Literature update week 52 (2018)


ABSTRACT
Background Although rare, familial hypertriglyceridemia can cause acute and life-threatening complications in pregnancy. Cases The first patient’s pregnancy was complicated by multiple admissions for pancreatitis due to hypertriglyceridemia and noncompliance with gemfibrozil. In her second pregnancy, she was compliant with gemfibrozil and only experienced pancreatitis episodes toward the end of pregnancy. The second patient had diabetes mellitus and familial hypertriglyceridemia. She required multiple hospitalizations for diabetic ketoacidosis secondary to insulin noncompliance. In both pregnancies, she was compliant with gemfibrozil and had no complications related to hypertriglyceridemia. Conclusion Treatment with gemfibrozil in pregnancies complicated by hypertriglyceridemia may prevent complications without adverse maternal or fetal effects and could be considered in treating pregnant patients with severe hypertriglyceridemia. These cases also demonstrate the importance of medication compliance in the prevention of poor outcomes.


ABSTRACT


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Sphingosine kinases phosphorylate sphingosine to sphingosine 1phosphate (S1P), which functions as a signaling molecule. We have previously shown that sphingosine kinase 2 (Sphk2) is important for insulin secretion. To obtain a better understanding of the role of Sphk2 in glucose and lipid metabolism, we have characterized 20- and 52-week old Sphk2(-/-) mice using glucose and insulin tolerance tests and by analyzing metabolic gene expression in adipose tissue. A detailed metabolic characterization of these mice revealed that aging Sphk2(-/-) mice are protected from metabolic decline and obesity compared to WT mice. Specifically, we found that 52-week male Sphk2(-/-) mice had decreased weight and fat mass, and increased glucose tolerance and insulin sensitivity compared to control mice. Indirect calorimetry studies demonstrated an increased energy expenditure and food intake in 52-week old male Sphk2(-/-) versus control mice. Furthermore, expression of adiponectin gene in adipose tissue was
increased and the plasma levels of adiponectin elevated in aged Sphk2(-/-) mice compared to WT. Analysis of lipid metabolic gene expression in adipose tissue showed increased expression of the Atgl gene, which was associated with increased Atgl protein levels. Atgl encodes for the adipocyte triglyceride lipase, which catalyzes the rate-limiting step of lipolysis. In summary, these data suggest that mice lacking the Sphk2 gene are protected from obesity and insulin resistance during aging. The beneficial metabolic effects observed in aged Sphk2(-/-) mice may be in part due to enhanced lipolysis by Atgl and increased levels of adiponectin, which has lipid- and glucose-lowering effects.


ABSTRACT
The medical importance of intra-abdominal candidiasis (IAC) contrasts with the limited number of pharmacological treatment options available and the increasing rate of resistance to antifungal drugs. Thus, the repositioning of compounds in clinical use can contribute to the broadening of treatment possibilities for this infection. Statins, a class of drugs used to reduce cardiovascular event risk, have shown antiparasitic, antibacterial, and antiviral activities; however, their antifungal effects remain poorly studied. In this context, the present study aimed to elucidate the antifungal potential of six statins in vitro, as well as to evaluate the therapeutic use of fluvasatin in a mouse model of IAC. The biological effects of statins were evaluated against Candida spp., through the determination of the minimum inhibitory concentration (MIC). For the statins that showed activity, the fungicidal concentration, toxicity/selectivity, synergism with azoles and polyenes, phenotypic effects, and activity against virulence factors were also determined. Atorvastatin, rosuvastatin and fluvasatin were highly active, especially against C. albicans (MIC < 1-128 mug.ml(-1)) and C. glabrata (MIC 32-64 mug.ml(-1)). Fluvasatin and atorvastatin were selective for C. albicans in baby hamster kidney (BHK) cells. Moreover, all active statins in the antifungal assay showed high selectivity for fungal cells over bacteria. The combination of atorvastatin, rosuvastatin, and fluvasatin with azoles was associated with a synergistic effect. Active statins do not act on the fungal membrane or wall, but instead stimulate farnesol-dependent pathogenicity factors such as yeast-to-hyphal transition and biofilm generation. Fluvasatin treatment was evaluated in a mouse model of IAC, showing stimulation of the extra-hepatic dissemination of C. albicans but improvements in renal, splenic, and hepatic histological aspects. In conclusion, statins have potent antifungal activity in vitro, but the therapeutic effect in vivo is restricted to their anti-inflammatory activity.


ABSTRACT
BACKGROUND: Liver transplantation is the best treatment for end-stage liver disease. The interruption of the blood supply to the donor liver during cold storage damages the liver, affecting how well the liver will function after transplant. The drug Simvastatin may help to protect donor livers against this damage and improve outcomes for transplant recipients. The aim of this study is to evaluate the benefits of treating the donor liver with Simvastatin compared with the standard transplant procedure. PATIENT AND METHODS: We propose a prospective, double-blinded, randomized phase 2 study of 2 parallel groups of eligible adult patients. We will compare 3-month, 6-month, and 12-month graft survival after LT, in order to identify a significant relation between the two homogenous groups of LT patients. The two groups only differ by the Simvastatin or placebo administration regimen while following the same procedure, with identical surgical instruments, and medical and nursing skilled staff. To reach these goals, we determined that we needed to recruit 106 patients. This sample size achieves 90% power to detect a difference of 14.6% between the two groups survival using a one-sided binomial test. DISCUSSION: This trial is designed to confirm the effectiveness of Simvastatin to protect healthy and steatotic livers undergoing cold storage and warm reperfusion before transplantation and to evaluate if the addition of Simvastatin translates into improved graft outcomes. TRIAL REGISTRATION: ISRCTN27083228.


ABSTRACT

INTRODUCTION: Familial hypercholesterolemia (FH) is an autosomal-dominant inherited genetic disease. High-throughput sequencing quickly and comprehensively detects causative variants of FH-related genes (LDLR, PCSK9, APOB and LDLRAP1). Although the presence of causative variants in FH-related genes correlates with future cardiovascular events, it remains unclear whether detection of causative gene mutation and disclosure of its associated cardiovascular risk affects outcomes in patients with FH. Therefore, this study intends to evaluate the efficacy of counselling future cardiovascular risk based on genetic testing in addition to standard patients' education programme in patients with FH. METHODS AND ANALYSIS: A randomised, waiting-list controlled, open-label, single-centre trial will be conducted. We will recruit patients with clinically diagnosed FH without previous history of coronary heart disease from March 2018 to December 2019, and we plan to follow up participants until March 2021. For the intervention group, we will perform genetic counselling and will inform an estimated future cardiovascular risk based on individuals' genetic testing results. The primary endpoint of this study is the plasma low-density lipoprotein cholesterol level at 24 weeks after randomisation. The secondary endpoints assessed at 24 and 48 weeks are as follows: blood test results; smoking status; changes of lipid-lowering agents' regimen and Patients Satisfaction Questionnaire Short Form scores among the four groups divided by the presence of genetic counselling and genetic status of FH. ETHICS AND DISSEMINATION: This study will be conducted in compliance with the Declaration of Helsinki, the Ethical Guidelines for Medical and Health Research Involving Human Subjects and all other applicable laws and guidelines in Japan. This study protocol was approved by the IRB at Kanazawa University.
TRIAL REGISTRATION NUMBER: UMIN000029375.


