Literature update week 03 (2017)


ABSTRACT
Uremic pruritus remains one of the most tormenting, frequent and potentially disabling problem in chronic kidney disease (CKD) patients. However, an area of substantial etiological interest with relation to uremic pruritus is the essential fatty acids deficiency. So we performed a literature review to elucidate the efficacy of omega-3 fatty acids on uremic pruritus. This review evaluated all of the studies published in English language, focusing on the clinical effects of omega-3 fatty acids on uremic pruritus. The literature review was conducted in December 2015 and carried out by searching Scopus, Medline, Cochrane central register of controlled trials, and Cochrane database of systematic reviews. The search terms were "kidney injury", "kidney failure", "chronic kidney disease", "end-stage renal disease", "dialysis", "hemodialysis", "peritoneal dialysis", "pruritus", "itch", "skin problems", "fish oil", "omega 3", "n-3 fatty acids", "polyunsaturated fatty acids", "docosahexaenoic acid", and "eicosapentaenoic acid". Four small studies investigating potential benefits of omega-3 fatty acids on symptoms of uremic pruritus were found. Among them, three small randomized controlled trials have shown a significant improvement in pruritus symptoms (evaluated by a standard questionnaire) in CKD patients who took omega-3 supplement compared to omega-6, omega-9, and placebo supplementation. Despite numerous limitations of the studies, it is worth noting that even minor reduction in itching symptoms may be clinically significant for CKD patients. Therefore, and considering multiple health benefits of omega-3 fatty acids in advanced CKD and negligible risk profile, omega-3 intake can wisely be applied to CKD patients with uremic pruritus.


ABSTRACT


ABSTRACT
BACKGROUND AND AIMS: Familial hypercholesterolemia (FH) is an autosomal dominant disease caused by mutations in the genes for LDL receptor (LDLR), apolipoprotein B (APOB) and proprotein convertase subtilisin/kexin type9 (PCSK9). The purpose of the current investigation was to define the current spectrum of mutations causing FH in Israel. METHODS: New families were collected through the MEDPED (Make Early Diagnosis Prevent Early Death) FH program. Molecular analysis of the LDLR, PCSK9 and APOB genes was done using High Resolution Melt and direct sequencing in 67 index cases. A 6-SNP LDL-C gene score calculation for polygenic hypercholesterolaemia was done using TaqMan genotyping. RESULTS: Mean serum cholesterol was 7.48 +/- 1.89 mmol/L and the mean serum LDL-C was 5.99 +/- 1.89 mmol/L. Mutations in the LDLR and APOB gene were found in 24 cases (35.8%), with 16 in LDLR, none in PCSK9 and
one, p.(R3527Q), in the APOB gene, which is the first APOB mutation carrier identified in the Israeli population. Of the LDLR mutations, two were novel; p.(E140A) and a promoter variant, c.-191C > A. The c.2479G > A p.(V827I) in exon 17 of the LDLR gene was found in 8 patients (33.3% of the mutations) with modestly elevated LDL-C, but also in a compound heterozygous patient with a clinical homozygous FH phenotype, consistent with this being a "mild" FH-causing variant. A significantly higher 6-SNP LDL-C score was found in mutation-negative cases compared with a normal Caucasian cohort (p = 0.03), confirming that polygenic inheritance of common LDL-C raising SNPs can produce an FH phenocopy. CONCLUSIONS: The results indicate a different spectrum of genetic causes of FH from that found previously, in concordance with the heterogeneous and changing origins of the Israeli population, and confirm that a polygenic cause is also contributing to the FH phenotype in Israel.


ABSTRACT
Rupture of carotid atherosclerotic plaque may cause stroke, while few biomarker in clinic can evaluate carotid plaque vulnerability. In this study, we divided the recruited participants into no plaque, stable plaque, and vulnerable plaque group according to carotid ultrasonography, and screened the differentially expressed proteins in plasma of these participants using isobaric tags for relative and absolute quantitation labeling coupled with liquid chromatography-tandem mass spectrometry. 28 proteins were identified differentially expressed, among which alpha-2-macroglobulin (alpha2M) and heparin cofactor II (HcII) were found to be at hub position in the interactions of these proteins by STRING analysis and were selected for enzyme-linked immunosorbent assay measurement to assess their relevance with carotid plaques vulnerability and diagnostic efficiency. The plasma level of alpha2M was found positively correlated, while HcII level was negatively correlated with higher vulnerability of carotid plaques. Both proteins were efficient in differentiating stable and vulnerable carotid plaques. These findings provide potential new targets for the research of carotid plaque vulnerability. Plasma alpha2M and HcII may be potential biomarkers for evaluation of the vulnerability of carotid plaques if further studied.


ABSTRACT
The aim of the present study was to investigate the potential antiatherosclerotic activities of simvastatin in rabbits. Twenty-two, male, New Zealand rabbits were divided into the following groups: Control group (group C); cholesterol group (group A), in which the rabbits were fed a commercial rabbit chow supplemented with 0.5% w/w cholesterol for 8 weeks and then fed with normal chow for an additional 8 weeks; and a treatment group (group B), in which the rabbits initially received standard commercial rabbit chow along with being administered
simvastatin for 8 weeks, following which they consumed a high-cholesterol diet for a further 8 weeks. The rabbits pre-treated with simvastatin presented significantly lower serum cholesterol and low-density lipoprotein cholesterol levels when compared with the non simvastatin-treated cholesterol-fed animals. Furthermore, none of the rabbits in the simvastatin group presented with atherosclerotic lesions in the aorta. Thus, simvastatin was demonstrated to exhibit preventive properties against the formation of atherosclerosis in the atherosclerosis model in the current study, predominantly via its hypolipidemic activity.


**ABSTRACT**

Atherosclerosis is a self-sustaining inflammatory fibroproliferative disease that progresses in discrete stages and involves a number of cell types and effector molecules. Recently, [18F]fluoro-2-deoxy-D-glucose- ([18F]FDG-) positron emission tomography (PET) has been suggested as a tool to evaluate atherosclerotic plaques by detecting accumulated macrophages associated with inflammation progress. However, at the cellular level, it remains unknown whether only macrophages exhibit high uptake of [18F]FDG. To identify the cellular origin of [18F]FDG uptake in atherosclerotic plaques, we developed a simian atherosclerosis model and performed PET and ex vivo macro- and micro-autoradiography (ARG). Increased [18F]FDG uptake in the aortic wall was observed in high-cholesterol diet-treated monkeys and WHHL rabbits. Macro-ARG of [18F]FDG in aortic sections showed that [18F]FDG was accumulated in the media and intima in the simian model as similar to that in WHHL rabbits. Combined analysis of micro-ARG with immunohistochemistry in the simian atherosclerosis model revealed that most cellular [18F]FDG uptake observed in the media was derived not only from the infiltrated macrophages in atherosclerotic plaques but also from the smooth muscle cells (SMCs) of the aortic wall in atherosclerotic lesions.


