analysis showed that the AA/EPA ratio was reduced from 17.6 to <1.5 after 10 days of fish oil treatment. The retinal ganglion cell (RGC) densities and the P1-N2 amplitude of flash visual-evoked potentials (FVEP) were significantly higher in the omega-3 PUFA-treated group, compared with the PBS-treated group (P < 0.05). The number of apoptotic cells in the RGC layer of the omega-3 PUFA-treated rats was significantly decreased (P < 0.05) compared with that of the PBS-treated rats. Treatment with omega-3 PUFAs reduced the macrophage recruitment at the optic nerve (ON) by 3.17-fold in the rAION model. The M2 macrophage markers, which decrease inflammation, were induced in the omega-3 PUFA-treated group in contrast to the PBS-treated group. In addition, the mRNA levels of tumor necrosis factor-alpha, interleukin-1 beta, and inducible nitric oxide synthase were significantly reduced in the omega-3 PUFA-treated group. Conclusions: The administration of omega-3 PUFAs has neuroprotective effects
in rAION, possibly through dual actions of the antiapoptosis of RGCs and anti-inflammation via decreasing inflammatory cell infiltration, as well as the regulation of macrophage polarization to decrease the cytokine-induced injury of the ON.


ABSTRACT

BACKGROUND: Hypercholesterolaemia is an important modifiable risk factor for cardiovascular disease (CVD) which requires monitoring and management at a population level. AIMS: This study aims to describe the distribution of serum cholesterol in a community living population of older adults in Ireland and to examine the awareness, treatment and control of hypercholesterolaemia according to CVD risk status. METHOD: This is a cross-sectional study in a nationally representative sample of adults aged 50-79 years (n = 5287). Hypercholesterolaemia was defined as low-density lipoprotein cholesterol (LDL-C) in excess of the recommended CVD risk category target and/or on lipid-lowering medication. RESULTS: This study reports a mean total cholesterol (TC) of 5.1 mmol/L (95% CI 5.0-5.1 mmol/L) and a mean LDL-C of 2.9 mmol/L (95% CI 2.8-2.9 mmol/L) in those aged 50-79 years. In a subgroup aged 50-64 years, 73% (95% CI 71.5-74.5%) were hypercholesterolaemic. LDL-C was controlled to the guideline target in 57% of those with CVD and 49% of those with diabetes. Lack of awareness of hypercholesterolaemia was high across the remainder of the population. CONCLUSION: Despite a substantial reduction in population mean TC from a high of 6.0 mmol/L in the 1980s to 5.1 mmol/L, this study reports a failure to control hypercholesterolaemia to recommended risk-stratified targets in the Irish adult population. Recommendations for policy include continued monitoring of those at highest risk and CVD risk assessment in those perceived to be at low risk in order to inform shared decision making in relation to lifestyle modification and medication management.


ABSTRACT

BACKGROUND: Hyperlipidemia is a risk factor for neurodegenerative diseases. Proprotein convertase subtilisin / Kexin type 9 (PCSK9) degrades hepatic low-density lipoprotein receptor (LDLR) to regulate lipid metabolism. It is unclear if PCSK9 plays a role in neurodegenerative diseases. OBJECTIVE: This study was designed to determine whether PCSK9 is crucial between hyperlipidemia and Alzheimer’s disease. The interrelationship between PCSK9 and neuronal apoptosis was explored in PC12 cells in response to treatment with oxidized low-density lipoprotein (oxLDL). METHODS: Cultured PC12 cells were serum-starved and incubated with different concentrations of oxLDL for 24 h. Intracytoplasmic lipid droplets were observed by oil red O staining. Morphological assessment of apoptotic cells was performed using Hoechst 33258 staining and flow cytometry analysis. The expression of mRNA and protein was detected by reverse-transcription polymerase chain reaction (RT-PCR) and western blot analyses,
respectively. Transfection of small interfering RNA (siRNA) into PC12 cells was conducted using HiperFect Transfection Reagent. Concentrations of Abeta40 and Abeta42 were detected by enzyme-linked immunosorbent assay (ELISA) kit. RESULTS: Intracellular lipid content, the number of apoptotic cells, and PCSK9 expression were increased in PC12 cells after oxLDL treatment. Transfection with PCSK9 siRNA reduced the oxLDL-induced apoptosis of PC12 cells. We further confirmed the involvement of Bcl-2/Bax-Caspase (9, 3) signaling pathway in the regulation of PC12 cells apoptosis. beta-Secretase 1, another target gene of PCSK9, was downregulated in PC12 cells in response to oxLDL treatment. Abeta40 and Abeta42 contents were also decreased. CONCLUSION: PCSK9 promotes oxLDL-induced PC12 cell apoptosis through the Bcl-2/Bax-Caspase 9/3 signaling pathway.


ABSTRACT

BACKGROUND: The role of insulin resistance (IR) in the pathogenesis of cognitive performance is not yet clear. OBJECTIVE: To examine the associations between IR and cognitive performance and change in cognitive functions two decades later in individuals with cardiovascular disease with and without diabetes. METHODS: A subset of 489 surviving patients (mean age at baseline 58 +/- 6.6 y) with coronary heart disease who previously participated in the secondary prevention Bezafibrate Infarction Prevention (BIP trial; 1990-1997), were included in the current neurocognitive study. Biochemical parameters including IR (using the homeostasis model of assessment; HOMA-IR) were measured at baseline. During 2004-2008, computerized cognitive assessment and atherosclerosis parameters were measured (T1; n = 558; mean age 72.6 +/- 6.4 years). A second cognitive assessment was performed during 2011-2013 (T2; n = 351; mean age 77+/-6.4 years). Cognitive function, overall and in specific domains, was assessed. We used linear regression models and linear mixed models to evaluate the differences in cognitive performance and decline, respectively. RESULTS: Controlling for potential confounders, IR (top HOMA-IR quartile versus others) was associated with subsequent poorer cognitive performance overall (beta= -4.45 +/- Standard Error (SE) 1.54; p = 0.004) and on tests of memory and executive function among non-diabetic patients (beta= -7.16 +/- 2.38; p = 0.003 and beta= -3.33 +/- 1.84; p = 0.073, respectively). Moreover, among non-diabetic patients, IR was related to a greater decline overall (beta= -0.17 +/- 0.06; p = 0.008), and in memory (beta= -0.22 +/- 0.10; p = 0.024) and executive function (beta= -0.19 +/- 0.08; p = 0.012). The observed associations did not differ after excluding subjects with prevalent stroke or dementia. CONCLUSION: IR is related to subsequent poorer cognitive performance and greater cognitive decline among patients with cardiovascular disease.


ABSTRACT
BACKGROUND: Many patients report adverse reactions to, and may not tolerate, statin therapy. These patients may be at increased risk for coronary heart disease (CHD) events and mortality. OBJECTIVES: This study evaluated the risk for recurrent myocardial infarction (MI), CHD events, and all-cause mortality in Medicare beneficiaries with statin intolerance and in those with high adherence to statin therapy. METHODS: We studied 105,329 Medicare beneficiaries who began a moderate- or high-intensity statin dosage after hospitalization for MI between 2007 and 2013. Statin intolerance was defined as down-titrating statins and initiating ezetimibe therapy, switching from statins to ezetimibe monotherapy, having International Classification of Diseases, 9th revision, diagnostic codes for rhabdomyolysis or an antihyperlipidemic adverse event, followed by statin down-titration or discontinuation, or switching between >/=3 types of statins within 1 year after initiation. High statin adherence over the year following hospital discharge was defined as proportion of days covered >/=80%. Recurrent MI, CHD events (recurrent MI or a coronary revascularization procedure), and mortality were identified from 1 year after hospital discharge through December 2014. RESULTS: Overall, 1,741 patients (1.65%) had statin intolerance, and 55,567 patients (52.8%) had high statin adherence. Over a median of 1.9 to 2.3 years of follow-up, there were 4,450 recurrent MIs, 6,250 CHD events, and 14,311 deaths. Compared to beneficiaries with high statin adherence, statin intolerance was associated with a 36% higher rate of recurrent MI (41.1 vs. 30.1 per 1,000 person-years, respectively), a 43% higher rate of CHD events (62.5 vs. 43.8 per 1,000 person-years, respectively), and a 15% lower rate of all-cause mortality (79.9 vs. 94.2 per 1,000 person-years, respectively). The multivariate-adjusted hazard ratios (HR) comparing beneficiaries with statin intolerance versus those with high statin adherence were 1.50 (95% confidence interval [CI]: 1.30 to 1.73) for recurrent MI, 1.51 (95% CI: 1.34 to 1.70) for CHD events, and 0.96 (95% CI: 0.87 to 1.06) for all-cause mortality. CONCLUSIONS: Statin intolerance was associated with an increased risk for recurrent MI and CHD events but not all-cause mortality.