ABSTRACT
Recent research focusing on brown adipose tissue (BAT) function emphasizes its importance in systemic metabolic homeostasis. We show here that genetic and pharmacological inhibition of the mevalonate pathway leads to reduced human and mouse brown adipocyte function in vitro and impaired adipose tissue browning in vivo. A retrospective analysis of a large patient cohort suggests an inverse correlation between statin use and active BAT in humans, while we show in a prospective clinical trial that fluvastatin reduces thermogenic gene expression in human BAT. We identify geranylgeranyl pyrophosphate as the key mevalonate pathway intermediate driving adipocyte browning in vitro and in vivo, whose effects are mediated by geranylgeranyltransferases (GGTases), enzymes catalyzing geranylgeranylation of small GTP-binding proteins, thereby regulating YAP1/TAZ signaling through F-actin modulation. Conversely, adipocyte-specific ablation of GGTase I leads to impaired adipocyte browning, reduced energy expenditure, and glucose intolerance under obesogenic conditions, highlighting the importance of this pathway in modulating brown adipocyte functionality and systemic metabolism.


ABSTRACT
RATIONALE: Glucagon is a key hormone that regulates the adaptive metabolic responses to fasting. In addition to maintaining glucose homeostasis, glucagon participates in the regulation of cholesterol metabolism, however, the molecular pathways underlying this effect are incompletely understood. OBJECTIVE: We sought to determine the role of hepatic glucagon receptor (Gcgr) signaling in plasma cholesterol regulation and identify its underlying molecular mechanisms. METHODS AND RESULTS: We show that Gcgr signaling plays an essential role in low-density lipoprotein (LDL) cholesterol homeostasis through regulating the proprotein convertase subtilisin/kexin type 9 (PCSK9) levels. Silencing of hepatic Gcgr or inhibition of glucagon action increased hepatic and plasma PCSK9 and resulted in lower LDL receptor protein and increased plasma LDL-cholesterol. Conversely, treatment of WT mice with glucagon lowered LDL-cholesterol levels, whereas this response was abrogated in Pcsk9(-/-) and Ldlr(-/-) mice. Our gain- and loss-of-function studies identified exchange protein activated by cAMP-2 (Epac2) and Ras-related protein-1 (Rap1) as the downstream mediators of glucagon's action on PCSK9 homeostasis. Moreover, mechanistic studies revealed that glucagon affected the half-life of PCSK9 protein without changing the level of its mRNA, indicating that Gcgr signaling regulates PCSK9 degradation. CONCLUSIONS: These findings provide novel insights into the molecular interplay between hepatic glucagon signaling and lipid metabolism and describe a new post-transcriptional mechanism of PCSK9 regulation.
BACKGROUND: Sex differences are known to exist in the management of older patients presenting with acute myocardial infarction (AMI). Few studies have examined the incidence and risk factors of AMI among young patients, or whether clinical management differs by sex.

METHODS: The Atherosclerosis Risk in Communities (ARIC) Surveillance study conducts hospital surveillance of AMI in 4 US communities (MD, MN, MS, and NC). AMI was classified by physician review, using a validated algorithm. Medications and procedures were abstracted from the medical record. Our study population was limited to young patients aged 35-54 years. RESULTS: From 1995-2014, 28,732 weighted hospitalizations for AMI were sampled among patients aged 35-74. Of these, 8,737 (30%) were young. The annual incidence of AMI hospitalizations increased for young women but decreased for young men. The overall proportion of AMI admissions attributable to young patients steadily increased, from 27% in 1995-1999 to 32% in 2010-2014 (P for trend =0.002), with the largest increase observed in young women. History of hypertension (59% to 73%, P for trend<0.0001) and diabetes mellitus (25% to 35%, P for trend<0.0001) also increased among young AMI patients. Compared to young men, young women presenting with AMI were more often black and had a greater comorbidity burden. In adjusted analyses, young women had a lower probability of receiving lipid-lowering therapies (RR = 0.87; 95% CI: 0.80 - 0.94), non-aspirin antiplatelets (RR = 0.83; 95% CI: 0.75 - 0.91), beta blockers (RR = 0.96; 95% CI: 0.91 - 0.99), coronary angiography (RR = 0.93; 95% CI: 0.86 - 0.99) and coronary revascularization (RR = 0.79; 95% CI: 0.71 - 0.87). However, 1-year all-cause mortality was comparable for women vs. men (HR=1.10; 95% CI: 0.83 - 1.45). CONCLUSIONS: The proportion of AMI hospitalizations attributable to young patients increased from 1995-2014 and was especially pronounced among women. History of hypertension and diabetes among young patients admitted with AMI increased over time as well. Compared with young men, young women presenting with AMI had a lower likelihood of receiving guideline based AMI therapies. A better understanding of factors underlying these changes is needed to improve care of young patients with AMI.

ABSTRACT

ABSTRACT
BACKGROUND: Lipoprotein(a) [Lp(a)] may play a causal role in atherosclerosis. Proprotein convertase subtilisin/kexin 9 (PCSK9) inhibitors have been shown to significantly reduce plasma Lp(a) concentration. However, the relationship between Lp(a) levels, PCSK9 inhibition and cardiovascular (CV) risk reduction remains undefined. METHODS: Lp(a) was measured in 25,096 patients in FOURIER, a randomized trial of evolocumab versus placebo in patients with established atherosclerotic CV disease (median follow-up 2.2 years). Cox models were used to assess the independent prognostic value of Lp(a) and the efficacy of evolocumab for coronary risk reduction by baseline Lp(a) concentration. RESULTS: The median [IQR] baseline Lp(a) concentration was 37[13-165] nmol/L. In the placebo arm, patients with baseline Lp(a) in the highest quartile had a higher risk of coronary heart disease (CHD) death, MI or urgent revascularization (UR) (adjusted HR Q4:Q1 1.22, 95% CI 1.01-1.48) independent of LDL-C. At 48 weeks, evolocumab significantly reduced Lp(a) by a median [IQR] of 26.9% [6.2-46.7%]. The percent change in Lp(a) and LDL-C at 48 weeks in evolocumab patients was moderately positively correlated (r=0.37, 95% CI 0.36-0.39, P<0.001). Evolocumab reduced the risk of CHD death, MI or UR by 23% (HR 0.77, 95% CI 0.67-0.88) in patients with a baseline Lp(a) >median, and by 7% (HR 0.93, 0.80-1.08; P interaction=0.07) in those <=median. Coupled with the higher baseline risk, the absolute risk reductions and NNT3y were 2.49% and 40 vs. 0.95% and 105, respectively. CONCLUSIONS: Lp(a) is associated with the risk of CV events in patients with established CV disease irrespective of LDL-C. Evolocumab significantly reduced Lp(a) levels, and patients with higher baseline Lp(a) levels experienced greater absolute reductions in Lp(a) and tended to derive greater coronary benefit from PCSK9 inhibition. CLINICAL TRIAL REGISTRATION: URL: https://clinicaltrials.gov Unique Identifier: NCT01764633.