**ABSTRACT**


**ABSTRACT**

Evacetrapib is a cholesteryl ester transfer protein (CETP) inhibitor that has been recently studied as a cholesterol modifying agent to reduce cardiovascular risk and mortality in high risk cardiovascular disease patients. Evacetrapib acts to decrease lipid exchange through CETP inhibition. CETP acts to transfer cholesteryl esters from high-density lipoprotein cholesterol (HDL-C) to low-density lipoprotein cholesterol (LDL-C) and very low-density lipoprotein cholesterol (VLDL-C). HDL-C is involved in reverse cholesterol transport and its blood levels have been shown to be inversely correlated with cardiovascular risk. Thus, a pharmacologic agent
that can elevate HDL-C has been seen as an exciting area of research. In recent studies, evacetrapib was shown to be safe and efficacious. It produced an increase in HDL-C up to 128% and a 35% decrease in LDL-C, in comparison to placebo. In addition, evacetrapib was also shown to be more potent than previous CETP inhibitors. HDL-C particles treated with evacetrapib remained functional and had improved cholesterol efflux. A previously studied CETP inhibitor, torcetrapib, exhibited side effects of hyperaldosteronism, manifesting in electrolyte disturbances and hypertension. These detrimental effects were not seen with evacetrapib. Recently, the results of evacetrapib's phase III ACCELERATE trial showed no significant reduction in major adverse cardiovascular events or mortality, and the drug will not be marketed. Although beneficial cholesterol effects were seen with this drug, more needs to be known to understand what role, if any, evacetrapib has in the reduction of cardiovascular risk.


**ABSTRACT**
Indirect evidence from human studies suggests that brown adipose tissue (BAT) thermogenesis is fueled predominantly by fatty acids hydrolyzed from intracellular triglycerides (TGs). However, no direct experimental evidence to support this assumption currently exists in humans. The aim of this study was to determine the role of intracellular TG in BAT thermogenesis, in cold-exposed men. Using positron emission tomography with 11C-acetate and 18F-fluorodeoxyglucose, we showed that oral nicotinic acid (NiAc) administration, an inhibitor of intracellular TG lipolysis, suppressed the cold-induced increase in BAT oxidative metabolism and glucose uptake, despite no difference in BAT blood flow. There was a commensurate increase in shivering intensity and shift toward a greater reliance on glycolytic muscle fibers without modifying total heat production. Together, these findings show that intracellular TG lipolysis is critical for BAT thermogenesis and provides experimental evidence for a reciprocal role of BAT thermogenesis and shivering in cold-induced thermogenesis in humans.


**ABSTRACT**
BACKGROUND: Inflammation markers have been associated with cardiovascular diseases including atrial fibrillation. This arrhythmia is the most frequent, with an incidence of 38/1000 person-years. PURPOSE OF REVIEW: The aims of this study are to discuss the association between inflammation, atherosclerosis and atrial fibrillation and its clinical implications. Atherosclerosis is a chronic inflammatory disease and inflammation is a triggering factor of atherosclerotic plaque rupture. In addition to coronary artery disease, clinical conditions identified as risk factors for atrial fibrillation (AF) are also associated with the inflammatory state such as obesity, diabetes mellitus, hypertension, heart failure, metabolic syndrome and
sedentary lifestyle. Biomarkers of inflammation, oxidative stress, coagulation, and myocardial necrosis have been identified in patients with atrial fibrillation and these traditional risk factors. Some markers of inflammation were identified as predictors of recurrence of this arrhythmia, subsequent myocardial infarction, stroke by embolism, and death. Thus, approaches to manipulate the inflammatory pathways may be therapeutic interventions, benefiting patients with AF and increased inflammatory markers.


**ABSTRACT**

**BACKGROUND:** Sodium-glucose cotransporter 2 inhibitors (SGLT2i) are a novel category of oral antidiabetic drugs that inhibit renal glucose reabsorption and increase renal glucose excretion, thus lowering plasma glucose levels. This unique mechanism of SGLT2i action is insulin independent, thus improving glycemic control without promoting hypoglycemia in the absence of exogenously administered insulin. METHODS: The present narrative review addresses the putative associations between SGLT2i and several cardiovascular (CV) and microvascular risk factors, as well as their effects on cardiac and renal function. RESULTS: SGLT2i improve several CV risk factors, including fasting and postprandial plasma glucose levels, lipids, blood pressure, body weight, serum uric acid and arterial stiffness. These drugs may also favorably modulate cardiac and renal function via their effects on inflammation, oxidative stress, diuresis, fluid and sodium retention, myocardial function, vascular resistance and 'fuel' metabolism. In the EMPA-REG OUTCOME study, the first published large CV outcome SGLT2i trial, empagliflozin significantly reduced the primary composite outcome (i.e. CV death, nonfatal myocardial infarction or stroke) and all-cause death as well as hospitalization for heart failure. In addition, empagliflozin was associated with a slower progression of kidney disease and lower rates of clinically relevant renal events than was placebo when added to standard care in patients at high CV risk. CONCLUSION: Multiple metabolic benefits may account for the positive clinical outcomes in the EMPA-REG OUTCOME study. Ongoing CV outcome trials involving other SGLT2i will help establish whether the reported CV and microvascular risk benefits are compound-specific or drug class effects.


**ABSTRACT**

Bezafibrate (BF) is a peroxisome proliferator-activated receptor (PPAR) agonist used as a lipid-lowering agent to treat both the familial or acquired combined forms of hyperlipidemia. BF is the only available fibrate drug that acts on all PPAR subtypes of alpha, beta, and delta. Although there are studies that indicate a genotoxic potential associated with the use of fibrates, to our knowledge, the genotoxicity of BF in human peripheral blood lymphocytes has not been studied. In the present study, the genotoxic potential of BF was evaluated using chromosome aberration (CA) and micronucleus (MN) assays in peripheral blood lymphocytes of healthy human subjects. In addition, a high performance liquid chromatography (HPLC) method was
used to identify and quantitate the drug passage into the cells. Human peripheral blood lymphocytes were exposed to four different concentrations (100, 175, 250 and 325 mug/mL) of BF for 24- and 48-h treatment periods. As shown by HPLC, in spite of significant passage of BF into human peripheral blood lymphocytes in 24- and 48-h treatment periods, BF was not found to increase the CA and MN frequency. On the other hand, exposing cells to BF for 24- and 48-h treatment periods caused significant concentration-dependent decreases in the mitotic index (r = -0.995, p < 0.01 for 24-h; r = -0.992, p < 0.01 for 48-h) and nuclear division index (r = -0.990, p < 0.01 for 24-h; r = -0.981, p < 0.01 for 48-h). Our results suggest that BF has cytotoxic effect on cultured human peripheral blood lymphocytes.


ABSTRACT

EXECUTIVE SUMMARY

This algorithm for the comprehensive management of persons with type 2 diabetes (T2D) was developed to provide clinicians with a practical guide that considers the whole patient, their spectrum of risks and complications, and evidence-based approaches to treatment. It is now clear that the progressive pancreatic beta-cell defect that drives the deterioration of metabolic control over time begins early and may be present before the diagnosis of diabetes (1). In addition to advocating glycemic control to reduce microvascular complications, this document highlights obesity and prediabetes as underlying risk factors for the development of T2D and associated macrovascular complications. In addition, the algorithm provides recommendations for blood pressure and lipid control, the two most important risk factors for cardiovascular disease (CVD). Since originally drafted in 2013, the algorithm has been updated as new therapies, management approaches, and important clinical data have emerged. The 2017 edition includes an updated section on lifestyle therapy as well as discussion of all classes of obesity, antihyperglycemic, lipid-lowering, and antihypertensive medications approved by the US Food and Drug Administration (FDA) through December 2016. This algorithm supplements the American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) 2015 Clinical Practice Guidelines for Developing a Diabetes Mellitus Comprehensive Care Plan (2) and is organized into discrete sections that address the following topics: the founding principles of the algorithm, lifestyle therapy, obesity, prediabetes, glucose control with noninsulin antihyperglycemic agents and insulin, management of hypertension, and management of dyslipidemia. In the accompanying algorithm, a chart summarizing the attributes of each antihyperglycemic class and the principles of the algorithm appear at the end.