ABSTRACT

AIMS: The pleiotropic effects of statins on recurrent stroke remain unclear. We investigated the effects of pravastatin on high-sensitivity C-reactive proteins (Hs-CRP) in ischemic stroke, and explored the impact of Hs-CRP on recurrent stroke and vascular events. METHODS: This randomized open-label trial was ancillary to the J-STARS trial. One thousand and ninety-five patients with non-cardiogenic ischemic stroke were assigned to the pravastatin (n=545) or control groups (n=550). The primary and secondary endpoints were serum Hs-CRP reduction and stroke recurrence, including both ischemic and hemorrhagic ones, respectively. Onset of vascular events and each stroke subtype in relation to Hs-CRP levels were also determined. RESULTS: In the pravastatin treatment group, Hs-CRP levels (median 711 microg/L, IQR 344-1500) significantly decreased 2 months later (median 592 microg/L, IQR 301-1390), and they remained significantly lower until the end of the study. However, in the control group, baseline Hs-CRP levels were similar to those 2 months later. The reduction of Hs-CRP levels from the
baseline to 2 months in the pravastatin group was statistically significant compared with the control (p=0.007). One SD increase in log-transformed Hs-CRP increased the risk of stroke recurrence (HR 1.17, 95% CI 0.97-1.40) and vascular events (HR 1.30, 95% CI 1.12-1.51). With an Hs-CRP cut-off of 1000 microg/L, higher Hs-CRP significantly increased the risk of recurrent stroke (HR 1.50, 95% CI 1.03-2.17) and vascular events (HR 1.68, 95% CI 1.23-2.29).

CONCLUSION: In non-cardiogenic ischemic stroke, pravastatin treatment may reduce vascular inflammation as assessed by Hs-CRP, and higher Hs-CRP levels appeared to increase the risk of recurrent stroke and vascular events.


ABSTRACT

Even though it is only a little over a decade from the discovery of proprotein convertase subtilisin/kexin type 9 (PCSK9) as a plasma protein that associates with both high and low cholesterol syndromes, a rich body of knowledge has developed, and drugs inhibiting this target have been approved in many markets. While the majority of research in recent years has focused on the impact of therapeutic antagonism of this molecule, important lines of investigation have emerged characterizing its unique physiology as it relates to cholesterol metabolism and atherosclerosis. The PCSK9 story is unfolding rapidly but is far from complete. One chapter that is of particular interest is the possible direct link between PCSK9 and atherosclerosis. This review specifically examines this relationship drawing from data produced from experimental models of plaque biology and inflammation, atherosclerosis imaging studies, and observational epidemiology.


ABSTRACT

The correlation between simvastatin use and acute pancreatitis is explored. A case-control study was conducted to analyze claim data from the Taiwan National Health Insurance Program. The case group comprising a total of 3882 subjects aged 20 to 84 years with their first acute pancreatitis episode occurring between 1998 and 2011 formed the case group, against 3790 randomly selected controls matched for sex, age, comorbidities, and index year of acute pancreatitis diagnosis. Recent use of simvastatin was defined as subjects whose last remaining simvastatin tablet was noted <=7 days before the date of acute pancreatitis diagnosis. Remote use of simvastatin was defined as subjects whose last remaining 1 tablet for simvastatin was noted >7 days before the date of acute pancreatitis diagnosis. Never use of simvastatin was defined as subjects who had never been prescribed simvastatin. A multivariable unconditional logistic regression model was used to estimate the odds ratio and 95%CI to explore the correlation between simvastatin use and acute pancreatitis. After adjustment for confounders, multivariable logistic regression analysis revealed that the adjusted odds ratio of acute pancreatitis was 1.3 for subjects with recent use of simvastatin (95%CI 1.02, 1.73), when compared with those with never use of simvastatin. The crude odds ratio decreased to 1.1 for
those with remote use of simvastatin (95%CI 0.93, 1.34) but without statistical significance. Recent use of simvastatin is associated with acute pancreatitis. Clinicians should consider the possibility of simvastatin-associated acute pancreatitis for patients presenting for acute pancreatitis without known cause.


ABSTRACT
BACKGROUND: Simvastatin (SMV), a new locally delivered drug of class statins, is a specific competitive inhibitor of 3-hydroxy-2-methyl-glutaryl coenzyme A reductase. Statins, besides having lipid-lowering abilities, also have pleiotropic effects like host modulation and bone regeneration. The present study was designed to investigate the effectiveness of SMV, 1.2 mg, in an indigenously prepared biodegradable controlled-release gel as an adjunct to scaling and root planing (SRP). MATERIALS AND METHODS: A total of 60 sites, with pocket depth >/=5 mm, two from each of 30 patients after SRP, were categorized into two treatment groups, for subgingival placement of placebo (Gp 1) or SMV (Gp 2). Clinical parameters were recorded at baseline and at 1, 3 and 6 months comprising plaque index, gingival index, probing pocket depth (PPD) and clinical attachment level (CAL). The osseous changes were evaluated radiographically by measuring vertical gain, INFRA 1 and angle of the defect, INFRA 2 from baseline to 6 months. RESULTS: All subjects tolerated the drug, without any post-application complication. The treatment improved the periodontal condition in both the groups but significant reductions in PPD (p= 0.04), and INFRA 1 (p= 0.000), along with gain in CAL (p= 0.02) and INFRA 2 (p= 0.000) were observed in Gp 2. In one site, an unexpected 5 mm decrease in INFRA 1 was found. CONCLUSION: Local drug delivery of SMV enhanced the beneficial effect of SRP, in pocket reduction, gain in CAL and bone fill.


ABSTRACT
Following the continuous accumulation of evidence supporting the beneficial role of reducing low-density lipoprotein cholesterol (LDL-C) levels in the treatment and prevention of atherosclerotic cardiovascular disease and its complications, therapeutic possibilities now exist to lower LDL-C to very low levels, similar to or even lower than those seen in newborns and nonhuman species. In addition to the important task of evaluating potential side-effects of such treatments, the question arises whether extremely low LDL-C levels per se may provoke adverse effects in humans. In this review, we summarize information from studies of human cellular and organ physiology, phenotypic characterization of rare genetic diseases of lipid metabolism, and experience from clinical trials. Specifically, we emphasize the importance of the robustness of the regulatory systems that maintain balanced fluxes and levels of cholesterol at both cellular and organismal levels. Even at extremely low LDL-C levels, critical capacities of steroid hormone and bile acid production are preserved, and the presence of a cholesterol
blood-brain barrier protects cells in the central nervous system. Apparent relationships sometimes reported between less pronounced low LDL-C levels and disease states such as cancer, depression, infectious disease and others can generally be explained as secondary phenomena. Drug-related side-effects including an increased propensity for development of type 2 diabetes occur during statin treatment, while further evaluation of more potent LDL-lowering treatments such as PCSK9 inhibitors is needed. Experience from the ongoing large event-driven trials will be of great interest, and further evaluation including careful analysis of cognitive functions will be important. This article is protected by copyright. All rights reserved.


ABSTRACT

OBJECTIVE This article describes the use of ultrasound measurements of physical strain within carotid atherosclerotic plaques as a measure of instability and the potential for vascular cognitive decline, microemboli, and white matter changes. METHODS Asymptomatic patients with significant (> 60%) carotid artery stenosis were studied for dynamic measures of plaque instability, presence of microemboli, white matter changes, and vascular cognitive decline in comparison with normative controls and premorbid state. RESULTS Although classically asymptomatic, these patients showed vascular cognitive decline. The degree of strain instability measured within the atherosclerotic plaque directly predicted vascular cognitive decline in these patients thought previously to be asymptomatic according to classic criteria. Furthermore, 26% of patients showed microemboli, and patients had twice as much white matter hyperintensity as controls. CONCLUSIONS These data show that physical measures of plaque instability are possible through interpretation of ultrasound strain data during pulsation, which may be more clinically relevant than solely measuring degree of stenosis. The data also highlight the importance of understanding that the definition of symptoms should not be limited to motor, speech, and vision function but underscore the role of vascular cognitive decline in the pathophysiology of carotid atherosclerotic disease. Clinical trial registration no.: NCT02476396 ( clinicaltrials.gov ).


ABSTRACT

Statins are cholesterol-lowering drugs that inhibit 3-hydroxy-3- methylglutaryl-coenzyme A (HMG-CoA) reductase, a rate-limiting enzyme of the mevalonate pathway. The anti-inflammatory effect of statins has been reported in recent years. The present study investigated therapeutic effects of the local administration of statin in osteoarthritis (OA). We assessed clinically used statins and selected fluvastatin for further experimentation, as it showed potent anabolic and anti-catabolic effects on human OA chondrocytes. To achieve controlled intra-articular administration of statin, we developed an intra-articular injectable
A prespecified analysis of the IMPROVE-IT Trial. JAMA cardiology 2017.