ABSTRACT

Since the start of percutaneous coronary intervention (PCI), the field has seen a rapid explosion in technology from initial catheters, balloons, to metallic, now drug coated stents. However, unique to the field of coronary intervention in comparison to other areas of technological advances in medicine, the iterative advances have been progressively tested, and when possible, randomized against control groups to determine the best and most appropriate care. In fact, the field has matured in such rapid fashion over the 40 years since inception (1) in part due to the scientific culture started by the initial report of angioplasty from Gruntzig in which he concluded "A prospective randomized trial will be necessary to evaluate it usefulness in comparison with surgical and medical management." Hence, each new therapy has been in general vetted and tested for improvements in patient outcomes from technologies such as coronary pressure wires, drug eluting stents, to strategies such as primary PCI for acute myocardial infarction. It is with these therapies and more importantly advances in effective medical therapy including anti-platelet and antithrombotic therapy, lipid lowering drugs, and overall preventive care that cardiovascular mortality rates have fallen by 22% over the last decade. (2) However, in parallel with the maturation of coronary intervention has been the baby boom and aging population living with coronary heart disease and multiple co-morbidities and more complex coronary anatomy. In fact, despite the noted improvements, patients
presenting between 2011-2013 with acute MI and cardiogenic shock were significantly more likely to have comorbidities, including diabetes, dyslipidemia, previous PCI, and end-stage renal disease when compared with similar patients between 2005-2006. (3) It is in this context that as the clinical community attempts to determine how to best use percutaneous support devices, Kapur and colleagues provide the initial findings of the Door-to-Unload in STEMI Pilot trial in Circulation. (4).


ABSTRACT
BACKGROUND: To optimize preventive strategies for coronary heart disease (CHD), it is essential to understand and appropriately quantify the contribution of its key risk factors. Our objective was to compare the associations of key modifiable CHD risk factors—specifically lipids, systolic blood pressure (SBP), diabetes, and smoking—with incident CHD events based on their prognostic performance, attributable risk fractions, and treatment benefits, overall and by age.

METHODS: Pooled participant-level data from four observational cohort studies sponsored by the National Heart, Lung, and Blood Institute were used to create a cohort of 22,626 individuals aged 45-84 years who were initially free of cardiovascular disease. Individuals were followed for 10 years from baseline evaluation for incident CHD. Proportional hazards regression was used to estimate metrics of prognostic model performance (likelihood ratio, C index, net reclassification, discrimination slope), hazard ratios, and population attributable fractions (PAFs) for SBP, non-high-density lipoprotein cholesterol (non-HDL-C), diabetes, and smoking. Expected absolute risk reductions (ARRs) for antihypertensive and lipid-lowering treatment were assessed.

RESULTS: Age, sex, and race capture 63-80% of the prognostic performance of cardiovascular risk models. In contrast, adding either SBP, non-HDL-C, diabetes, or smoking to a model with other risk factors increases the C index by only 0.004-0.013. However, primordial prevention could have a substantial effect as demonstrated by PAFs of 28% for SBP>=130 mmHg and 17% for non-HDL-C>=130 mg/dL. Similarly, lowering the SBP of all individuals to <130 mmHg or lowering low-density lipoprotein cholesterol by 30% would be expected to lower a baseline 10-year CHD risk of 10.7% to 7.0 and 8.0, respectively (ARR 3.7 and 2.7%, respectively). Prognostic performance decreases with age (C indices for age groups 45-54, 55-64, 65-74, 75-84 are 0.75, 0.72, 0.66, and 0.62, respectively), whereas ARRs increase (SBP: 1.1, 2.3, 5.4, 10.3%, respectively; non-HDL-C: 1.1, 2.0, 3.7, 5.9%, respectively). CONCLUSIONS: Although individual modifiable CHD risk factors contribute only modestly to prognostic performance, our models indicate that eliminating or controlling these individual factors would lead to substantial reductions in total population CHD events. Metrics used to judge importance of risk factors should be tailored to the research objectives.


ABSTRACT
In the recently presented ODYSSEY Outcomes trial, alirocumab use in patients with acute coronary syndrome (ACS) and LDL-C ≥70mg/dL (or non-HDL-C >100mg/dL or Apo B ≥80mg/dL) resulted in a 15% relative (1.6% absolute) reduction in the risk of major adverse cardiovascular events. We evaluated what proportion of patients in the VA Health Care System would qualify for alirocumab based on ODYSSEY Outcomes criteria, how they are currently treated with LDL-C lowering medications, and the cost implications if other evidence-based medications were utilized first prior to considering a PCSK9 inhibitor.