ABSTRACT
The aim of the present study was to assess the role of simvastatin on osteoporosis of the vertebrae by examining the effect of simvastatin on the osteogenesis of the lumbar vertebra in ovariectomized (OVX) rats. A total of 60 6-month-old female Sprague Dawley rats were divided into one sham group and five ovariectomized groups, consisting of four simvastatin groups and one control group. Four dosages of simvastatin (5, 10, 20 and 40 mg/kg/d) were administered by gavage for three months. L4 vertebrae were examined by dual-energy X-ray absorptiometry (DEXA) and peripheral quantitative computed tomography (pQCT) to determine the mineral apposition rate (MAR). L5 vertebrae were examined using a compression biomechanical test. Although the measurements from DEXA, pQCT and MAR, and the biomechanical parameters in the OVX + simvastatin rats were higher than those for the OVX + vehicle group, no significant
differences were detected. Therefore, simvastatin may not improve osteogenesis of the lumbar vertebra in OVX rats or prevent osteoporosis of the spinal vertebrae.


ABSTRACT
Atherosclerosis (AS), which is triggered by endothelial cell injury, evolves into a chronic inflammatory disease. Oxidized low-density lipoprotein (ox-LDL) is an important risk factor for the development of atherosclerosis; ox-LDL induces atherosclerotic plaque formation via scavenging receptors. The present study used ox-LDL-treated human umbilical vein endothelial cells (HUVECs) to investigate the effect of ox-LDL on angiogenesis. ox-LDL decreased HUVEC proliferation by MTT, induced apoptosis by Annexin V-fluorescein isothiocyanate (FITC) staining and markedly suppressed HUVEC tube formation by the Matrigel assay in a dose-dependent manner. Angiogenesis has been correlated with monocyte invasion, plaque instability and atherosclerotic lesion formation. In addition, ox-LDL induced the overproduction of reactive oxygen species using DCFH-DA staining and increased caspase-3 activity. Vascular endothelial growth factor receptor 2 (VEGFR2) were detected by quantitative polymerase chain reaction and western blot analysis and has previously been observed to have a key role in angiogenesis. Furthermore, the present study demonstrated that the abundance of VEGFR2 was decreased in ox-LDL-treated HUVECs. These results suggested that ox-LDL impairs angiogenesis via VEGFR2 degradation, thus suggesting that VEGFR2 may be involved in adaptation to oxidative stress and AS.


ABSTRACT
OBJECTIVES: Clinician utilization of the 2013 cholesterol lowering guidelines remains variable and unknown. We sought to examine statin prescribing patterns and compare rates among specialists who treat high-risk cardiovascular patients admitted to the hospital. METHODS: We retrospectively (via chart review) examined four specialty groups: (i) Cardiology, (ii) Cardiovascular or Vascular (CV) Surgery, (iii) Neurology, and (iv) Internal Medicine. Adult patients were included based on a discharge diagnosis of acute coronary syndrome, coronary artery bypass graft surgery, carotid endarterectomy, acute ischemic stroke, transient ischemic attack, or high-risk chest pain. Prescribing patterns were evaluated 6 months and 18 months after the release of the 2013 guidelines. High-intensity statin was defined as atorvastatin 40-80 mg or rosuvastatin 20-40 mg per day. RESULTS: 632 patients were included in our study. The following percentages of patients were discharged on high-intensity statin (6 months; 18 months): (i) Cardiology (80%; 85%), (ii) CV Surgery (52%, 65%), (iii) Neurology (59%; 66%), and (iv) Internal Medicine (45%; 48%). Among the four groups, Cardiology was the most likely to discharge patients on high-intensity statin (p < 0.001) in 2014 and in 2015. Cardiology, CV
Surgery, and Neurology significantly increased the percentage of patients on high-intensity statin from pre-admission to time of discharge in both years. CONCLUSION: High-intensity statin therapy is underutilized among high-risk cardiovascular patients admitted to the hospital. Variations exist in prescribing patterns of different specialties who manage high-risk populations. This data can be used to test quality improvement interventions to improve rates of high-intensity statin utilization among high-risk patients prior to hospital discharge.


ABSTRACT
'Cardiometabolic memory' has been proposed based on clinical evidence to explain how, even after the cessation of a clinical trial, the superiority of one treatment over the outcome persists. To understand the cardiometabolic memory phenomenon, we performed a systematic review of randomized controlled trials (RCTs) using PubMed in August 2016. The search terms 'randomized controlled trial', 'post-trial follow-up' and 'diabetes, hypertension or dyslipidemia' were used, and articles published after the year 2000 were searched. We judged the memory phenomenon to be positive when the cardiovascular outcome at the end of the post-trial follow-up period in the intervention group was significantly superior even though the favorable control of a risk factor (blood glucose, blood pressure or lipid level) during the trial period was lost after the cessation of the intervention. Among 907 articles retrieved in the initial screening, 21 articles were judged as describing a positive memory phenomenon. Eight, six and seven of the articles concerned diabetes, hypertension and dyslipidemia, respectively. Transient intensive glucose lowering rather easily induced memory for the suppression of diabetic microangiopathies, while memory for the suppression of macroangiopathies tended to be first evident in the post-trial follow-up period. Transient intensive blood pressure lowering was generally effective in the formation of memory for the suppression of cardiovascular events and had an especially strong impact on risk reduction of chronic heart failure. Transient intensive LDL cholesterol lowering clearly had a long-term beneficial effect on risk reduction of cardiovascular events. Our systematic review revealed the clinical relevance of cardiometabolic memory. Hypertension Research advance online publication, 19 January 2017; doi:10.1038/hr.2016.192.


ABSTRACT
OBJECTIVE: Elevated aldosterone is associated with increased risk of atherosclerosis complications, whereas treatment with mineralocorticoid receptor (MR) antagonists decreases the rate of cardiovascular events. Here we test the hypothesis that aldosterone promotes early atherosclerosis by modulating intercellular adhesion molecule-1 (ICAM-1) expression and investigate the molecular mechanisms by which aldosterone regulates ICAM-1 expression.
METHODS AND RESULTS: Apolipoprotein-E (ApoE)-/- mice fed an atherogenic diet and treated
Lowering therapies led to the discovery of the proprotein convertase subtilisin/kexin Type 9 inhibitors for perioperative clinicians. Luciferase reporter assays performed in HUVECs using deletion constructs of the human ICAM-1 gene promoter showed that a region containing a predicted MR-responsive element (MRE) is required for MR-dependent transcriptional regulation of ICAM-1. CONCLUSIONS: Pro-atherogenic effects of aldosterone are mediated by increased ICAM-1 expression, through transcriptional regulation by endothelial MR. These data enhance our understanding of the molecular mechanism by which MR activation promotes atherosclerosis complications.


**ABSTRACT**

Statin use leads to a reduction in the downstream products of the mevalonate pathway. Knowledge of this pathway has led scientists to investigate the role of statins in cancer prevention and treatment. Statins appear to possess a variety of pleiotropic effects, including inhibition of cell proliferation; enhanced apoptosis; and modulation of inflammation, endothelial function, and angiogenesis. In cancer specifically, experimental studies have found that statins may induce cancer cell apoptosis and inhibit tumor growth, angiogenesis, and metastasis. These mechanisms have steered researchers into evaluating the possible benefit of statins in the prevention and treatment of malignancies. This review will discuss the literature supporting the use of statins to prevent and treat cancer.