ABSTRACT

Importance: In the Improved Reduction of Outcomes: Vytorin Efficacy International Trial, intensive low-density lipoprotein cholesterol (LDL-C)-reducing therapy with ezetimibe/simvastatin compared with simvastatin alone was associated with a significant reduction in cardiovascular events in 18144 patients after acute coronary syndrome. The safety of very low LDL-C levels over the long-term is unknown. Objective: To assess the safety and clinical efficacy of achieving a very low (<30 mg/dL) level of LDL-C at 1 month using data from the Improved Reduction of Outcomes: Vytorin Efficacy International Trial. Design, Setting, and Participants: This prespecified analysis compared outcomes in patients stratified by achieved LDL-C level at 1 month in the Improved Reduction of Outcomes: Vytorin Efficacy International Trial and adjusted for baseline characteristics during 6 years' median follow-up. Patients were enrolled from October 26, 2005, to July 8, 2010, and the data analysis was conducted from December 2014 to February 2017. Main Outcomes and Measures: Safety end points included adverse events leading to drug discontinuation; adverse muscle, hepatobiliary, and neurocognitive events; and hemorrhagic stroke, heart failure, cancer, and noncardiovascular death. Efficacy events were as specified in the overall trial. Results: Among the 15281 patients included in the study, 11645 (76.2%) were men and the median age was 63 years (interquartile range, 56.6-70.7 years). In these patients without an event in the first month, the achieved LDL-C values at 1 month were less than 30 mg/dL, 30 to 49 mg/dL, 50 to 69 mg/dL, and 70 mg/dL or greater in 6.4%, 31%, 36%, and 26% of patients, respectively. Patients with LDL-C values less than 30 mg/dL (median, 25 mg/dL; interquartile range, 21-27 mg/dL) at 1 month were more likely randomized to ezetimibe/simvastatin (85%), had lower baseline LDL-C values, and were more likely older, male, nonwhite, diabetic, overweight, statin naïve, and presenting with a first myocardial infarction. After multivariate adjustment, there was no significant association between the achieved LDL-C level and any of the 9 prespecified safety events. The adjusted risk of the primary efficacy composite of cardiovascular death, major coronary events, or stroke was significantly lower in patients achieving an LDL-C level less than 30 mg/dL at 1 month (adjusted hazard ratio, 0.79; 95% CI, 0.69-0.91; P = .001) compared with 70 mg/dL or greater. Conclusions and Relevance: Patients achieving an LDL-C level less than 30 mg/dL at 1 month had a similar
Literature update week 11 (2017)
safety profile (and numerically the lowest rate of cardiovascular events) over a 6-year period compared with patients achieving higher LDL-C concentrations. These data provide reassurance regarding the longer-term safety and efficacy of the continuation of intensive lipid-lowering therapy in very higher-risk patients resulting in very low LDL-C levels. Trial Registration: clinicaltrials.gov Identifier: NCT00202878.


ABSTRACT
Importance: The Open-Label Study of Long-term Evaluation Against LDL-C (OSLER-1) evaluated the durability of long-term efficacy and safety during long-term therapy with evolocumab, a monoclonal antibody against proprotein convertase subtilisin/kexin type 9 (PCSK9). Objective: To determine whether LDL-C level reductions with evolocumab persist across different populations. Secondary objectives included assessment of adverse events, antidrug antibodies, and factors contributing to treatment discontinuation. Design, Setting, and Participants: This ongoing, randomized open-label extension trial (OSLER-1) was conducted at 192 sites in 18 countries. A total of 1324 of 1666 patients randomized into 1 of 5 12-week double-blind phase 2 parent studies completed a parent study and chose to participate in OSLER-1; 1255 received 1 or more evolocumab doses. As of August 2016, 812 of 1324 (61%) had 208 weeks of follow-up. This current study was conducted from October 2011 to August 2016, with a data cutoff of August 26, 2016. Interventions: During year 1, patients were randomized to evolocumab, 420 mg, plus standard of care (SOC) or SOC alone. After year 1, all patients continuing the study received evolocumab, 420 mg, plus SOC. Main Outcomes and Measures: Lipids, safety, and tolerability every 12 weeks. A multivariate model identified factors associated with discontinuation of evolocumab. Results: At parent study baseline, the mean (SD) age of the population was 57.1 (11.6) years, with 52.9% being women. The median LDL-C level was 133 mg/dL (to convert to millimoles per liter, multiply by 0.0259). After 52 weeks, evolocumab plus SOC was associated with a significant reduction in LDL-C level by 61% (95% CI, -63% to -60%) vs 2% (95% CI, -5% to -0.2%) with SOC alone (P < .001). At approximately 2, 3, and 4 years of study follow-up, the median LDL-C level was reduced by 59% (95% CI, -60% to -57%), 59% (95% CI, -61% to -58%), and 57% (95% CI, -59% to -55%), respectively, from parent study baseline. For patients receiving statin therapy unchanged from baseline, at week 208, the median LDL-C level reduction was 58%. No neutralizing antibodies to evolocumab were detected. The annualized incidence of new-onset diabetes was 4% in the SOC alone group and, adjusting for duration of evolocumab exposure, 2.8% in the evolocumab plus SOC group. Neurocognitive event rates were 0% (SOC alone) and 0.4% (evolocumab plus SOC). A total of 79% of patients persisted with evolocumab treatment, with a mean exposure duration of 44 months. Conclusions and Relevance: In the longest clinical trial exposure to a PCSK9 inhibitor to date, evolocumab produced sustained reductions in LDL-C levels. The annual frequency of adverse events did not occur more frequently with cumulative exposure during open-label observation. Trial Registration: clinicaltrials.gov identifier: NCT01439880.
ABSTRACT

AIM: To study relation of lipoproteina - Lp(a) and subfractional composition of apoB containing lipoproteins to the presence of ischemic heart disease (IHD). Manerial and methods. Parameters of lipid spectrum, Lp(a), and subfractions of apoB containing lipoproteins were determined in blood serum of 187 patients with known data of instrumental examination.

RESULTS: Lp(a) concentration was not linked to any of risk factors, levels total cholesterol (TC), low and high density lipoprotein CH, and subfractions of lipoproteins. In total group triglyceride (TGG) level correlated with content of small dense LDL (sdLDL) \((r=0.445, <0.0001)\) and mean dimension of LDL particles \((r=-0.424, p<0.0001)\). This correlation was absent in the subgroup with Lp(a) more or equal 30 mg/dl and was strengthened among patients with normal Lp(a) level. In total group presence of IHD was associated with sex \((r=0.325, p<0.0001)\), Lp(a) concentration \((r=0.271, p=0.0001)\), and level of triglycerides \((r=0.159, p=0.030)\). In multiple regression analysis levels of TG, Lp(a) and sdLDL were selected as factors independently associated with presence of IHD. Detection of subfractions sdLDL>2 mg/dl in blood plasma (atherogenic profile B), as well as lowering of concentration of large LDL subfractions significantly increased probability of IHD presence in patients with elevated Lp(a) concentration Lp(a) concentration. CONCLUSION: Lp(a) is an independent factor of risk of coronary atherosclerosis more significant than shifts in subfractional composition of apoB containing lipoproteins. In patients with Lp(a) concentration less or equal 30 mg/dl subfractions of sdLDL were directly related to TG. Level of sdLDL and large lipoproteins of intermediate density are directly related to the presence of IHD. Large LDL correlates with concentration of HDL DL C and probably is cardioprotective. sdLDL content>2 mg/l or hypertriglyceridemia \((TG>1.7 \text{ mmol/l})\) significantly increase chances of detection of confirmed IHD in patients with elevated Lp(a).


ABSTRACT

In the literature review covered issues opening protein-proprotein convertase, subtilisin/kexin-type9 (PCSK9), its modern terminology, the results of its biochemical, molecular and genetic studies, metabolic regulation, functions and clinical findings in the blood content of PCSK9 in lipid disorders and clinical pharmacological studies of monoclonal antibodies to this protein for the correction of lipid metabolism of major interest for cardiology and lipidology.


ABSTRACT

AIM: To evaluate the efficacy and safety of amlodipin, lisinopril and rosvastatin therapy in metabolic syndrome and high cardiovascular risk patients with nonalcoholic fatty liver disease (NAFLD). PATIENTS AND METHODS: 6 months randomized study of fixed combination of amlodipin and lisinopril with or without rosvastatin of 20 patients with 2 grade of arterial hypertension, dyslipidemia with metabolic syndrome and nonalcoholic fatty liver disease (NAFLD). Efficacy and safety was revealed: office BP, ABPM, NAFLD Fibrosis scale, insulin resistance index (HOMA-IR), serum lipids were measured basically and after 6 months of therapy. RESULTS: 6 months amlodipin and lisinopril therapy results: office BP decreased from 153,4+/−2,9/83,3+/−2,5 to 131,0+/−2,4/79,9+/−4,5 mm Hg (=0,001, for systolic BP).159/91 to 132/77 mm Hg. 24-hours BP decreased from 153,6+/−3,6/89,5+/−3,2 to 127,1+/−3,0/73,5+/−2,9 (=0,002); in 85% of patients BP normalized. Low density lipoprotein cholesterol (LDL-C) decreased lower 2.5 mmol/l in all patients and lower 1.8 mmol/l in 45% patients on rosvastatin therapy. Before therapy 3 patients had elevated ALT levels, after 6 months therapy all patients had normal levels of ALT and AST. ALT decreased from 33,7+/−4,3 to 23,2+/−3,5 U/l (=0,01). Alkaline phosphatase decreased from 65,4+/−4,1 to 51,1+/−6,9 U/l (=0,02), gamma glutamyl transeptidease level was stable. NAFLD Fibrosis index revealed fibrosis and was stable -0,9+/−0,2 and -0,9+/−0,2 (>0,05). HOMA-IR decreased from 4.2+/−0,4 to 2,9+/−0,4 (=0,02). DISCUSSION: Some antihypertensive drugs and statins can be hepatotoxic especially in patients with metabolic syndrome and NAFLD. Antihypertensive drugs and statins with minimal liver metabolism can be preferable in NAFLD patients. CONCLUSION: Amlodipin, lisinopril and rosvastatin therapy is effective and safe in patients with metabolic syndrome of high cardiovascular risk and liver steatosis.