ABSTRACT
BACKGROUND: The 2013 American College of Cardiology/American Heart Association guidelines for the treatment of blood cholesterol found little evidence to support the use of nonstatin lipid-modifying medications to reduce atherosclerotic cardiovascular disease (ASCVD) events. Since publication of these guidelines, multiple randomized controlled trials evaluating nonstatin lipid-modifying medications have been published. METHODS: We performed a systematic review to assess the magnitude of benefit and/or harm from additional lipid-modifying therapies compared with statins alone in individuals with known ASCVD or at high risk of ASCVD. We included data from randomized controlled trials with a sample size of >1,000 patients and designed for follow-up >1 year. We performed a comprehensive literature search and identified 10 randomized controlled trials for intensive review, including trials evaluating ezetimibe, niacin, cholesterol-ester transfer protein inhibitors, and PCSK9 inhibitors. The prespecified primary outcome for this review was a composite of fatal cardiovascular events, nonfatal myocardial infarction, and nonfatal stroke. RESULTS: The cardiovascular benefit of nonstatin lipid-modifying therapies varied significantly according to the class of medication. There was evidence for reduced ASCVD morbidity but not mortality with ezetimibe and 2 PSCK9 inhibitors. Reduced ASCVD mortality rate was reported for 1 PCSK9 inhibitor. The use of ezetimibe/simvastatin versus simvastatin in IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) reduced the primary outcome by 1.8% over 7 years (hazard ratio: 0.90; 95% CI: 0.84-0.96), 7-year number needed to treat: 56). The PSCK9 inhibitor evolocumab in the FOURIER study (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk) decreased the primary outcome by 1.5% over 2.2 years (hazard ratio: 0.80; 95% CI: 0.73-0.88; 2.2=year number needed to treat: 67). In ODYSSEY OUTCOMES (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab), alirocumab reduced the primary outcome by 1.6% over 2.8 years (hazard ratio: 0.86; 95% CI: 0.79-0.93; 2.8-year number needed to treat: 63). For ezetimibe and the PSCK9 inhibitors, rates of musculoskeletal, neurocognitive, gastrointestinal, or other adverse event risks did not differ between the treatment and control groups. For patients at high risk of ASCVD already on background statin therapy, there was minimal evidence for improved ASCVD risk or adverse events with cholesterol-ester transfer protein inhibitors. There was no evidence of benefit for the addition of niacin to statin therapy. Direct comparisons of the results of the 10 randomized controlled trials were limited by significant differences in
sample size, duration of follow-up, and reported primary outcomes. CONCLUSIONS: In a systematic review of the evidence for adding nonstatin lipid-modifying therapies to statins to reduce ASCVD risk, we found evidence of benefit for ezetimibe and PCSK9 inhibitors but not for niacin or cholesterol-ester transfer protein inhibitors.


**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=30591287

**ABSTRACT**

**PURPOSE:** Secondary medication prevention after acute myocardial infarction (MI) is strongly recommended in international guidelines, but actual use, adherence, and outcomes in current clinical practice are largely unknown. Therefore, the aims of this study were to determine the current adherence to medications for secondary prevention after MI and to estimate the association between medication adherence and mortality and major adverse cardiovascular events (MACE) in a large real-world population. **METHODS:** Using a large health care claims database, patients were selected who had been hospitalized with MI between 2012 and 2015 (N = 4349). Adherence to drug therapy after discharge was measured as the medication possession rate (MPR) per year (0%-100%, indicating the number of days with medication supplied relative to the total number of days) for the individual drug classes. The relationship between MPR and the risk of MACE and death was assessed by using Cox proportional hazards regression models. **FINDINGS:** A high proportion of patients with low MPR (0%-79%) was observed for all drug classes (47.6% for dual antiplatelet therapy (DAPT), 23.5% for lipid-lowering drugs (LLDs), 47.3% for angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, and 88.1% for beta-blockers (BB). Women and elderly patients were less likely to receive LLDs. Patients with high adherence to DAPT, LLDs, and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (MPR >/=80%) had a significantly reduced risk for all-cause mortality and MACE (LLD-group). **IMPLICATIONS:** In a real-life setting, adherence to drug therapy for secondary cardiovascular prevention after MI was only moderate. Increased use of evidence-based treatment such as DAPT and LLDs in current clinical practice may improve long-term outcomes of patients with MI. Moreover, providing clear information, improved care transition, and a close collaboration between clinicians and physicians involved in an early outpatient follow-up is required.


**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=30581577

**ABSTRACT**

**AIMS:** Study of IL4 in relation to the anthropometric, biochemical and immunological parameters in patients with obesity and/or diabetes. **METHODS:** The relationship between IL4 and clinical and biological parameters was studied in 76 patients divided into 4 groups: obese diabetics (OD), n = 25; obese without diabetes (O), n = 25; non obese diabetics (NOD), n = 11; controls (M), n = 15. IL4 was determined using the ELISA method. Statistical analysis was done
using the MedCalc statistical software, version 16.1. RESULTS: Serum IL4 was 0.38 +/-0.40 pg / mL in the Control group, 0.366 (0.100-2.35) pg / ml in group O, 4.66+/-.3.73 pg / ml in group OD, 0.30 (0.10-1.35) pg / ml in NOD. When IL4 levels were compared between the four groups, statistical significance was reached for the comparison between groups OD and M. Statistically significant correlations were detected between IL4 and age, waist circumference and hip circumference, blood glucose, glycated hemoglobin (HbA1c), VLDL, triglycerides and serum protein fraction beta1. In univariate regression, the IL4 level predictors were age, height, BMI, abdominal circumference, hip circumference, beta 1% glucose, HbA1c, total lipids, total cholesterol, VLDL triglycerides, CRP. In multivariate regression, waist circumference and glycemia were significant predictors of levels of IL4 (p = 0.0001).

ABSTRACT
PURPOSE OF REVIEW: Lipid emulsions are an integral part of parenteral nutrition. Enteral nutrition is the preferred route to feed critically ill patients and parenteral nutrition is used in case of contraindications or when enteral nutrition does not reach the nutritional goals. n-3 Lipids are included into some newer lipid emulsions including fish oil or may be added by a fish-oil-based lipid emulsion to lipid emulsion without fish oil. This review focuses on recent clinical trials, metaanalyses, and guidelines of parenteral nutrition with n-3 lipids in critically ill patients. RECENT FINDINGS: Two single-center studies report a mortality benefit of adding fish-oil-based lipid emulsions to the parenteral nutrition. Metaanalyses performed without these two studies had demonstrated beneficial effects of n-3 lipids regarding infections, length of stay, and time of mechanical ventilation but not on mortality. However, all metaanalyses judged the database derived from the underlying studies as not sufficient for a firm recommendation. Consecutively, guidelines and expert groups issue very cautious recommendations for the use of n-3 lipids in parenteral nutrition. SUMMARY: Beneficial effects of n-3 lipids in trials and metaanalyses became available; however, high-quality multicenter randomized controlled trials are needed before more endorsing recommendation will be available.

ABSTRACT
PURPOSE OF REVIEW: Bempedoic acid has emerged as a potent inhibitor of ATP-citrate lyase (ACLY), a target for the reduction of LDL cholesterol (LDL-C). We review the impact of bempedoic acid treatment on lipoprotein metabolism and atherosclerosis in preclinical models and patients with hypercholesterolemia. RECENT FINDINGS: The liver-specific activation of bempedoic acid inhibits ACLY, a key enzyme linking glucose catabolism to lipogenesis by catalyzing the formation of acetyl-CoA from mitochondrial-derived citrate for de novo synthesis of fatty acids and cholesterol. Adenosine monophosphate-activated protein kinase activation by bempedoic acid is not required for its lipid-regulating effects in vivo. Mendelian randomization
of large human study cohorts has validated ACLY inhibition as a target for LDL-C lowering and atheroprotection. In rodents, bempedoic acid decreases plasma cholesterol and triglycerides, and prevents hepatic steatosis. In apolipoprotein E-deficient (ApoE) mice, LDL receptor-deficient (Ldlr) mice and LDLR-deficient miniature pigs, bempedoic acid reduces LDL-C and attenuates atherosclerosis. LDLR expression and activity are increased in primary human hepatocytes and in Apoe mouse liver treated with bempedoic acid suggesting a mechanism for LDL-C lowering, although additional pathways are likely involved. Phase 2 and 3 clinical trials revealed that bempedoic acid effectively lowers LDL-C as monotherapy, combined with ezetimibe, added to statin therapy and in statin-intolerant hypercholesterolemic patients. Treatment does not affect plasma concentrations of triglyceride or other lipoproteins.