**ABSTRACT**

Statins are a mainstay of hyperlipidemia treatment. These drugs inhibit the enzyme 3-hydroxy-3-methylglutaryl coenzyme A reductase and have beneficial effects on atherosclerosis including plaque stabilization, reduction of platelet activation, and reduction of plaque proliferation and inflammation. Statins also have a benefit beyond atherosclerotic plaque, including anticoagulation, vasodilatation, antioxidant effects, and reduction of mediators of inflammation. In the perioperative period, statins appear to contribute to improved outcomes via these mechanisms. Both vascular and nonvascular surgery patients have been shown in prospective studies to have lower risk of adverse cardiac outcomes when initiated on statins preoperatively. However, not all patients can tolerate statins; the search for novel lipid-lowering therapies led to the discovery of the proprotein convertase subtilisin/kexin Type 9 inhibitors for perioperative clinicians. Luciferase reporter assays performed in HUVECs using deletion constructs of the human ICAM-1 gene promoter showed that a region containing a predicted MR-responsive element (MRE) is required for MR-dependent transcriptional regulation of ICAM-1. CONCLUSIONS: Pro-atherogenic effects of aldosterone are mediated by increased ICAM-1 expression, through transcriptional regulation by endothelial MR. These data enhance our understanding of the molecular mechanism by which MR activation promotes atherosclerosis complications.


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(PCSK9) inhibitors. These drugs are fully-humanized, injectable monoclonal antibodies. With lower PCSK9 activity, low-density lipoprotein cholesterol (LDL-C) receptors are more likely to be recycled to the hepatocyte surface, where they serve to clear plasma LDL-C. Evidence from several prospective studies shows that these new agents can significantly lower LDL-C levels. While PCSK9 inhibitors offer hope of effective therapy for patients with familial hyperlipidemia or intolerance of statins, several important questions remain, including the results of long term cardiovascular outcome studies. The perioperative effects of new LDL-C-lowering drugs are unknown at present but are likely to be similar to the older agents.


**ABSTRACT**

BACKGROUND: Adiponectin is an important adipocyte-related protein that has been postulated to participate in prevention of the development of metabolic syndrome. The relationship between adiponectin serum levels and risk of coronary artery disease (CAD) has been widely investigated and remains controversial. The aim of the present study was to evaluate the effects of rosuvastatin and/or omega-3 fatty acid on adiponectin serum levels in patients with insulin resistance (IR) and CAD. PATIENTS AND METHODS: This study involved 87 patients with CADs and IR of different etiology, the patients were divided into three groups; 24 patients on treatment with rosuvastatin, 22 patients on treatment with omega-3 fatty acid, 23 patients on treatment with omega-3 fatty acid and rosuvastatin, 18 patients were not previously or currently treated with either rosuvastatin or omega-3 fatty acid, those regarded as control patients. Anthropometric measures, adiponectin serum levels, and other biochemical parameters were assessed in each treated group. RESULTS: Rosuvastatin therapy leads to a significant elevation in adiponectin serum levels from 4.1 +/- 0.99 ng/mL to 6.76 +/- 1.03 ng/mL compared to control P < 0.01. Omega-3 fatty acid therapy leads to a significant elevation in adiponectin serum levels from 4.1 +/- 0.99 ng/mL to 6.11 +/- 1.29 ng/mL compared to control P < 0.01. Rosuvastatin plus omega-3 fatty acid therapy lead to a significant elevation in adiponectin serum levels from 4.1 +/- 0.99 ng/mL to 7.99 +/- 1.76 ng/mL compared to control P < 0.01. CONCLUSIONS: Rosuvastatin and/or omega-3 fatty acid lead to significant cardiometabolic protection through an increment in adiponectin serum levels.


**ABSTRACT**

Peroxisome proliferator-activated receptors (PPARs) are ligand-activated transcription factors involved in several physiological processes including modulation of cellular differentiation, development, metabolism of carbohydrates, lipids, proteins, and tumorigenesis. The aim of this review is to examine how different PPAR ligands act, and discuss their use in clinical practice. PPAR ligands have a lot of effects and applications in clinical practice. Some PPAR ligands such as fibrates (PPAR-alpha ligands) are currently used for the treatment of dyslipidemia, while
Ezetimibe is widely used in combination with statins to reduce low-density lipoprotein. We sought to examine the impact of ezetimibe when added to statins on patient-important outcomes. Medline, EMBASE, CINAHL, and CENTRAL were searched through July, 2016. Randomized controlled trials (RCTs) of ezetimibe combined with statins versus statins alone that followed patients for at least 6 months and reported on at least one of all-cause mortality, cardiovascular deaths, non-fatal myocardial infarctions (MI), and non-fatal strokes were included. Pairs of reviewers extracted study data and assessed risk of bias independently and in duplicate. Quality of evidence was assessed using the GRADE approach. We conducted a narrative review with complementary subgroup and sensitivity analyses. IMPROVE-IT study enrolled 93% of all patients enrolled in the 8 included trials. Our analysis of the IMPROVE-IT study results showed that in patients at high risk of cardiovascular events, ezetimibe added to statins was associated with i) a likely reduction in non-fatal MI (17 fewer/1000 treated over 6 years, moderate certainty in evidence); ii) a possible reduction in non-fatal stroke (6 fewer/1000 treated over 6 years, low certainty); iii) no impact on myopathy (moderate certainty); iv) potentially no impact on all-cause mortality and cardiovascular death (both moderate certainty); and v) possibly no impact on cancer (low certainty). Addition of ezetimibe to moderate-dose statins is likely to result in 17 fewer MIs and possibly 6 fewer strokes/1000 treated over 6 years but is unlikely to reduce all-cause mortality or cardiovascular death. Patients who place a high value on a small absolute reduction in MI and are not adverse to use of an additional medication over a long duration may opt for ezetimibe in addition to statin therapy. Our analysis revealed no increased specific harms associated with addition of ezetimibe to statins.
investigate the relationship between inflammation and cholesterol accumulation in HCC cells. METHODS: Human HCC cells HepG2 and Huh7 were cultured and stimulated with lipopolysaccharide (LPS) for 24 h. The changes of HCC cells related to cholesterol metabolism including intracellular cholesterol concentrations, cholesterol uptake, and the expression of cholesterol-related genes 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR), LDL receptor (LDLR), sterol regulatory element-binding transcription factor 2 (SREBF2), and proprotein convertase subtilisin/kexin 9 (PCSK9) were comparatively analyzed. Simultaneously, the effects of nuclear factor-kappa B (NF-kappaB) signaling pathway on cholesterol metabolism were clarified by knocking-down of nuclear factor kappa-B kinase subunit alpha (IKKalpha) and TGF-beta-activated kinase 1 and MAP3K7-binding protein 3 (TAB3) via RNAi and microRNA (miR)-195. Subsequently, the roles of cholesterol accumulation in LPS induced pro-inflammatory effects were further investigated. RESULTS: Pro-inflammatory factor LPS significantly increased intracellular cholesterol accumulation by upregulating the expression of HMGCR, LDLR, and SREBF2, while downregulating the expression of PCSK9. These effects were revealed to depend on NF-kappaB signaling pathway by knocking-down and overexpression of IKKalpha and TAB3. Additionally, miR-195, a regulator directly targeting IKKalpha and TAB3, blocked the effects of cholesterol accumulation, further supporting the critical role of pro-inflammation NF-kappaB signaling in regulating cholesterol accumulation. Intriguingly, the accumulation of cholesterol conversely exerted an augmented pro-inflammation effects by further activating NF-kappaB signaling pathway. CONCLUSIONS: These results indicated that pro-inflammation effects of NF-kappaB signaling could be augmented by a positive feedback via enhancing the cholesterol accumulation in liver cancer cells.