[52] Bart BY, Luchinkina EE, Gordeev IG et al. [Comparative Analysis of the Efficacy and Safety of Rosuvastatin and Original Rosuvastatin]. Kardiologiya 2016; 56:46-49.

ABSTRACT

The study is one of the priority points of the Russian Scientific Medical Society of Internal Medicine, initiated due to known high average level of LDL cholesterol in Russian population and necessity for its optimized control by better access to treatment. AIM: To conduct comparative analysis of efficacy and safety of the rosvastatin compound akorta and original rosvastatin crestor. MATERIAL AND METHODS: To randomized crossover study (PARITET) 60 patients were included with the diagnosis dyslipidemia. Total duration of treatment phase was 14 weeks - two times by 7 weeks, when the drugs were crossed, separated by 4 weeks washout. Main endpoints were the rate of low density lipoprotein cholesterol (LDL-C) decrease comparing to baseline, and reach of LDL-C guidelines-based target level. RESULTS: After the first 7-week treatment the rate of decrease in akorta group was 49.0+/−15.6%, in crestor 52.6+/−17.4% (p=0.606). After the second period, in respective groups prescription of crestor led to LDL-C decrease by 43.4+/−17.9%, akorta - by 47.2+/−16.3% (p=0.724). After the first period of treatment the value of target levels reach did not differ significantly (akorta - 70.0%, crestor - 83.3%; p>0.05). After the second period in the group crestor-akorta the value was significantly better than in akorta-crestor group (60.0% and 83.3%; p<0.05). Secondary efficacy endpoints were comparable in both groups. Safety parameters were comparable in both groups.
CONCLUSION: The study has shown equivalence of the original rosuvastatin compound crestor and generic compound acorta within the aim of dyslipidemia correction.


ABSTRACT
The article is devoted to the actual problem - the prevention of stroke in patients with arterial hypertension (AH). Mechanisms of cerebral complications of AH, the key areas of prevention of stroke are presented. On the basis of earlier large randomized trials justified the use of fixed combination products (polypills) comprising, along with antihypertensive lipid-lowering drugs, which is the key to improving treatment adherence and effectiveness of pharmacological prevention of stroke.


ABSTRACT


ABSTRACT

AIM: to elucidate relationship between parameters of negative ischemic stress test and subclinical atherosclerosis of carotid arteries. MATERIAL AND METHODS: Electrocardiographic stress test on treadmill and ultrasound study of carotid arteries (CA) were carried out in 204 patients (100 women and 104 men, mean age 54.16 +/- 8.07 years without verified ischemic heart disease and with more or equal 1 traditional factors of cardiovascular risk). Measurements of intima media thickness (IMT) in three extracranial CA segments and identification of atherosclerotic plaques (AP) were used for detection of subclinical atherosclerosis. CA total atherosclerotic plaque area (TAPA) was calculated when appropriate. RESULTS: Multifactorial regression analysis revealed the following predictors of increased IMT and TAPA: physical working capacity, increment and reserve of heart rate (HR), HR restoration, and increment of systolic arterial pressure (SAP). Presence of atherosclerotic plaque was associated with SAP rise >42% during exercise test and slow HR restoration ( < less or equal 42 bpm at 2-nd minute of recovery period). CONCLUSION: Analysis of nonelectrocardiographic parameters of negative relative to ischemia induction exercise test allows predicting severity of atherosclerotic changes in CA. The information obtained can supplement assessment of traditional factors of cardiovascular risk.

ABSTRACT

OBJECTIVE: This open randomized study compares the effects of 24-week-long treatment with rosvuastatin and with atorvastatin coadministered with ezetimibe on the parameters of carbohydrate metabolism and the plasma levels of adipokynes in patients with coronary artery disease and type 2 diabetes mellitus or impaired glucose tolerance (IGT). METHOD: A total of 31 patients with coronary artery disease and type 2 diabetes mellitus or IGT were recruited in the study. Patients were randomized into two groups: group 1 included patients who received rosvuastatin therapy in an average dose of 12.5 mg/day (n=16); group 2 included patients who received combination treatment with atorvastatin in an average dose of 13.3 mg/day and ezetimibe (10 mg) (n=15). Plasma levels of lipids, apoB, apoA1, glucose, insulin, leptin, and adiponectin were evaluated; HOMA-IR index (an empty stomach insulin, μU/l x fasting glucose, mmol/l) / 22.5) was calculated. RESULTS: During the therapy, the LDL-C and apoB levels decreased by 51.7% and 42.3% in group 1 and by 51.8% and 44.9% in group 2, respectively. Reduction in the triglyceride levels was significantly more pronounced in group 2 than in group 1: 43.2% vs 17.4% (p<0.02), whereas we did not observed significant changes of HDL-C and apoA1 in either group. The increases in basal glycemia, basal insulinemia, HbA1c levels (from 6.47% [6.10-7.02%] to 6.98% [6.23-8.18%]), and HOMA-IR (from 2.14 [1.68-3.51] to 4.30 [2.31-5.77]) were found only in group 2 (p<0.05 for all). These changes were observed in 75% of patients of group 2 independently of the presence of diabetic state or IGT, but the changes were more pronounced in patients with disturbed carbohydrate metabolism. Changes of leptin levels during the therapy were diverse: 73% patients of group 1 demonstrated decrease in the leptin levels, whereas 67% of patients in group 2 experienced 57%-increase in the leptin concentrations. Degree of increased basal glycemia was associated with increase in the leptin levels (r=0.37, p=0.04) in the entire group of patients (n=31). Furthermore, changes in leptin levels were negatively associated with decreased adiponectin levels (r=-0.57, p=0.034).

CONCLUSIONS: In case of equivalent degree of the decrease in LDL-C levels, 24-week combination therapy with atorvastatin and ezetimibe, unlike rosvuastatin treatment, induced increases in basal glycemia, insulinemia, HbA1c, and HOMA-IR index irrespective of the presence of carbohydrate metabolism disturbances before treatment. Our data suggest that adiponectin and leptin are involved in the mechanisms of adverse metabolic effects of the combination of atorvastatin and ezetimibe.


ABSTRACT
Currently, pharmacotherapy of coronary heart disease, based on antianginal drugs directly improve coronary blood flow, antiplatelet, and lipid-lowering drugs, includes a new class of drugs - cardiocytoprotectors. Recent ischemic cardiomyocytes improve security in the ATP, by optimizing the energy metabolism by reducing the need for oxygen cardiomyocytes and has an antioxidant effect, protecting cellular structures and enzymes from oxidative stress accompanying hypoxia.


ABSTRACT
Examined 52 patients with a diagnosis Ischemic heart disease: stable angina II-III FC CHF I-IIA stage, in combination with hypercholesterolemia aged 53-65 years (58,2+-6,5), receiving together with traditional antianginal therapy generic atorvastatin Torvakard in the dose of 10 mg/day (20 people) with the level of total cholesterol from 5.0 to 6.50 mmol/l, patients with cholesterol levels from is 6.51 to 8.0 mmol/l was taking Torvakard 20 mg/day (32 person). As a result of 3 months therapy with low doses of Torvakard a decreased level of CRP, endothelin-1, IMT, improving the parameters of endothelium-dependent vasodilation, which shows the positive impact of the drug on morphological and functional parameters of the vascular wall.


ABSTRACT
BACKGROUND AND AIM: The increasing number of coronary artery bypass grafting (CABG) is associated with a need for active introduction of methods improving immediate and long-term results of these interventions. Results of a number of studies conducted during recent years allow to consider high dose statin therapy one of such methods. In this article we present results of rosuvastatin administration to patients with ischemic heart disease (IHD) prior to surgery. METHODS: Rosuvastatin (40 mg/day) was given for 4 weeks before CABG to patients who had previously taken simvastatin (20 mg/day). RESULTS: This regimen was associated with reduction of desquamation of endothelium of the intima, reduction of the number of smooth muscle cells in the media, as well as the proliferation index according to the immunohistochemical analysis in sections of the great saphenous vein selected for the coronary anastomosis. CONCLUSION: It is assumed that the antiproliferative effects of high-dose rosuvastatin therapy may have a positive impact in relation to the viability of a remote arteriovenous grafts.