SUMMARY: The LDL-C-lowering and attenuated atherosclerosis in animal models and reduced LDL-C in hypercholesterolemic patients has validated ACLY inhibition as a therapeutic strategy. Positive results from phase 3 long-term cardiovascular outcome trials in high-risk patients are required for bempedoic acid to be approved for prevention of atherosclerosis.


ABSTRACT

BACKGROUND: Type 2 diabetes (TD2) is a sustained metabolic disorder, characterized by high blood glucose, insulin resistance (IR). Dipeptidyl peptidase-4 (DPP4) functions as an antigenic enzyme involved in hyperglycaemia, oxidative stress, and inflammation-associated IR. Therefore, association between DPP4 and TD2 warrants to be investigated. METHODS: In this study, blood samples of clinically diagnosed TD2 patients were harvested for biochemical tests. In addition, diabetic mice induced by high-fat diet (HFD) and single dose of streptozotocin (STZ) were used to assess the biological characteristics of DPP4 through biochemical and enzyme-linked immunosorbent assay (ELISA) tests, immunofluorescence staining, and western blot assay. RESULTS: Compared to controls, the clinical data of patients with TD2 resulted in increased contents of fasting blood glucose (FBG), glycated hemoglobin (HbA1c), homeostatic model assessment (HOMA)-IR, blood lipids of triglyceride (TG), total cholesterol (TC), low-density lipoprotein (LDL-C), and interleukin 6 (IL6) in plasma samples (p < 0.05). Notably, blood levels of DPP4 in TD2 patients were increased significantly in comparison to that in non-diabetic adults (p < 0.01). In animal study, diabetic mice showed increased levels of glucose, insulin, lipids, DPP4 activity in sera. Visibly, hepatocellular DPP4 expression was up-regulated in diabetic mice. Interestingly, DPP4 inhibitor-treated mice showed significantly reduced DPP4 expression in serum (p < 0.01), and lowered DPP4-positive cells and protein content in the liver were observed when compared to those in diabetic mice (p < 0.01). CONCLUSIONS: Collectively, these findings reveal that DPP4 biomolecule may be positively associated with TD2 development, and the underlying mechanism may be attributed to activation of DPP4 expression in liver cells.

ABSTRACT
AIMS/HYPOTHESIS: Cardiovascular disease is the leading cause of morbidity and mortality in people with type 2 diabetes. MEDI4166 is a proprotein convertase subtilisin/kexin type 9 (PCSK9) antibody and glucagon-like peptide-1 (GLP-1) analogue fusion molecule designed to treat patients with type 2 diabetes who are at risk for cardiovascular disease. In this completed, first-in-human study, we evaluated the safety and efficacy of single or multiple doses of MEDI4166 in participants with type 2 diabetes. METHODS: In this phase 1 study that was conducted across 11 clinics in the USA, eligible adults had type 2 diabetes, a BMI of >/=25 kg/m(2) to </=42 kg/m(2), and LDL-cholesterol levels >/=1.81 mmol/l. Participants were randomised 3:1 to receive MEDI4166 or placebo using an interactive voice/web response system, which blinded all participants, investigators and study site personnel to the study drug administered. In 'Part A' of the study, five cohorts of participants received a single s.c. injection of MEDI4166 at 10 mg, 30 mg, 100 mg, 200 mg or 400 mg, or placebo. 'Part B' of the study consisted of three cohorts of participants who received an s.c. dose of MEDI4166 once weekly for 5 weeks at 50 mg, 200 mg or 400 mg, or placebo. The primary endpoint in Part A was safety. The co-primary endpoints in Part B were change in LDL-cholesterol levels and area under the plasma glucose concentration-time curve (AUC0-4h) post-mixed-meal tolerance test (MMTT) from baseline to day 36. The pharmacokinetics and immunogenicity of MEDI4166 were also evaluated. RESULTS: MEDI4166 or placebo was administered to n = 30 or n = 10 participants, respectively, in Part A of the study, and n = 48 or n = 15 participants, respectively, in Part B. The incidence of treatment-emergent adverse events (TEAEs) were comparable between MEDI4166 and placebo in both Part A (60% vs 50%) and Part B (79% vs 87%) of the study. Common TEAEs with MEDI4166 included injection-site reactions, diarrhoea and headache; there was no evidence for dose-related increases in TEAEs. In Part B of the study, at all tested doses of MEDI4166, there was a significant decrease in LDL-cholesterol levels vs placebo (least squares mean [95% CI]; MEDI4166 50 mg, -1.25 [-1.66, -0.84]; MEDI4166 200 mg, -1.97 [-2.26, -1.68]; MEDI4166 400 mg, -1.96 [-2.23, -1.70]; placebo, -0.03 [-0.35, 0.28]; all p < 0.0001). However, there were no clinically relevant reductions or significant differences between MEDI4166 vs placebo in glucose AUC0-4h post-MMTT (least squares mean [95% CI]; MEDI4166 50 mg, -10.86 [-17.69, -4.02]; MEDI4166 200 mg, -4.23 [-8.73, 0.28]; MEDI4166 400 mg, -2.59 [-7.14, 1.95]; placebo, -4.84 [-9.95, 0.28]; all p > 0.05). MEDI4166 was associated with a pharmacokinetic profile supportive of weekly dosing and an overall treatment-induced anti-drug antibody-positive rate of 22%. CONCLUSIONS/INTERPRETATION: MEDI4166 was associated with an acceptable tolerability profile and significantly decreased LDL-cholesterol levels in a dose-dependent manner in overweight or obese patients with type 2 diabetes. However, there were no significant reductions in postprandial glucose levels at any dose of MEDI4166. TRIAL REGISTRATION: ClinicalTrials.gov NCT02524782 FUNDING: This study was funded by MedImmune LLC, Gaithersburg, MD, USA.