ABSTRACT

AIM: To estimate real-world cardiovascular disease (CVD) burden and value-based price range of evolocumab for a US-context, high-risk, secondary-prevention population. MATERIALS AND METHODS: Burden of CVD was assessed using the UK-based Clinical Practice Research Datalink (CPRD) in order to capture complete CV burden including CV mortality. Patients on standard of care (SOC; high-intensity statins) in CPRD were selected based on eligibility criteria of FOURIER, a phase 3 CV outcomes trial of evolocumab, and categorized into four cohorts: high-risk prevalent atherosclerotic CVD (ASCVD) cohort (n = 1448), acute coronary syndrome (ACS) (n = 602), ischemic stroke (IS) (n = 151), and heart failure (HF) (n = 291) incident cohorts. The value-based price range for evolocumab was assessed using a previously published economic model. The model incorporated CPRD CV event rates and considered CV event reduction rate ratios per 1 mmol/L reduction in low-density lipoprotein-cholesterol (LDL-C) from a meta-analysis of statin trials by the Cholesterol Treatment Trialists Collaboration (CTTC), i.e. CTTC relationship. RESULTS: Multiple-event rates of composite CV events (ACS, IS, or coronary revascularization) per 100 patient-years were 12.3 for the high-risk prevalent ASCVD cohort, and 25.7, 13.3, and 23.3, respectively, for incident ACS, IS, and HF cohorts. Approximately one-half (42%) of the high-risk ASCVD patients with a new CV event during follow-up had a subsequent CV event.
Combining these real-world event rates and the CTTC relationship in the economic model, the value-based price range (credible interval) under a willingness-to-pay threshold of $150,000/quality-adjusted life-year gained for evolocumab was $11,990 ($9,341-$14,833) to $16,856 ($12,903-$20,678) in ASCVD patients with baseline LDL-C levels \(\geq70\) mg/dL and \(\geq100\) mg/dL, respectively. CONCLUSION: Real-world CVD burden is substantial. Using the observed CVD burden in CPRD and the CTTC relationship, the cost-effectiveness analysis showed that, accounting for uncertainties, the expected value-based price for evolocumab is higher than its current annual cost, as long as the payer discount off list price is greater than 20%.


**ABSTRACT**

Consumption of food products enriched with plant sterols and the use of ezetimibe reduce cholesterol absorption in the intestine and effectively reduce low-density lipoprotein (LDL) plasma levels. We evaluated the therapeutic effect of the ezetimibe+plant sterol association in patients with coronary artery disease still not reaching recommended lipid levels despite the use of statins. We performed a prospective open-label study with 41 patients with stable coronary disease and LDL >70 mg/dL. Patients were randomized into four groups for a 6-week treatment: the control (CT) group remained on the same statin therapy, the ezetimibe (EZ) group received 10 mg/day of ezetimibe, the plant sterol (PS) group received spread enriched with 2 g of plant sterols, and the ezetimibe+PS (EZ+PS) group received 10 mg/day EZ +2 g PS. Initial mean LDL level was 97.4 +/- 31.1 mg/dL in control group, 105.1 +/- 23.1 mg/dL in EZ group, 95.4 +/- 27.7 mg/dL in PS group, and 97.0 +/- 8.3 mg/dL in EZ+PS group (P > .05). After 6 weeks of treatment, LDL of patients slightly increased in the control group (+8.9%; P > .05) and dropped in EZ group (-19.1%; P = .06), PS group (-16.6%; P = .01), and EZ+PS group (-27.3%; P < .01). Mean LDL levels after treatment were 70.5 +/- 17.9 mg/dL in EZ+PS group, lower than the other groups (control was 106.1 +/- 34.9 mg/dL, EZ group was 85.0 +/- 35.6 mg/dL, and PS was 79.6 +/- 29.7 mg/dL) (P = .05 variance analysis factor [ANOVA]). Body weight, body-mass index, and glucose plasma levels did not change significantly after intervention. The combination of PS+ezetimibe was associated with lower LDL levels and suggests beneficial therapeutic effect against major cardiovascular events.


**ABSTRACT**

Sacubitril/valsartan (LCZ696) has been approved for the treatment of heart failure. Sacubitril is an in vitro inhibitor of OATPs. In clinical studies, LCZ696 increased atorvastatin Cmax by 1.7-fold and AUC by 1.3-fold, but had little or no effect on simvastatin or simvastatin acid exposure. A PBPK modelling approach was applied to explore the underlying mechanisms behind the statin-
specific LCZ696 drug interaction observations. The model incorporated OATP-mediated clearance (C\text{LInT,T}) for simvastatin and simvastatin acid to successfully describe the PK profiles of either analyte in the absence or presence of LCZ696. Moreover, the model successfully described the clinically observed drug effect with atorvastatin. The simulations clarified the critical parameters responsible for the observation of a low, yet clinically relevant, DDI between sacubitril and atorvastatin and the lack of effect with simvastatin acid. Atorvastatin is administered in its active form and rapidly achieves C\text{max} that coincide with the low C\text{max} of sacubitril. In contrast, simvastatin requires a hydrolysis step to the acid form and therefore is not present at the site of interactions at sacubitril concentrations that are inhibitory. Similar models were used to evaluate the DDI risk for additional OATP-transported statins which predicted to maximally result in a 1.5-fold exposure increase.


**ABSTRACT**

Several studies indicate that blockade of the renin-angiotensin-aldosterone system (RAAS) can prevent atherosclerosis and vascular events, but the precise mechanisms involved are still unclear. In this study, we investigated the effect of the AT 1-receptor blocker, candesartan, in the prevention of atherosclerosis in Watanabe heritable hyperlipidaemic (WHHL) rabbits and also the effect of AT1-receptor blockade in the uptake of oxidised LDL by macrophage cell cultures. In the first set of experiments, 12 WHHL rabbits were randomly assigned to three groups: placebo, atenolol 5 mg/kg daily or candesartan 2 mg/kg daily for six months. Compared with controls and atenolol-treated rabbits, candesartan treatment resulted in a significant 50-60% reduction of atherosclerotic plaque formation and a 66% reduction in cholesterol accumulation in the thoracic aorta. Studies in macrophage cultures indicated that candesartan prevented uptake of oxidised LDL-(oxLDL)-cholesterol by cultured macrophages. Candesartan inhibited the uptake of oxLDL in a dose-dependent manner, reaching a maximum inhibition of 70% at concentrations of 5.6 microg/ml. Further studies in other animal models and well-designed trials in humans are warranted to further explore the role of AT1-receptor blockade in the prevention of atherosclerosis.


**ABSTRACT**

BACKGROUND: Statins have been suggested to have a protective effect on venous thromboembolism (which includes deep vein thrombosis and pulmonary embolism), but the evidence is uncertain. We sought to evaluate the extent to which statins are associated with first venous thromboembolism events. METHODS: We did a systematic review and meta-analysis of observational cohort studies and randomised controlled trials (RCTs). Relevant studies that reported associations between statins and first venous thromboembolism
outcomes were identified from MEDLINE, Embase, Web of Science, Cochrane Library, and a manual search of bibliographies for studies published up until July 18, 2016, and from email correspondence with investigators. Observational cohorts that assessed the association of statin use with venous thromboembolism, deep vein thrombosis, or pulmonary embolism in adults were included, as were intervention studies that assessed the effects of statin therapy compared with a placebo or no treatment and collected data on venous thromboembolism, deep vein thrombosis, or pulmonary embolism outcomes. Studies that compared statins with another statin or lipid-lowering agent were excluded. Study specific relative risks (RRs) were aggregated using random-effects models and were grouped by study-level characteristics. The review has been registered with PROSPERO, number CRD42016035622. FINDINGS: 36 eligible studies (13 cohort studies comprising 3 148 259 participants and 23 RCTs of statins vs placebo or no treatment comprising 118 464 participants) were included. In observational studies, the pooled RR for venous thromboembolism was 0.75 (95% CI 0.65-0.87; p<0.0001) when statin use was compared with no statin use. This association remained consistent when grouped by various study-level characteristics. In RCTs, the RR for venous thromboembolism was 0.85 (0.73-0.99; p=0.038) when statin therapy was compared with placebo or no treatment. Subgroup analyses suggested significant differences in the effect of statins by type of statin, with rosuvastatin having the lowest risk on venous thromboembolism compared with other statins 0.57 (0.42-0.75; p=0.015). There was no evidence of an effect of statin use on pulmonary embolism. Statin use was associated with a significant reduction in risk of the specific endpoint of deep vein thrombosis compared with no statin use (RR 0.77, 95% CI 0.69-0.86; p<0.0001). INTERPRETATION: Available evidence from observational and intervention studies suggest a beneficial effect of statin use on venous thromboembolism. In intervention studies, therapy with rosuvastatin significantly reduced venous thromboembolism compared with other statins. Further evidence is however needed to validate these findings. FUNDING: None.