ABSTRACT
The results of the Russian part of the EUROASPIRE IV study show that we have a large room for improvement of traditional risk factors management in CAD patients hospitalized for acute myocardial infarction, acute coronary syndromes, PCI or CABG (at average in 1.7 years of follow-up after index events). It is also true for other European countries, although certain differences exist between Russian and whole study population. In some respects, the results of secondary prevention in Russian patients were even more successful: e.g. effective blood pressure control was achieved in 73.4% of our patients taking antihypertensive drugs vs 53.5% in whole study population. In contrast, smoking was more prevalent among Russian patients (22.2% vs 15.0% in other countries). Obviously, it was related to lower frequency of smoking cessation support offered to our patients: only 1.1% were referred to a smoking cessation program, 3.2% were prescribed nicotine replacement therapy, none were prescribed varenicline (vs 18.6, 22.9, 6.2%, respectively, in whole study population). The Russian cohort had the highest rate of overweight and obesity compared to other European countries (93.1 vs 82.1% in whole study population). 74.9% our patients received lipid lowering drugs (vs 86.6% in Europe), although the LDL-C goal was achieved only in 15.9% of our patients taking lipid lowering drugs (vs 21.1% in whole study population).


ABSTRACT
Aim of the study was to analyze the validity of pharmacoepidemiological purpose and structure of lipid-lowering therapy (LLT) in patients with hypertension and dyslipidemia in clinical practice. Demonstrated commitment to the basic principles of medical verification of cardiovascular events with an adequate definition of risk SCORE scale for patients with high and very high risk. However, the lack of definition of fractions of cholesterol is not allowed to make the right decision on the appointment of GLT for a number of patients with low and moderate risk. The advantage in the appointment of atorvastatin used (32.3%), simvastatin (27.8%) and rosuvastatin (20.9%), and from the antihypertensive subgroups - angiotensin converting enzyme inhibitors, -blockers, calcium antagonists, sartan. Revealed insufficient control of blood lipid in the dynamics on the background of LLT, low activity of doctors in the statin dose titration and use of combined LLT (6.9%) in order to achieve target levels of atherogenic key biochemical parameters. Taking into account the literature data on the most effective and priorities destination rosuvastatin and its high safety in clinical situations of forced polypharmacy we conducted pharmacoeconomic comparison of rosuvastatin several manufacturers of direct cost. Established a price advantage of rosuvastatin (tevastor) with respect to both the original drug, and to a number specified in the prescribing of generics. No fixed assignment LLT is testimony not revealed irrational combinations of drugs with contraindications recommendations, including the appointment of antihypertensive drugs. CONCLUSION: Further work is needed to evaluate pharmacoeconomic indicators LLT, to raise awareness of physicians to enhance quality control of medical assistance and measures to reduce the risk of complications in patients with cardiovascular disease of atherosclerotic origin.
Chronic obstructive pulmonary disease (COPD) is the third leading cause of death in the list of common causes of mortality after cardiovascular diseases. The processes of atherogenesis and cardiovascular diseases are accelerated in patients with COPD. The key mechanisms of COPD pathogenesis are oxidative stress, depletion of antioxidant protection, development of the pulmonary and systemic inflammation and the development of endothelial dysfunction. This article discusses the pleiotropic effects of statins in patients with COPD.


ABSTRACT

PURPOSE: Determination of computed tomography angiography (CTA) informativeness in assessment of state of atherosclerotic coronary plaque (ACP) and identification of signs of its instability compared with intravascular ultrasound (IVUS). MATERIALS AND METHODS: Coronary CTA was carried out in 52 patients with clinical presentation of non-ST elevation (NSTE) acute coronary syndrome on the first day of hospitalization. ACPs were identified in 32 of 52 patients (61.5%). IVUS was performed in 32 patients (mean age 58+/-11.4 years, 27 men, 5 women, 22 with unstable angina, 10 with NSTE myocardial infarction) and 50 plaques in 45 coronary arteries were characterized (39 with spectral analysis of IVUS data). All data were compared with the results of coronary CTA. RESULTS: Sensitivity and specificity of CTA in the detection of stenosis >50% were 97.67 and 71.40%, respectively. Correlation analysis showed a high comparability of methods in determining plaque burden (r=0.80, 95% confidence interval [CI] 0.67 - 0.88, p<0.0001), plaque length (r=0.75, 95%CI 0.60 - 0.85, p<0.0001), and remodeling index (r=0.62, 95%CI 0.40 - 0.77, p<0.0001). Threshold value for "low-density areas" of plaques typical for thin cap fibroatheroma was less or equal 41 Hounsfield units (sensitivity 82%; specificity 86%; area under the curve 0.824; 95% CI 0.615 - 0.947, p<0.0005). CONCLUSION: Coronary CT is a non-invasive method for rapid characterization of ACP. CT results correlate well with IVUS data, including identification of such important signs of plaque instability as presence of "low-density zone" and positive remodeling at the plaque level.


ABSTRACT
THE AIM OF THE STUDY: to analyze the dynamics of lymphocytic composition of human atherosclerotic plaques in ex vivo culture system. MATERIALS AND METHODS: The study included 15 atherosclerotic plaques obtained from patients who underwent carotid endarterectomy. Plaques were cultured as ring-shaped explants on collagen rafts in culture medium of special composition in CO2 incubator according to the previously developed technique. On day 0, and also on the 4th and 19th days of culture we extracted cells from plaque explants and analyzed B- and T-lymphocytic content of the plaque, as well as the percentage of CD16+ natural killer (NK) cells, using multichromatic flow cytometry. For this purpose we digested the explants with an original enzymatic cocktail, which allows preservation of cell surface markers, and we stained extracted cells with fluorescence-labelled monoclonal antibodies against CD45, CD3, CD19, CD4, CD8, CD16. In addition, we estimated the amount of interleukin 2 (IL-2) and interferon-gamma (IFN-γ)-producing T-cells by means of flow cytometry. RESULTS: After 4 days of culture the amount of lymphocytes in plaques explants decreased, however live lymphocytes were still preserved (2619.3 [1680.4, 3478.2] cells/100mg tissue). Viable lymphocytes population included T cells (2123.4 [484.9; 3181.2] cells/100 mg tissue), B cells (5.6 [3.4, 27.9] cell/100 mg tissue) and CD16+ NK cells (10.6 [1.8, 23.7] cell/100mg tissue). On the 4th day of culture T cells were presented by CD4+CD8- (797 [475.5, 1000.7] cells/100mg tissue, 37.5 [32.1, 46.3]% and CD4-CD8+ (686.2 [423.6, 1158.4] cells/100 mg tissue, 45.6 [38.1, 47.9]% populations. The percentage of CD4+CD8- T cell population decreased compared to the 1st day of culture, and this decrease correlated with the increase in CD4-CD8+ T cells content (p<0.05). Additionally, after 4 days of culture we found in tissue explants both CD8+ (17.5[13.3,19.9]% and CD8-(9.9 [6.4, 14]% IFN--producing T-cells, however, their percentage, as well as the percentage of IL-2-producing T cells tended to decrease. After 19 days of culture explants of atherosclerotic plaques also contained lymphocytes (2830.1 [2350.3, 5900.2] cells/100mg tissue). Lymphocytes population included T cells (2594.5 [2035.7, 5306.7] cells/100mg tissue), presented by CD4+CD8- (1016.8 [671.2, 2201.7] cells/100mg tissue, 42.3 [34.3, 47.8]% and CD4-CD8+ (1534.3 [813.8; 2207.2] cells/100mg tissue, 50.8 [45.6, 56.5]% subsets, B cells (31 [18.3, 64.4] cell/100 mg tissue) and CD16+ NK cells (44.9 [33.4, 138.9] cells/100 mg of tissue). DISCUSSION: An ex vivo model of human atherosclerotic plaque culture that we previously developed enables to preserve viability of various lymphocyte subsets for up to 19 days. We also found that cultured tissue explants retain T cells that can maintain T-helper-1-dependent immune response, which demonstrates inflammation in atherosclerotic plaques. Our results allow to perform experiments on immunological mechanisms of atherogenesis and to develop new approaches for treatment of atherosclerosis, devoted to the suppression of local inflammatory processes in atherosclerotic plaques. CONCLUSIONS: An ex vivo model of human atherosclerotic plaque preserves CD4+CD8- and CD4-CD8+ T cells, B cells, and CD16+ NK cells for a long time. Moreover, after 4 days of culture tissue explants also retain IFN-++ T cells.


Abstract
ABSTRACT

BACKGROUND: Effects of simvastatin on serum level of adiponectin, a protein conferring benefits in both cardiovascular and metabolic system, are not fully determined. METHODS: A meta-analysis of randomized controlled trials (RCTs) was performed. Studies were identified by searching of Pubmed, Embase, and the Cochrane Library databases. Heterogeneity among the RCTs was determined by Cochrane’s Q test and I² statistics. Meta-analysis was performed with random-effect model or fixed-effect model according to the heterogeneity. Meta-regression and subgroup analyses were performed to analyze the source of heterogeneity. RESULTS: Twelve RCTs with 16 comparisons and 1042 patients were included. Overall, serum adiponectin was not significantly affected by simvastatin (WMD: 0.42 mg/mL; 95% CI, -0.66-1.50 mg/mL). However, significant heterogeneity was detected (Cochrane’s Q test: p < 0.01; I² = 83%). Subsequent meta-regression analyses indicated that treatment duration was a significant determinant of the effects of simvastatin treatment on serum adiponectin (Coefficient 0.04, p = 0.03). Subgroup analyses demonstrated that simvastatin treatment was associated with increased adiponectin in studies with treatment duration of 12 weeks (WMD: 3.65 mg/mL; p < 0.01), but not in studies with treatment duration of <= 8 weeks (WMD: -0.20 mg/mL; p = 0.38). The different between the two strats was significant (p < 0.01). CONCLUSIONS: Treatment with simvastatin of 12 weeks may increase the serum level adiponectin in patients at risk for cardiovascular diseases, but not for the short term treatment of <= 8 weeks.