ABSTRACT

Purpose: Fenofibrate (Fbt) is a prodrug that has been used to reduce low-density-lipoprotein cholesterol, triglycerides, and increase high-density-lipoprotein cholesterol. Simvastatin (Svt) is a classic lipid-lowering drug that is widely used in the treatment of hypercholesterolemia and hypertriglyceridemia, while berberine chloride (Bbr) is a novel hypolipidemic agent and its blood-lipid-reducing mechanism is distinct from traditional drugs. Currently, drug combination is the trend in treating hyperlipidemia to improve clinical efficacy. The purpose of this study was to evaluate drug interaction from the perspective of pharmacokinetics between Bbr and Fbt/Svt and the tolerability of combined administration in healthy Chinese subjects. Methods: Healthy subjects (n=60) were randomly allocated to five treatment groups: Bbr alone, Fbt alone, Svt alone, Bbr plus Fbt, and Bbr plus Svt. The experiment was divided into two parts: single-dose administration and multiple-dose administration. Bbr, Fbt, and Svt were taken once every 8 hours, 24 hours, and 24 hours, respectively, over 7 days in the multidose group. Plasma samples were collected and liquid chromatography-mass spectrometry/mass spectrometry was used to detect drug concentrations. Results: No serious adverse reactions or intolerance were observed throughout the trial. More importantly, the combined-administration groups did not show an increase in incidence of side effects. Coadministration of Fbt and Svt with Bbr had no significant effect on the pharmacokinetic parameters of Bbr, except time to maximum concentration, apparent volume of distribution, and apparent clearance. Concurrent coadministration of Bbr had no obvious impact on the pharmacokinetic behavior of Fbt or Svt. Additionally, there was no significant correlation between sex and pharmacokinetic results. Conclusion: All treatments were well tolerated. No clinically obvious pharmacokinetic interactions between Bbr and Fbt/Svt were observed with combined administration. The results demonstrated that Bbr can be coadministered safely with Fbt and Svt without dose adjustment.


ABSTRACT

INTRODUCTION: Despite advances in drug eluting technologies, neointimal hyperplasia (NIH) and restenosis still plagues endovascular therapy in atherosclerotic diseases. By appreciating atherosclerosis and NIH as complex inflammatory processes, specialized pro-resolving mediators (SPMs) are a superfamily of endogenous unsaturated fatty-acid derived lipids with the potential for inflammatory resolution. Areas covered: Inquiry into SPMs in this context is a novel approach and is the focus of this review, with emphasis on our understanding with NIH. Prior mechanistic understandings of SPM deficiency with atherosclerosis has offered insight, as well as the complexity and diversity of the SPM superfamily. Therapeutic investigation using SPMs to combat NIH is also evaluated here. Expert commentary: Endogenous deficiency of SPMs synthesis by 12/15-lipoxygenase underlies resolution deficits in atherosclerosis and NIH. Upstream PDGF inhibition by SPMs, most notably RvD1 and LXA4, confers a multifactorial attenuation of NIH that involves interconnected anti-inflammatory efforts, most notably switch pro-resolving smooth muscle cells (vSMCs) and macrophages. The ALX/FPR2 is one receptor system identified on vSMCs that interacts with these SPMs to promote NIH resolution.
Therapeutically, while shown to be promising with less stent burden or cytotoxicity, SPMs must be balanced by necessary mechanistic, pharmacokinetic and anatomical considerations.

ABSTRACT
Context: Hypertension (HTN) is a well-known modifiable risk factor for cardiovascular disease (CVD), chronic kidney disease and mortality. Positive effects of blood pressure (BP) lowering for prevention of CVD and death have been documented in several meta-analyses of randomized controlled trials. Evidence Acquisition: This review focuses on the key findings derived from the Tehran lipid and glucose study (TLGS) papers on different aspects of BP and HTN. Results: A prevalence of 23% for HTN has been reported in the TLGS population, aged >/= 20 years. Over a decade long follow-up, the crude incidence rate (95% CI) of new-onset HTN defined as systolic BP (SBP) >/= 140 mmHg and/or diastolic BP (DBP) >/= 90 mmHg, and not using antihypertensive medication was 33.63 (32.0 - 35.3) per 1000 person-years. Age, baseline SBP and body mass index were significant risk factors for development of isolated systolic HTN; regarding isolated diastolic HTN, baseline DBP and waist circumference were recognized as important risk factors whereas age, female gender and marriage were shown to be protective factors. SBP decreased significantly in both diabetic and non-diabetic participants; DBP showed a non-significant decrease in diabetic men and a statistically significant decrease in non-diabetic men. Among women, both those with and without diabetes (DM) generally experienced statistically significant decreases in DBP. Cox proportional hazard models showed that neither SBP nor DBP were associated with incident DM in the total population and in either gender, separately. All BP components were associated with CVD and all-cause mortality in the middle-aged population. Contribution of HTN to cerebrovascular events was also documented in the TLGS participants, aged >/= 50 years. Conclusions: Several important findings regarding BP/HTN have been derived from the TLGS. According to data regarding the prevalence and incidence of preHTN and HTN and their contribution to cardiovascular morbidity and mortality in the TLGS population as a representative sample of Tehranian population, it is recommended that interventions be prioritized for lifestyle modifications for the prevention and appropriate management of preHTN/HTN.

ABSTRACT
Context: Dyslipidemia, including elevated serum total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), and triglycerides (TG), and low high density lipoprotein cholesterol (HDL-C) is a major modifiable risk factor for non-communicable diseases (NCDs). This review summarizes many of the key findings on lipid measures in the Tehran lipid and glucose study (TLGS), a large scale community-based study with an approximately two decade follow-up.
Evidence Acquisition: A systematic literature search was conducted using PubMed, Scopus, Web of Science databases, and the library of the Research Institute for Endocrine Sciences, using the following keywords: Lipid measures, lipid ratios, lipid profile, dyslipidemia, and "Tehran lipid and glucose study". Articles were categorized based on fields of prevalence, trends, and impact of lipid profile on incident NCDs and mortality. Results: Between 1999-2001, the prevalence of high risk lipids ranged from 14% (low HDL-C) to 17% (high LDL-C) among adolescents, although among adults the lowest and highest prevalence were observed for low HDL-C (19%) and high TG (28%). Despite favorable trends for lipid parameters among adolescents, adults, and the elderly population, a considerable number of diabetic individuals, failed to achieve the optimum level of serum lipids. During follow-up, consumption of lipid-lowering drugs increased from 1.5 to 9.0% and 3.7 to 11.4% among adult men and women, respectively. The association between different lipid parameters and related ratios for incident type 2 diabetes (T2D), hypertension, metabolic syndrome and cardiovascular diseases differed between genders. Interestingly, each 1-unit increase in TC/HDL-C increased risk of hypertension among women (odds ratio (OR): 1.19, 95% confidence interval (CI): 1.00 - 1.27) and T2D among men (OR: 1.27, 95% CI: 1.06 - 1.51). Moreover, TC, LDL-C, non-HDL-C, Ln-TG, TC/HDL-C, and Ln-TG/HDL were inversely associated with non-cardiovascular mortality. Conclusions: Despite high prevalence of high risk lipid profiles among the TLGS population at baseline, favorable trends were observed in levels of all lipid components, which might be attributable to increased consumption of lipid-lowering medications and improvement in the general knowledge of Iranians regarding limited consumption of hydrogenated oil. Considering the impact of lipid profiles on incident NCDs, more attention should be paid to at-risk groups for screening and treatment purposes.