ABSTRACT
BACKGROUND: Quercetin, one of the most widely distributed flavonoids in plants, has been demonstrated to reduce hyperlipidaemia and atherosclerotic lesion formation. Reverse cholesterol transport (RCT) plays a crucial role in exporting cholesterol from peripheral cells, which is one mechanism utilized in the prevention and treatment of atherosclerosis. The aim of this study is to investigate whether quercetin reduces lipid accumulation by improving RCT in vivo. METHODS: Apolipoprotein E-deficient mice fed a high-fat diet were used to investigate the effect of quercetin on RCT by an isotope tracing method, and the underlying mechanisms were clarified by molecular techniques. RESULTS: These novel results demonstrated that quercetin significantly improved [3H]-cholesterol transfer from [3H]-cholesterol-loaded macrophages to the plasma (approximately 34% increase), liver (30% increase), and bile (50% increase) and finally to the feces (approximately 40% increase) for excretion in apolipoprotein E-deficient mice fed a high-fat diet. Furthermore, quercetin markedly increased the cholesterol accepting ability of plasma and high-density lipoprotein (HDL) and dramatically decreased the content of malondialdehyde in plasma and oxidized phosphocholine carried by HDL. Therefore, the
underlying mechanisms of quercetin in improving RCT may be partially due to the elevated cholesterol accepting ability of HDL, the increased expression levels of proteins related to RCT, such as ATP-binding cassettes (ABC) A1 and G1, and the improved antioxidant activity of HDL. CONCLUSION: Quercetin accelerates RCT in an atherosclerosis model, which is helpful in clarifying the lipid-lowering effect of quercetin.


ABSTRACT
Atherosclerosis represents a significant cause of morbidity and mortality in both the developed and developing countries. Animal models of atherosclerosis have served as valuable tools for providing insights on its aetiology, pathophysiology and complications. They can be used for invasive interrogation of physiological function and provide a platform for testing the efficacy and safety of different pharmacological therapies. Compared to studies using human subjects, animal models have the advantages of being easier to manage, with controllable diet and environmental risk factors. Moreover, pathophysiological changes can be induced either genetically or pharmacologically to study the harmful effects of these interventions. There is no single ideal animal model, as different systems are suitable for different research objectives. A good understanding of the similarities and differences to humans enables effective extrapolation of data for translational application. In this article, we will examine the different mouse models for the study and elucidation of the pathophysiological mechanisms underlying atherosclerosis. We also review recent advances in the field, such as the role of oxidative stress in promoting endoplasmic reticulum stress, mitochondrial dysfunction and mitochondrial DNA damage, which can result in vascular inflammation and atherosclerosis. Finally, novel therapeutic approaches to reduce vascular damage caused by chronic inflammation using microRNA and nano-medicine technology, are discussed.


ABSTRACT
BACKGROUND: The transient global cerebral hypoperfusion/reperfusion achieved by induction of Bilateral Common Carotid Artery Occlusion followed by Reperfusion (BCCAO/R) may trigger a physiological response in an attempt to preserve tissue and function integrity. There are several candidate molecules among which the endocannabinoid system (ECS) and/or peroxisome-proliferator activated receptor-alpha (PPAR-alpha) may play a role in modulating oxidative stress and inflammation. The aims of the present study are to evaluate whether the ECS, the enzyme cyclooxygenase-2 (COX-2) and PPAR-alpha are involved during BCCAO/R in rat brain, and to identify possible markers of the ongoing BCCAO/R-induced challenge in plasma.
METHODS: Adult Wistar rats underwent BCCAO/R with 30 min hypoperfusion followed by 60 min reperfusion. The frontal and temporal-occipital cortices and plasma were analyzed by high performance liquid chromatography-mass spectrometry (HPLC-MS) to determine
concentrations of endocannabinoids (eCBs) and related molecules behaving as ligands of PPAR-alpha, and of oxidative-stress markers such as lipoperoxides, while Western Blot and immunohistochemistry were used to study protein expression of cannabinoid receptors, COX-2 and PPAR-alpha. Unpaired Student's t-test was used to evaluate statistical differences between groups. RESULTS: The acute BCCAO/R procedure is followed by increased brain tissue levels of the eCBs 2-arachidonoylglycerol and anandamide, palmitoylethanolamide, an avid ligand of PPAR-alpha, lipoperoxides, type 1 (CB1) and type 2 (CB2) cannabinoid receptors, and COX-2, and decreased brain tissue concentrations of docosahexaenoic acid (DHA), one of the major targets of lipid peroxidation. In plasma, increased levels of anandamide and lipoperoxides were observed. CONCLUSIONS: The BCCAO/R stimulated early molecular changes that can be easily traced in brain tissue and plasma, and that are indicative of the tissue physiological response to the reperfusion-induced oxidative stress and inflammation. The observed variations suggest that the positive modulation of the ECS and the increase of proinflammatory substances are directly correlated events. Increase of plasmatic levels of anandamide and lipoperoxides further suggests that dysregulation of these molecules may be taken as an indicator of an ongoing hypoperfusion/reperfusion challenge.


**ABSTRACT**

The general aim of this study was to evaluate the disease spectrum in patients presenting with a pure polymyositis (pPM) phenotype. Specific objectives were to characterize clinical features, autoantibodies (aAbs), and membrane attack complex (MAC) in muscle biopsies of patients with treatment-responsive, statin-exposed necrotizing autoimmune myositis (NAM). Patients from the Centre hospitalier de l’Universite de Montreal autoimmune myositis (AIM) Cohort with a pPM phenotype, response to immunosuppression, and follow-up >/=3 years were included. Of 17 consecutive patients with pPM, 14 patients had a NAM, of whom 12 were previously exposed to atorvastatin (mean 38.8 months). These 12 patients were therefore suspected of atorvastatin-induced AIM (atorAIM) and selected for study. All had aAbs to 3-hydroxy-3-methylglutaryl coenzyme A reductase, and none had overlap aAbs, aAbs to signal recognition particle, or cancer. Three stages of myopathy were recognized: stage 1 (isolated serum creatine kinase [CK] elevation), stage 2 (CK elevation, normal strength, and abnormal electromyogram [EMG]), and stage 3 (CK elevation, proximal weakness, and abnormal EMG). At diagnosis, 10/12 (83%) patients had stage 3 myopathy (mean CK elevation: 7247 U/L). The presenting mode was stage 1 in 6 patients (50%) (mean CK elevation: 1540 U/L), all of whom progressed to stage 3 (mean delay: 37 months) despite atorvastatin discontinuation. MAC deposition was observed in all muscle biopsies (isolated sarcolemmal deposition on non-necrotic fibers, isolated granular deposition on endomysial capillaries, or mixed pattern). Oral corticosteroids alone failed to normalize CKs and induce remission. Ten patients (83%) received intravenous immune globulin (IVIG) as part of an induction regimen. Of 10 patients with >/=1 year remission on stable maintenance therapy, IVIG was needed in 50%, either with methotrexate (MTX) monotherapy or combination immunosuppression. In the remaining
patients, MTX monotherapy or combination therapy maintained remission without IVIG. AtorAIM emerged as the dominant entity in patients with a pPM phenotype and treatment-responsive myopathy. Isolated CK elevation was the mode of presentation of atorAIM. The new onset of isolated CK elevation on atorvastatin and persistent CK elevation on statin discontinuation should raise early suspicion for atorAIM. Statin-induced AIM should be included in the differential diagnosis of asymptomatic hyperCKemia. Three patterns of MAC deposition, while nonpathognomonic, were pathological clues to atorAIM. AtorAIM was uniformly corticosteroid resistant but responsive to IVIG as induction and maintenance therapy.