ABSTRACT

BACKGROUND: Previous studies established a possible link among hyperhomocysteinemia (HHcy), dyslipidemia, and atherosclerosis. However, there was limited epidemic data concerning the relation between HHcy and lipid profiles, especially in community-based Chinese populations. This study aim to investigate the association of plasma homocysteine (Hcy) level with lipid profiles in a Chinese community-based population without lipid-lowering treatment. METHOD: A total of 4660 Chinese subjects from a cohort of the Shijingshan district in Beijing were included in the analysis. Plasma total Hcy, serum lipid files including total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) as well as relevant metabolic risk factors were measured. Multivariate regression models adjusting for age, gender, smoking, drinking, physical activity, vitamin B supplement, body mass index, fasting blood glucose level, serum creatinine, systolic and diastolic blood pressure were used to evaluate associations of Hcy and lipid profiles. RESULT: Subjects were 56.75 +/- 8.91 years old, and 38.15% were male. Median (IQR) Hcy was 11.98 (10.00-14.93) mumol/L, and 24.4% had HHcy (defined as Hcy >= 15 mumol/L). Mean (SD) baseline TC was 5.34 +/- 0.98 mmol/L, LDL-C was 3.27 +/- 0.81 mmol/L, and HDL-C was 1.43 +/- 0.38 mmol/L. Median (IQR) of TG was 1.28 (0.91-1.85) mmol/L. In multivariable linear-regression analyses, lnHcy (ln transformation for Hcy) level was positively associated with lnTG.


ABSTRACT

BACKGROUND: Low circulating levels of adiponectin, an anti-inflammatory and vasculoprotective adipokine, are associated with obesity, type 2 diabetes, and atherosclerotic disease. Presence of unstable plaques in the carotid artery is a known etiological factor causing ischemic strokes. Herein, we systematically reviewed the association between circulating adiponectin and progression of carotid atherosclerotic disease, particularly evaluating the occurrence of (1) carotid atherosclerotic plaques, (2) ischemic stroke, and (3) mortality in subjects who suffered a previous ischemic stroke. METHODS: Medline, Embase, Biosis, Scopus, Web of Science, and Pubmed were searched for published studies and conference abstracts. The effect size and 95% confidence intervals (CIs) of the individual studies were pooled using fixed-effect or random-effect models. The quality of the eligible studies was evaluated using the Newcastle-Ottawa quality assessment scale. Sensitivity, subgroup, and meta-regression analyses were performed to address the impact of various risk factors on the association between adiponectin and ischemic stroke risk. RESULTS: Twelve studies fulfilled the inclusion criteria for 3 independent meta-analyses. The association of increasing circulating adiponectin levels (5µg/mL-increment) with presence of carotid plaque was not conclusive (n=327; OR: 1.07; 95% CI: 0.85-1.35; 2 studies), whereas high adiponectin levels showed a significant 8% increase in risk of ischemic stroke (n=13,683; 7 studies), with a more sizable association observed among men compared to women. HDL was observed to have a marginal effect on the association between adiponectin and ischemic stroke, while other evaluated parameters were not found to be effect modifiers. A non-significant association of adiponectin with mortality was yielded (n=663; OR: 2.58; 95% CI: 0.69-9.62; 3 studies). Although no publication bias was evident, there was significant between-study heterogeneity in most analyses. CONCLUSION: It appears that the direction of the relationship between adiponectin and carotid atherosclerotic plaque presence is dependent on the duration, severity, and nature of the underlying disease, while increased adiponectin levels were associated with an increase in risk for ischemic stroke. Lastly, the results from the mortality meta-analysis remain inconclusive. Future properly designed studies are necessary to further elucidate the role of adiponectin on atherosclerotic plaque development, and its related outcomes.
BACKGROUND: There is strong evidence indicating that gut microbiota have the potential to modify, or be modified by the drugs and nutritional interventions that we rely upon. This study aims to characterize the compositional and functional effects of several nutritional, nutraceutical, and pharmaceutical cardiovascular disease interventions on the gut microbiome, through metagenomic and metabolomic approaches. Apolipoprotein-E-deficient mice were fed for 24 weeks either high-fat/cholesterol diet alone (control, HFC) or high-fat/cholesterol in conjunction with one of three dietary interventions, as follows: plant sterol ester (PSE), oat beta-glucan (OBG) and bile salt hydrolase-active Lactobacillus reuteri APC 2587 (BSH), or the drug atorvastatin (STAT). The gut microbiome composition was then investigated, in addition to the host fecal and serum metabolome. RESULTS: We observed major shifts in the composition of the gut microbiome of PSE mice, while OBG and BSH mice displayed more modest fluctuations, and STAT showed relatively few alterations. Interestingly, these compositional effects imparted by PSE were coupled with an increase in acetate and reduction in isovalerate (p < 0.05), while OBG promoted n-butyrate synthesis (p < 0.01). In addition, PSE significantly dampened the microbial production of the proatherogenic precursor compound, trimethylamine (p < 0.05), attenuated cholesterol accumulation, and nearly abolished atherogenesis in the model (p < 0.05). However, PSE supplementation produced the heaviest mice with the greatest degree of adiposity (p < 0.05). Finally, PSE, OBG, and STAT all appeared to have considerable impact on the host serum metabolome, including alterations in several acylcarnitines previously associated with a state of metabolic dysfunction (p < 0.05).

CONCLUSIONS: We observed functional alterations in microbial and host-derived metabolites, which may have important implications for systemic metabolic health, suggesting that cardiovascular disease interventions may have a significant impact on the microbiome composition and functionality. This study indicates that the gut microbiome-modifying effects of novel therapeutics should be considered, in addition to the direct host effects.


ABSTRACT

Glioblastoma multiform (GBM) is a primary malignant brain tumor with a few therapeutic targets available for it. The interaction between the immune system and glioma is an important factor that could lead to novel therapeutic approaches to fight glioma. In this study, we investigated in vitro anti-inflammatory and apoptotic activity of atorvastatin in different concentrations 1, 5, and 10 μM on glioma spheroid cells cultured in a three-dimensional model in fibrin gel that indicate the complex in vivo microenvironment better than a simple two-dimensional cell culture. A mechanistic insight into the role of IL-17RA, TRAF3IP2, and
apoptotic genes in progression of glioma could provide an important way for therapy of malignant tumors with manipulation of this inflammatory axis. To reach for these aims, after 24 and 48 h exposure with different concentrations of atorvastatin, caspase-8, caspase-3, Bcl-2, TRAF3IP2, and IL-17RA gene expression were assayed. Terminal deoxynucleotidyl transferase-mediated dUTP nick-end labeling assay and cell cycle assay were used for evaluating the cell apoptosis and proliferation. The results showed that atorvastatin has anti-inflammatory and apoptotic effects against glioma spheroids. Atorvastatin induced the expression of caspase-3 and caspase-8 and downregulated the expression of Bcl-2, TRAF3IP2, and IL-17RA especially at 10 μM concentration. These effects are dose dependent. The most likely mechanisms are the inhibition of inflammation by IL-17RA interaction with TRAF3IP2 and NF-kappaB signaling pathway. Finally, these results suggest that atorvastatin could be used as an anti-cancer agent for glioblastoma treatment.


ABSTRACT


ABSTRACT

Background In a previous study, a single injection of inclisiran, a chemically synthesized small interfering RNA designed to target PCSK9 messenger RNA, was found to produce sustained reductions in low-density lipoprotein (LDL) cholesterol levels over the course of 84 days in healthy volunteers. Methods We conducted a phase 2, multicenter, double-blind, placebo-controlled, multiple-ascending-dose trial of inclisiran administered as a subcutaneous injection in patients at high risk for cardiovascular disease who had elevated LDL cholesterol levels. Patients were randomly assigned to receive a single dose of placebo or 200, 300, or 500 mg of inclisiran or two doses (at days 1 and 90) of placebo or 100, 200, or 300 mg of inclisiran. The primary end point was the change from baseline in LDL cholesterol level at 180 days. Safety data were available through day 210, and data on LDL cholesterol and proprotein convertase subtilisin-kexin type 9 (PCSK9) levels were available through day 240. Results A total of 501 patients underwent randomization. Patients who received inclisiran had dose-dependent reductions in PCSK9 and LDL cholesterol levels. At day 180, the least-squares mean reductions in LDL cholesterol levels were 27.9 to 41.9% after a single dose of inclisiran and 35.5 to 52.6% after two doses (P<0.001 for all comparisons vs. placebo). The two-dose 300-mg inclisiran regimen produced the greatest reduction in LDL cholesterol levels: 48% of the patients who received the regimen had an LDL cholesterol level below 50 mg per deciliter (1.3 mmol per liter) at day 180. At day 240, PCSK9 and LDL cholesterol levels remained significantly lower than at baseline in association with all inclisiran regimens. Serious adverse events occurred in 11% of the patients who received inclisiran and in 8% of the patients who received placebo. Injection-site reactions occurred in 5% of the patients who received injections of inclisiran. Conclusions In our trial, inclisiran was found to lower PCSK9 and LDL cholesterol levels among patients at high
cardiovascular risk who had elevated LDL cholesterol levels. (Funded by the Medicines Company; ORION-1 ClinicalTrials.gov number, NCT02597127.).