**ABSTRACT**

AIM: Cardio-ankle vascular index (CAVI) reflects arterial stiffness and has been established as a useful surrogate marker of atherosclerosis. Contrary to the abundant data indicating slower progression of atherosclerosis with statins, studies on fibrates remain scarce. The aim of this study was thus to clarify the effect of bezafibrate on CAVI as well as on oxidative stress. METHODS: A randomized, open-label, controlled study was performed. 66 hypertriglyceridemic patients with type 2 diabetes were assigned to two groups: bezafibrate (400 mg/day) group and eicosapentaenoic acid (EPA 1.8 g/day) group. Patients were administered the respective treatment for 12 weeks. CAVI, glycolipid metabolic parameters, and diacron-reactive oxygen metabolites (d-ROMs) were evaluated before and after the study period. RESULTS: Serum triglycerides (TG), remnant-like particle cholesterol (RLP-C), fasting plasma glucose, HbA1c and d-ROMs decreased, while HDL-cholesterol increased significantly in the bezafibrate group but did not change in the EPA group. The decreases in TG, RLP-C, HbA1c and d-ROMs were significantly greater in the bezafibrate group than in the EPA group. CAVI decreased significantly only in the bezafibrate group and the decrease was significantly greater in bezafibrate group than in EPA group. Simple regression analysis showed no significant
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relationship between the change in CAVI and changes in other variables. Multivariate logistic regression analysis identified high baseline CAVI, low HDL-cholesterol level, and bezafibrate administration as significant independent predictors of CAVI decrease. CONCLUSION: Bezafibrate treatment ameliorates arterial stiffness accompanied by improvement of glycolipid metabolism and oxidative stress. These effects potentially have important beneficial health consequences in hypertriglyceridemic patients with type 2 diabetes.


ABSTRACT
Cardiovascular disease has been the leading cause of death throughout the world for nearly two decades. Hypertriglyceridemia affects more than one-third of the population in the United States and is an independent risk factor for cardiovascular disease. Despite the frequency of hypertriglyceridemia, treatment options are primarily limited to diet and exercise. Lipoprotein lipase (LPL) is an enzyme responsible for clearing triglycerides from circulation and its activity alone can directly control plasma triglyceride concentrations. Therefore, LPL is a good target for triglyceride-lowering therapeutics. One approach for treating hypertriglyceridemia may be to increase the amount of enzymatically active LPL by preventing its inhibition by angiopoietin-like protein 4 (ANGPTL4). However, little is known about how these two proteins interact. Therefore, we used hydrogen-deuterium exchange mass spectrometry to identify potential binding sites between LPL and ANGPTL4. We validated sites predicted to be located at the protein-protein interface using chimeric variants of LPL and an LPL peptide mimetic. We found that ANGPTL4 binds LPL near the active site at the lid domain and a nearby alpha-helix. Lipase lid domains cover the active site to control both enzyme activation and substrate specificity. Our findings suggest that ANGPTL4 specifically inhibits LPL by binding the lid domain, which could prevent substrate catalysis at the active site. The structural details of the LPL-ANGPTL4 interaction uncovered here may inform the development of therapeutics targeted to disrupt this interaction for the management of hypertriglyceridemia.


ABSTRACT
BACKGROUND: Although a recent clinical trial demonstrated that alirocumab, a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor, significantly reduces the incidence of acute coronary events, the impact of alirocumab on plaque stabilization remains uncertain. The Efficacy of ALirocumab for Thin-cap fibroatheroma in patients with coronary Artery disease estImated by optical coherence tomogRaphy (ALTAIR) study will investigate the effect of alirocumab on thin-cap fibroatheroma (TCFA) in Japanese patients who underwent recent percutaneous coronary intervention (PCI). METHODS AND DESIGN: ALTAIR is a phase IV, open-label, randomized, parallel-group, single-center study involving blinded optical coherence
tomography (OCT) image analysis in Japanese adults hospitalized for PCI and having suboptimal control of low-density lipoprotein cholesterol (LDL-C) levels (>70mg/dL) despite statin therapy. Patients will be randomized (1:1) to the alirocumab arm (alirocumab 75mg every 2 weeks added to rosuvastatin 10mg/day) or the standard-of-care arm (rosuvastatin 10mg/day, with initiation and/or dose adjustment of non-statin lipid-lowering to achieve an LDL-C target of <70mg/dL). OCT imaging will be conducted at baseline and at week 36 (post-treatment). The primary objective is to compare the alirocumab and standard-of-care arms regarding the change in TCFA fibrous-cap thickness after 9 months of treatment. CONCLUSION: The outcomes of ALTAIR (ClinicalTrials.gov identifier: NCT03552432) will provide insights into the effect of alirocumab on plaque vulnerability following PCI in patients with suboptimal LDL-C control despite stable statin therapy.


ABSTRACT
BACKGROUND: Data on the impact of glycemic status on coronary plaque progression have been limited. This study evaluated the association between glycemic status and coronary plaque volume change (PVC) using coronary computed tomography angiography (CCTA).

METHODS: A total of 1296 subjects (61+/-9, 56.9% male) who underwent serial CCTA with available glycemic status were enrolled and analyzed from the Progression of Atherosclerotic Plaque Determined by Computed TomoGraphic Angiography IMaging (PARADIGM) registry. The median inter-scan period was 3.2 (2.6-4.4) years. Quantitative assessment of coronary plaques was performed at both scans. All participants were categorized into the following groups according to glycemic status: normal, pre-diabetes (pre-DM), and diabetes mellitus (DM).

RESULTS: During the follow-up, significant differences in PVC (normal: 51.3+/-83.3mm(3) vs. pre-DM: 51.0+/-84.3mm(3) vs. DM: 72.6+/-95.0mm(3); p<0.001) and annualized PVC (normal: 14.9+/-24.9mm(3) vs. pre-DM: 15.7+/-23.8mm(3) vs. DM: 21.0+/-27.7mm(3); p=0.001) were observed among the 3 groups. Compared with normal individuals, individuals with pre-DM showed no significant differences in the adjusted odds ratio (OR) for plaque progression (PP) (1.338, 95% confidence interval [CI] 0.967-1.853; p=0.079). However, the adjusted OR for PP was higher in DM individuals than in normal individuals (1.635, 95% CI 1.126-2.375; p=0.010).

CONCLUSION: DM had an incremental impact on coronary PP, but pre-DM appeared to have no significant association with an increased risk of coronary PP after adjusting for confounding factors. CLINICAL TRIAL REGISTRATION: ClinicalTrials.govNCT02803411.