ABSTRACT
OBJECTIVE: Hyperglycemia causes the breakdown of the blood-retinal barrier by impairing endothelial nitric oxide synthase (eNOS) function. Statins have many pleiotropic effects such as improving endothelial barrier permeability and increasing eNOS mRNA stability. The objective of this study was to determine effect of simvastatin on l-arginine transport and NO production under high-glucose conditions in conditionally immortalized rat retinal capillary endothelial cell line (TR-iBRB). METHODS: Changes in l-arginine transport uptake and, expression levels of cationic amino acid transporter 1 (CAT-1) and eNOS mRNA were investigated after pretreatment with simvastatin and NOS inhibitors (l-NMMA and l-NAME) under high-glucose conditions using TR-iBRB, an in vitro model of iBRB. The NO level released from TR-iBRB cells was examined using Griess reagents. RESULTS: Under high glucose conditions, [3H]l-arginine uptake was decreased in TR-iBRB cells. Simvastatin pretreatment elevated [3H]l-arginine uptake, the expression levels of CAT-1 and eNOS mRNA, and NO production under high-glucose conditions. Moreover, the co-treatment with simvastatin and NOS inhibitors reduced [3H]l-arginine uptake compared to pretreatment with simvastatin alone. CONCLUSION: Our results suggest that, in the presence of high-glucose levels, increased l-arginine uptake due to simvastatin treatment was associated with increased CAT-1 and eNOS mRNA levels, leading to higher NO production in TR-iBRB cells. Thus, simvastatin might be a good modulator for diabetic retinopathy therapy by increasing of the l-arginine uptake and improving endothelial function in retinal capillary endothelial cells.


ABSTRACT
BACKGROUND: Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a key regulator of low-density lipoprotein cholesterol and cardiovascular disease risk, and is an emerging therapeutic target. OBJECTIVE: We compared serum PCSK9 levels in young adults, with and without type 2 diabetes. SUBJECTS AND METHODS: Cross-sectional analysis was conducted in a cohort, aged 15 to 26 years, in Cincinnati, OH, from 2005 to 2010. Serum PCSK9 levels were measured in 94 youth with type 2 diabetes, 93 obese control subjects, and 99 lean control subjects. Correlative
analyses were conducted to determine significant covariates of PCSK9 by group and sex, and multivariate linear regression models were used to study the independent determinants of PCSK9. RESULTS: In females, PCSK9 levels were significantly increased in the obese and type 2 diabetes subjects relative to the lean controls (P < .01). Moreover, PCSK9 was positively correlated with multiple metabolic parameters in females: body mass index, systolic blood pressure, fasting glucose, fasting insulin, and C-reactive protein levels (P < .02). In males, PCSK9 levels were decreased overall compared with females (P = .03), and did not differ between the lean, obese, or type 2 diabetes groups. CONCLUSIONS: Obesity and type 2 diabetes were associated with significantly higher levels of PCSK9 in young women, but not in young men. These data suggest that sex could modify the effects of obesity and diabetes on PCSK9 in young adults.


ABSTRACT
Randomized trials suggest that statin treatment may lower blood pressure and influence cardiovascular autonomic function (CVAF), but the impact of duration of usage, discontinuation, and adherence to this therapy is unknown. We examined these issues with regard to blood pressure (BP)-related variables in a large, population-based study. Participants were 4942 adults (58% male; aged 50-84 years): 2179 on statin treatment and 2763 untreated. Days of utilization, adherence (proportion of days covered >/=0.8), and discontinuation (non-use for >/=30 days immediately prior to BP measurement) of three statins (atorvastatin, pravastatin, and simvastatin) over a period of up to 2 years was monitored retrospectively from electronic databases. Systolic BP (SBP), diastolic BP (DBP), augmentation index, excess pressure, reservoir pressure, and CVAF (pulse rate and BP variability) parameters were calculated from aortic pressure waveforms derived from suprasystolic brachial measurement. Days of statin treatment had inverse relationships with pulse rate variability parameters in cardiac arrhythmic participants (20-25% lower than in statin non-users) and with most arterial function parameters in everyone. For example, compared to untreated participants, those treated for >/=659 days had 3.0 mmHg lower aortic SBP (P < 0.01). Discontinuation was associated with higher brachial DBP and aortic DBP (for both, beta = 2.0 mmHg, P = 0.008). Compared to non-adherent statin users, adherent users had lower levels of brachial SBP, brachial DBP, aortic DBP, aortic SBP, and peak reservoir pressure (beta = -1.4 to -2.6 mmHg). In conclusion, in a real-world setting, statin-therapy duration, non-discontinuation and adherence associate inversely with BP variables and, in cardiac arrhythmias, CVAF parameters.


ABSTRACT
BACKGROUND: Stroke is associated with the development of cognitive impairment and dementia. We assessed the effect of intensive blood pressure (BP) and/or lipid lowering on cognitive outcomes in patients with recent stroke in a pilot trial. METHODS: In a multicentre, partial-factorial trial, patients with recent stroke, absence of dementia, and systolic BP (SBP) 125-170 mmHg were assigned randomly to at least 6 months of intensive (target SBP <125 mmHg) or guideline (target SBP <140 mmHg) BP lowering. The subset of patients with ischaemic stroke and total cholesterol 3.0-8.0 mmol/l were also assigned randomly to intensive (target LDL-cholesterol <1.3 mmol/l) or guideline (target LDL-c <3.0 mmol/l) lipid lowering. The primary outcome was the Addenbrooke’s Cognitive Examination-Revised (ACE-R). RESULTS: We enrolled 83 patients, mean age 74.0 (6.8) years, and median 4.5 months after stroke. The median follow-up was 24 months (range 1-48). Mean BP was significantly reduced with intensive compared to guideline treatment (difference -10.6/-5.5 mmHg; p<0.01), as was total/LDL-cholesterol with intensive lipid lowering compared to guideline (difference -0.54/-0.44 mmol/l; p<0.01). The ACE-R score during treatment did not differ for either treatment comparison; mean difference for BP lowering -3.6 (95% CI -9.7 to 2.4), and lipid lowering 4.4 (95% CI -2.1 to 10.9). However, intensive lipid lowering therapy was significantly associated with improved scores for ACE-R at 6 months, trail making A, modified Rankin Scale and Euro-Qol Visual Analogue Scale. There was no difference in rates of dementia or serious adverse events for either comparison. CONCLUSION: In patients with recent stroke and normal cognition, intensive BP and lipid lowering were feasible and safe, but did not alter cognition over two years. The association between intensive lipid lowering and improved scores for some secondary outcomes suggests further trials are warranted. TRIAL REGISTRATION: ISRCTN ISRCTN85562386.