ABSTRACT
Background Bococizumab is a humanized monoclonal antibody that inhibits proprotein convertase subtilisin-kexin type 9 (PCSK9) and reduces levels of low-density lipoprotein (LDL) cholesterol. We sought to evaluate the efficacy of bococizumab in patients at high cardiovascular risk. Methods In two parallel, multinational trials with different entry criteria for LDL cholesterol levels, we randomly assigned the 27,438 patients in the combined trials to receive bococizumab (at a dose of 150 mg) subcutaneously every 2 weeks or placebo. The primary end point was nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina requiring urgent revascularization, or cardiovascular death; 93% of the patients were receiving statin therapy at baseline. The trials were stopped early after the sponsor elected to discontinue the development of bococizumab owing in part to the development of high rates of antidrug antibodies, as seen in data from other studies in the program. The median follow-up was 10 months. Results At 14 weeks, patients in the combined trials had a mean change from baseline in LDL cholesterol levels of -56.0% in the bococizumab group and +2.9% in the placebo group, for a between-group difference of -59.0 percentage points (P<0.001) and a median reduction from baseline of 64.2% (P<0.001). In the lower-risk, shorter-duration trial (in which the patients had a baseline LDL cholesterol level of >/=70 mg per deciliter [1.8 mmol per liter] and the median follow-up was 7 months), major cardiovascular events occurred in 173 patients each in the bococizumab group and the placebo group (hazard ratio, 0.99; 95% confidence interval [CI], 0.80 to 1.22; P=0.94). In the higher-risk, longer-duration trial (in which the patients had a baseline LDL cholesterol level of >/=100 mg per deciliter [2.6 mmol per liter] and the median follow-up was 12 months), major cardiovascular events occurred in 179 and 224 patients, respectively (hazard ratio, 0.79; 95% CI, 0.65 to 0.97; P=0.02). The hazard ratio for the primary end point in the combined trials was 0.88 (95% CI, 0.76 to 1.02; P=0.08). Injection-site reactions were more common in the bococizumab group than in the placebo group (10.4% vs. 1.3%, P<0.001). Conclusions In two randomized trials comparing the PCSK9 inhibitor bococizumab with placebo, bococizumab had no benefit with respect to major adverse cardiovascular events in the trial involving lower-risk patients but did have a significant benefit in the trial involving higher-risk patients. (Funded by Pfizer; SPIRE-1 and SPIRE-2 ClinicalTrials.gov numbers, NCT01975376 and NCT01975389.).

ABSTRACT
Background Bococizumab, a humanized monoclonal antibody targeting proprotein convertase subtilisin-kexin type 9 (PCSK9), reduces levels of low-density lipoprotein (LDL) cholesterol. However, the variability and durability of this effect are uncertain. Methods We conducted six
parallel, multinational lipid-lowering trials enrolling 4300 patients with hyperlipidemia who were randomly assigned to receive 150 mg of bococizumab or placebo subcutaneously every 2 weeks and who were followed for up to 12 months; 96% were receiving statin therapy at the time of enrollment. The patients were assessed for lipid changes over time, stratified according to the presence or absence of antidrug antibodies detected during the treatment period. Results At 12 weeks, patients who received bococizumab had a reduction of 54.2% in the LDL cholesterol level from baseline, as compared with an increase of 1.0% among those who received placebo (absolute between-group difference, -55.2 percentage points). Significant between-group differences were also observed in total cholesterol, non-high-density lipoprotein cholesterol, apolipoprotein B, and lipoprotein(a) (P<0.001 for all comparisons). However, high-titer antidrug antibodies developed in a substantial proportion of the patients who received bococizumab, which markedly diminished the magnitude and durability of the reduction in LDL cholesterol levels. In addition, among patients with no antidrug antibodies, there was wide variability in the reduction in LDL cholesterol levels at both 12 weeks and 52 weeks. Major cardiovascular events occurred in 57 patients (2.5%) who received bococizumab and in 55 (2.7%) who received placebo (hazard ratio, 0.96; 95% confidence interval, 0.66 to 1.39; P=0.83). The most common adverse event among patients who received bococizumab was injection-site reaction (12.7 per 100 person-years). Conclusions In six multinational trials evaluating bococizumab, antidrug antibodies developed in a large proportion of the patients and significantly attenuated the lowering of LDL cholesterol levels. Wide variation in the relative reduction in cholesterol levels was also observed among patients in whom antidrug antibodies did not develop. (Funded by Pfizer; SPIRE ClinicalTrials.gov numbers, NCT01968954 , NCT01968967 , NCT01968980 , NCT02100514 , NCT02135029 , and NCT02458287 ).


ABSTRACT

Background Evolocumab is a monoclonal antibody that inhibits proprotein convertase subtilisin-kexin type 9 (PCSK9) and lowers low-density lipoprotein (LDL) cholesterol levels by approximately 60%. Whether it prevents cardiovascular events is uncertain. Methods We conducted a randomized, double-blind, placebo-controlled trial involving 27,564 patients with atherosclerotic cardiovascular disease and LDL cholesterol levels of 70 mg per deciliter (1.8 mmol per liter) or higher who were receiving statin therapy. Patients were randomly assigned to receive evolocumab (either 140 mg every 2 weeks or 420 mg monthly) or matching placebo as subcutaneous injections. The primary efficacy end point was the composite of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization. The key secondary efficacy end point was the composite of cardiovascular death, myocardial infarction, or stroke. The median duration of follow-up was 2.2 years. Results At 48 weeks, the least-squares mean percentage reduction in LDL cholesterol levels with evolocumab, as compared with placebo, was 59%, from a median baseline value of 92 mg per deciliter (2.4 mmol per liter) to 30 mg per deciliter (0.78 mmol per liter) (P<0.001). Relative to placebo, evolocumab treatment significantly reduced the risk of the primary end point (1344 patients [9.8%] vs. 1563 patients [11.3%]; hazard ratio, 0.85; 95% confidence interval [CI], 0.79
Monocytes are heterogeneous effector cells involved in the maintenance and restoration of tissue integrity. Monocytes and macrophages are involved in cardiovascular disease progression, and are associated with the development of unstable atherosclerotic plaques. Hyperlipidaemia can accelerate cardiovascular disease progression. However, monocyte responses to hyperlipidaemia are poorly understood. In the past decade, accumulating data describe the relationship between the dynamic blood lipid environment and the heterogeneous circulating monocyte pool, which might have profound consequences for cardiovascular disease. In this Review, we explore the updated view of monocytes in cardiovascular disease and their relationship with macrophages in promoting the homeostatic and inflammatory responses related to atherosclerosis. We describe the different definitions of dyslipidaemia, highlight current theories on the ontogeny of monocyte heterogeneity, discuss how dyslipidaemia might alter monocyte production, and explore the mechanistic interface linking dyslipidaemia with monocyte effector functions, such as migration and the inflammatory response. Finally, we discuss the role of dietary and endogenous lipid species in mediating dyslipidaemic responses, and the role of these lipids in promoting the risk of cardiovascular disease through modulation of monocyte behaviour.


ABSTRACT

Monocytes are heterogeneous effector cells involved in the maintenance and restoration of tissue integrity. Monocytes and macrophages are involved in cardiovascular disease progression, and are associated with the development of unstable atherosclerotic plaques. Hyperlipidaemia can accelerate cardiovascular disease progression. However, monocyte responses to hyperlipidaemia are poorly understood. In the past decade, accumulating data describe the relationship between the dynamic blood lipid environment and the heterogeneous circulating monocyte pool, which might have profound consequences for cardiovascular disease. In this Review, we explore the updated view of monocytes in cardiovascular disease and their relationship with macrophages in promoting the homeostatic and inflammatory responses related to atherosclerosis. We describe the different definitions of dyslipidaemia, highlight current theories on the ontogeny of monocyte heterogeneity, discuss how dyslipidaemia might alter monocyte production, and explore the mechanistic interface linking dyslipidaemia with monocyte effector functions, such as migration and the inflammatory response. Finally, we discuss the role of dietary and endogenous lipid species in mediating dyslipidaemic responses, and the role of these lipids in promoting the risk of cardiovascular disease through modulation of monocyte behaviour.