ABSTRACT
Endothelial HMEC-1 cells incubated with pro-inflammatory cytokine TNF-alpha for 6 and 24 hours were studied as a model of inflammation using Raman imaging. Striking changes in distribution, composition and concentration of cellular lipids were observed after exposure to TNF-alpha compared to the control. In particular, 3D Raman imaging revealed a significant increase in the amount of lipid entities formed under inflammation. Lipid bodies were randomly distributed in the cytoplasm and two types of droplets were assembled: more saturated one, in spectral characteristics resembling phosphatidylcholine and saturated cholesteryl esters, observed also in the control, and highly unsaturated one, containing also cholesterols, being a hallmark of inflamed cells. The statistical analysis showed that the number of lipid bodies was significantly dependent on the exposure time to TNF-alpha. Overall, observed formation of unsaturated lipid droplets can be directly correlated with the increase in production of prostacyclins - endogenous inflammation mediators.

ABSTRACT
Dyslipoproteinemias represent a group of disorders closely related to alterations of cholesterol and triglycerides. The alterations of these lipids are considered important risk factors in coronary heart disease and indicate the need for clinically effective and safe drugs. Hypolipidemic agent therapy, however, does not appear without risk since the administration of these agents is by necessity, on a long-term basis. In the conduct of animal safety studies with some hypolipidemics, hyperplastic nodules or tumors developed in the liver of rodents. Data from the literature seem to indicate that the tumor response in rodents varies with the type of hypolipidemic drug administered. This paper summarizes the studies with the new lipid-regulating agent gemfibrozil. Aside from conventional long-term studies in rodents, the ultrastructural aspects of the liver were analyzed in several species and genotoxicity assays and short-term tests for hepatocarcinogenicity were conducted. Thus, it was possible to obtain an overview of these biological phenomena in order to allow for safety extrapolations. The biological behavior of these liver nodules showed that gemfibrozil and clofibrate-induced hepatocytes had not undergone malignant transformation. Further, the phenomenon of peroxisome proliferation, a characteristic event that follows hypolipidemic administration in rodents, was not confirmed in primate or human liver. Peroxisome proliferation has been linked to the process of hepatocarcinogenesis in rodents, although genotoxicity assays were negative and initiation/promotion tests failed to elicit tumors or nodules in a system where hepatocarcinogens manifest their activity. Thus, hypolipidemics such as gemfibrozil or Clofibrate may possess low tumorigenic potential with low risk due to the lack of correlation between these tests. Nevertheless, these agents are indicated for specific lipoprotein phenotype alteration with the resulting clinical benefits.


ABSTRACT
We previously found that hematoma worsens hydrocephalus after intraventricular hemorrhage (IVH) via increasing iron deposition and aggravating ependymal cilia injury; therefore, promoting hematoma absorption may be a promising strategy for IVH. Recently, some investigations imply that simvastatin has the ability of accelerating hematoma absorption. Thus, this study was designed to examine the efficacy of simvastatin for IVH in rats. Intracerebral hemorrhage with ventricular extension was induced in adult male Sprague-Dawley rats after autologous blood injection. Simvastatin or vehicle was administered orally at 1 day after IVH and then daily for 1 week. MRI studies were performed to measure the volumes of intracranial hematoma and lateral ventricle at days 1, 3, 7, 14, and 28 after IVH. Motor and neurocognitive functions were assessed at days 1 to 7 and 23 to 28, respectively. Iron deposition, iron-related protein expression, ependymal damage, and histology were detected at day 28. Expression of CD36 scavenger receptor (facilitating phagocytosis) was examined at day 3 after IVH using western blotting and immunofluorescence. Simvastatin significantly increased hematoma absorption ratio, reduced ventricular volume, and attenuated neurological dysfunction post-IVH. In addition, less iron accumulation and more cilia survival was observed in the simvastatin
group when compared with the control. What's more, higher expression of CD36 was detected around the hematoma after simvastatin administration. Simvastatin significantly enhanced brain hematoma absorption, alleviated hydrocephalus, and improved neurological recovery after experimental IVH, which may in part by upregulating CD36 expression. Our data suggest that early simvastatin use may be a novel therapy for IVH patients.


**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=28103332

**ABSTRACT**

Objective: The aim of this study was to investigate the relationship between bilirubin levels and hyperlipidemia in patients with glucocorticoid-resistant nephritic syndrome (NS). Methods: This study was a double-blind randomized controlled trial. A total of one hundred and seventy-two patients with glucocorticoid resistance met the inclusion criteria and were divided into 2 groups (the treatment and control groups), each comprising 86 patients. Due to worsening of renal and discharge functions among the patients, Simvastatin therapy (10 mg/d) was administered for four weeks to 68 patients from the treatment group while 78 patients from the control group were treated without lipid-lowering drugs for the same duration of time. Triglyceride (TG), total cholesterol (TCHO), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), serum total protein, serum albumin, total bilirubin, direct bilirubin, and 24-h urinary protein (UPr) levels were determined before and after treatment. Results: Total cholesterol, triglyceride, and lipoprotein cholesterol levels significantly decreased, but the bilirubin level significantly increased in the treatment group compared to the levels in the control group and those before treatment (P<0.01). Additionally, HDL-C and 24-h UPr levels were not significantly different between the treatment and control groups (P>0.05). Conclusion: Low bilirubin level was in primary nephritic syndrome patients with glucocorticoid resistance. After treatment with Simvastatin, blood lipid was reduced and total bilirubin level was increased. However, there was no improvement in urinary albumin, which indicated that bilirubin might be involved in dyslipidemia of nephrotic syndrome.


**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=28087914

**ABSTRACT**

Objective: To investigate the effect of atorvastatin on reflow in patients with acute ST-segment elevation myocardial infarction (STEMI) after percutaneous coronary intervention (PCI) and its relation to serum uric acid levels. Methods: One hundred and fourteen STEMI patients undergoing primary PCI were enrolled and randomly divided into two groups:55 cases received oral atorvastatin 20 mg before PCI (routine dose group) and 59 cases received oral atorvastatin 80 mg before PCI (high dose group). According to the initial serum uric acid level, patients in two groups were further divided into normal uric acid subgroup and hyperuricemia subgroup.
The changes of uric acid level and coronary artery blood flow after PCI were observed. Correlations between the decrease of uric acid, the dose of atorvastatin and the blood flow of coronary artery after PCI were analyzed. Results: Serum uric acid levels were decreased after treatment in both groups (all P<0.05), and patients with hyperuricemia showed more significant decrease in serum uric acid level (P<0.05). Compared with the routine dose group, serum uric acid level in patients with hyperuricemia decreased more significantly in the high dose group (P<0.05), but no significant difference was observed between patients with normal serum uric acid levels in two groups (P>0.05). Among 114 patients, there were 19 cases without reflow after PCI (16.7%). In the routine dose group, there were 12 patients without reflow, in which 3 had normal uric acid and 9 had high uric acid levels (P<0.01). In the high dose group, there were 7 patients without reflow, in which 2 had normal uric acid and 5 had high uric acid (P<0.05). Logistic regression analysis showed that hyperuricemia was one of independent risk factors for no-reflow after PCI (OR=1.01, 95% CI:1.01-1.11, P<0.01). The incidence of no-flow after PCI in the routine dose group was 21.8% (12/55), and that in the high dose group was 11.9% (7/59) (P<0.01). Conclusion: High dose atorvastatin can decrease serum uric acid levels and improve reflow after PCI in patients with STEMI.