ABSTRACT

An elevated serum level of LDL cholesterol is a well-known risk factor for cardiovascular disease (CVD), but the role of elevated triglyceride levels is debated. Controversies regarding hypertriglyceridaemia as an independent risk factor for CVD have occurred partly because elevated triglyceride levels are often a component of atherogenic dyslipidaemia - they are associated with decreased levels of HDL cholesterol and increased levels of small dense LDL particles, which are highly atherogenic. Findings from several large studies indicate that
elevated levels of triglycerides (either fasting or nonfasting) or, more specifically, triglyceride-rich lipoproteins and their remnants, are independently associated with increased risk of CVD. Possible mechanisms for this association include excessive free fatty acid release, production of proinflammatory cytokines, coagulation factors, and impairment of fibrinolysis. Therapeutic targeting of hypertriglyceridaemia could, therefore, reduce CVD and cardiovascular events, beyond the reduction achieved by LDL-cholesterol lowering. Elevated triglyceride levels are reduced with lifestyle interventions and fibrates, which can be combined with omega-3 fatty acids. Some new drugs are on the horizon, such as volanesorsen (which targets apolipoprotein C-III), pemafibrate, and others. However, CVD outcome studies with triglyceride-lowering agents have produced inconsistent results, meaning that no convincing evidence is available that lowering triglycerides by any approach can reduce mortality.


ABSTRACT

Marine long-chained n-3 polyunsaturated fatty acids (PUFA) are recognized for their cardio-protective effects, including potential lowering of blood pressure. We hypothesized that higher habitual fish intake and n-3 PUFA plasma levels were associated with lower blood pressure and being less likely to receive antihypertensive medication after one-year follow-up. In this prospective study of 115 patients, we assessed 24 h ambulatory and central blood pressure, plasma phospholipid fatty acid composition using gas chromatography and participants completed a food frequency questionnaire, including fish-eating habits. All measurements were repeated at one-year follow-up. At baseline, patients consuming fish >/=2 times per month for dinner had significantly higher plasma levels of total marine n-3 PUFA, docosahexaenoic acid and eicosapentaenoic acid as well as significantly lower central blood pressure and a trend towards lower peripheral blood pressure. At follow-up, 21 patients (18%) without antihypertensive medication had significantly higher plasma levels of n-3 PUFA, docosahexaenoic acid and eicosapentaenoic acid as well as a higher, but still acceptable 24 h ambulatory blood pressure (137/85 mmHg) compared to subjects receiving antihypertensive medication. The untreated group was more prone to take fish oil capsules and increased their plasma levels of n-3 PUFA compared to baseline. In patients with newly diagnosed, untreated hypertension, regular fish consumption was accompanied by lower blood pressure. After one year, patients without antihypertensive medication were characterized by a significant increase and higher plasma levels of n-3 PUFA. This supports a blood pressure-lowering effect and suggests an increase in marine n-3 PUFA intake as part of non-pharmacological treatment of hypertension.


ABSTRACT
Growing evidence has indicated that supplementation with probiotics improves lipid metabolism. We aimed to investigate the beneficial effects of a probiotics mixture (PM) of three strains belonging to the species Bifidobacterium (B. longum, B. lactis, and B. breve) and two strains belonging to the species Lactobacillus (L. reuteri and L. plantarum) on cholesterol-lowering efficacy in hypercholesterolemic rats. A hypercholesterolemic rat model was established by feeding a high-cholesterol diet for eight weeks. To test the effects of PM on hypercholesterolemia, hypercholesterolemic rats were assigned to four groups, which were treated daily with low (1.65 \times 10^8 \text{ cfu/kg}), medium (5.5 \times 10^8 \text{ cfu/kg}), or high (1.65 \times 10^10 \text{ cfu/kg}) doses of probiotic mixture or simvastatin for eight weeks. Significant reductions of serum total cholesterol (TC), triacylglycerol (TG), and low-density lipoprotein (LDL)-cholesterol levels, but increases of high-density lipoprotein (HDL)-cholesterol were observed after supplementation of PM in hypercholesterolemic rats. In PM-supplemented hypercholesterolemic rats, hepatic tissue contents of TC and TG also significantly decreased. Notably, the histological evaluation of liver tissues demonstrated that PM dramatically decreased lipid accumulation. For their underlying mechanisms, we demonstrated that PM reduced expressions of cholesterol synthesis-related proteins such as sterol regulatory element-binding protein 1 (SREBP1), fatty acid synthase (FAS), and acetyl-CoA carboxylase (ACC) in the liver. Taken together, these findings suggest that PM has beneficial effects against hypercholesterolemia. Accordingly, our PM might be utilized as a novel therapeutic agent for the management of hypercholesterolemia.


ABSTRACT

As part of its single technology appraisal (STA) process, the UK National Institute for Health and Care Excellence (NICE) invited the manufacturer of evolocumab (Amgen) to submit evidence on the clinical and cost effectiveness of evolocumab. The appraisal assessed evolocumab as monotherapy or in combination with a statin with or without ezetimibe, or in combination with ezetimibe (without statin therapy), in adult patients with primary hypercholesterolaemia (which includes mixed dyslipidaemia), for whom statins do not provide optimal control of their low-density lipoprotein cholesterol (LDL-C) levels and/or for whom statins are contraindicated or not tolerated. The School of Health and Related Research Technology Appraisal Group at the University of Sheffield was commissioned to act as the independent Evidence Review Group (ERG). The ERG produced a critical review of the evidence for the clinical and cost effectiveness of the technology based on the company’s submission to NICE. The evidence was derived mainly from four randomised controlled trials comparing evolocumab with either ezetimibe or placebo in adults with primary familial or non-familial hypercholesterolaemia, who were either able to take statins or who were statin intolerant. The clinical-effectiveness review found that evolocumab is efficacious at lowering LDL-C but that there was uncertainty regarding its impact on cardiovascular disease (CVD) outcomes. In response to the ERG’s critique of the submitted health economic model, the company submitted an amended model, which also included a patient access scheme (PAS). Based on this, the deterministic incremental cost-effectiveness
ratios (ICERs) for evolocumab against ezetimibe were above pound74,000 and pound45,000 per quality-adjusted life-year (QALY) gained within the non-familial primary and secondary prevention populations, respectively, whilst the ICER within the heterozygous familial hypercholesterolaemia (HeFH) population was approximately pound23,000 per QALY gained. The final determination was that evolocumab would be a clinically and cost-effective use of UK NHS resource in certain patient subgroups.


ABSTRACT

BACKGROUND: This study aimed to utilize high-resolution magnetic resonance imaging (MRI) to investigate the characteristics of stable and vulnerable carotid arteriosclerotic plaques, with correlations to histopathological findings. PATIENTS AND METHODS: High-resolution MRI was performed in 817 patients, using three-dimensional magnetic resonance angiography. Plaque composition was evaluated by measuring the areas occupied by calcification, a lipid-rich necrotic core, intra-plateau haemorrhage, and fibrous cap rupture. Plaque morphology was analysed by measuring vessel wall area, thickness, and luminal area at the bifurcation of the common carotid artery. Plaque tissues were sampled during carotid endarterectomy and examined using haematoxylin-eosin, Oil Red O, Masson trichrome staining, and immunohistochemical staining for CD68. RESULTS: Patients were divided into stable plaque group (n = 462) and vulnerable plaque group (n = 355), based on intraoperative observations and postoperative histopathological findings. Compared to the stable plaque group, the vulnerable plaque group exhibited increased vessel wall areas and thickness, and decreased mean luminal areas (P < 0.001). The vulnerable plaque group also had a lower collagen content, a higher lipid content, and higher CD68 expression in plaque tissues on histological examinations (P < 0.01). Incidences of lipid-rich necrotic core (38.1 % vs. 34.3 %), intra-plateau haemorrhage (26.9 % vs. 22.8 %), plaque calcification (45.2 % vs. 40.9 %), and fibrous cap rupture (36.0 % vs 39.8 %) in the plaques were concordant with MRI observations and histopathological findings (p > 0.05). CONCLUSIONS: Stable and vulnerable carotid plaques had different morphologies and compositions. High-resolution MRI can assess such differences qualitatively and quantitatively in vivo and provide guidance for risk stratification and management.


ABSTRACT

Hyperlipidemia is a well-established risk factor for developing cardiovascular disease (CVD). The recent American College of Cardiology and American Heart Association guidelines on lipid management emphasize treatment of individuals at increased risk for developing CVD events with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) at doses proven to reduce CVD events. However, there are limited options for patients who are either intolerant to
statin therapy, develop CVD despite being on maximally tolerated statin therapy, or have severe hypercholesterolemia. Recently the Food and Drug Administration approved two novel medications for low-density lipoprotein (LDL)-cholesterol reduction: Evolocumab and Alirocumab. These agents target and inactivate proprotein convertase subtilisin-kexin type 9 (PCSK9), a hepatic protease that attaches and internalizes LDL receptors into lysosomes hence promoting their destruction. By preventing LDL receptor destruction, LDL-C levels can be lowered 50%-60% above that achieved by statin therapy alone. This review explores PCSK-9 biology and the mechanisms available to alter it; clinical trials targeting PCSK9 activity, and the current state of clinically available inhibitors of PCSK9.