ABSTRACT
BACKGROUND: Patients with heterozygous familial hypercholesterolemia (HeFH) who completed the double-blind ODYSSEY LONG TERM parent trial and subsequently enrolled in the open-label extension (OLE) study, ODYSSEY OLE (NCT01954394), provide a unique opportunity to investigate effects of 2 doses of alirocumab, a proprotein convertase subtilisin/kexin type 9 inhibitor, within the same patient cohort. OBJECTIVE: The aim of the study was to characterize long-term efficacy and safety of 2 alirocumab dosages and utility of a dose titration strategy in patients with HeFH. METHODS: After an 8-week washout period, patients with HeFH who completed the LONG TERM study (receiving alirocumab 150 mg every 2 weeks [Q2W]) were eligible to enroll in OLE (n = 214) for up to 40 months' treatment duration. In OLE, patients started on alirocumab 75 mg Q2W. From Week 12, dose adjustment from 75 to 150 mg Q2W or vice versa was possible based on physician's clinical judgment. RESULTS: During the LONG TERM trial, alirocumab 150 mg Q2W reduced mean low-density lipoprotein cholesterol (LDL-C) from baseline (162.3 mg/dL) to Week 8 by 63.1%; during OLE, alirocumab 75 mg Q2W reduced mean LDL-C from baseline (166.6 mg/dL) by 47.3% within the same patient cohort. At Week 96, mean LDL-C reduction from OLE baseline was 55.4% vs 46.8% for patients with or without alirocumab dose increase, respectively. Treatment-emergent adverse events leading to permanent treatment discontinuation were observed in 4 patients (1.9%). CONCLUSIONS: In patients with HeFH, both alirocumab dosages provided consistent LDL-C reductions over a treatment duration of up to 4 years (including 1.5 years of the LONG TERM trial), allowing an individualized approach to LDL-C lowering, depending on baseline LDL-C levels.


ABSTRACT
Low plasma testosterone (T) levels correlated with metabolic syndrome, cardiovascular diseases, and increased mortality risk. T exerts a significant effect on the regulation of adipose tissue accumulation, and in the glucose and lipids metabolism. Adipocytes are the primary source of the most important adipocytokines responsible for inflammation and chronic diseases. This review aims to analyze the possible effect of T on the regulation of the proinflammatory cytokines secretion. A systematic literature search on MEDLINE, Google Scholar, and Cochrane using the combination of the following keywords: "testosterone" with "inflammation," "cytokines," "adiponectin, CRP, IL-1B, IL-6, TNFalpha, leptin" was conducted. Sixteen articles related to the effect of low T level and 18 to the effect of T therapy on proinflammatory cytokine were found. T exerts a significant inhibitory effect on adipose tissue formation and the expression of various adipocytokines, such as leptin, TNF-alpha, IL-6, IL-1, and is positively correlated with adiponectin level, whereas a low T level is correlated with increased expression of markers of inflammation. Further studies are necessary to investigate the role of T, integrated with weight loss and physical activity, on its action on the mechanisms of production and regulation of proinflammatory cytokines.

**ABSTRACT**

OBJECTIVE: Current prevention of peripheral vascular disease (PVD) focuses on blood pressure control, lipid lowering, and platelet inhibition with statins and aspirin. A critical role for inflammation in the pathophysiology of atherosclerosis has been established for decades and, although both statins and aspirin have anti-inflammatory properties, the management of inflammation is becoming increasingly recognized. Here, we summarize recent clinical and translational discoveries that outline how inflammation may become targeted in PVD in the future. METHODS: A PubMed search using a combination of the following MeSH terms-inflammation, pathophysiology, atherosclerosis, cancer, auto immune disease, therapy, and clinical trial-was performed and literature selected with a focus on basic pathophysiology of inflammation and clinical investigations targeting inflammation in cardiovascular disease, cancer, and autoimmune diseases. RESULTS: Based on this literature overview, we summarized the common features of inflammation in these different diseases and how inflammation may also translate into common therapeutic strategies. Finally, the results of recent clinical and translational investigations highlighting inflammation in cardiovascular disease are reviewed with a focus on hematopoietic mutations that generate more active immune cells and increase cardiovascular risk, treatment with anti-inflammatory biological pharmaceuticals that reduce cardiovascular risk, and translational studies demonstrating how the treatment of defective immune-mediated clearance of dying cells in lesions may prevent disease progression. CONCLUSIONS: Progress in clinical and translational atherosclerosis research has now brought inflammation in clinical focus, because recent discoveries with respect to cardiovascular risk prediction and pharmacotherapy targeting inflammation have shown the potential to improve future care of patients with PVD.


**ABSTRACT**

Atherosclerosis is a common disease whose complications, such as myocardial infarction, are a leading cause of mortality worldwide. Therefore, ideas which try to explain the circumstances of atherosclerotic plaque initiation and progression are warranted. We hypothesize that low-grade inflammation in early life (especially an imbalance between pro- and anti-inflammatory macrophages) triggers a "butterfly effect" within the arterial wall by initiating a sequence of processes that finally leads to atherosclerotic plaque development and progression. Therefore, pharmacological and non-pharmacological interventions aimed to prevent atherosclerosis development should be applied not only in the adult population over 40 years old (according to current American and European guidelines) but should start in early life.


**ABSTRACT**
The prevalence of adult and childhood obesity are increasing. Most of the human newborn’s body fat accumulates in the last half of intrauterine life. Fat in the fetus was thought to be mostly synthesized from glucose, but now it is commonly accepted that the bulk of it is the product of placental transfer of maternal fatty acids. Transported fatty acids originate in maternal plasma "free" fatty acids, fatty acids hydrolyzed from maternal plasma triglycerides, and the poly-unsaturated fatty acid component of maternal phospholipids. Glucose remains an important precursor of alpha-glycerol phosphate, to which most transported fatty acids are eventually esterified. Maternal plasma lipids are elevated in late pregnancy and even more in obese and diabetic pregnant women. This accelerates the placental transport of fatty acids. The hypothesis presented in this paper rests on the observations that the exponential increase in fat tissue in the human embryo’s body occurs in time to parallel the increase of lipids in the mother’s blood and depends on the chemical affinity of the transcription factor PPAR gamma to fatty acids and on fatty acid stimulation of adipocyte generation from precursor cells. The hypothesis asserts that transported maternal fatty acids activate the transcription factors in the fetus and initiate conversion of the mesenchymal stem cells into adipocytes. In obese and diabetic mothers, the higher plasma lipids facilitate increased placental fatty acid transfer. This will increase adipocyte generation and, through this, the prevalence of babies with increased fat cell size and number. Babies born with increased adipose tissue cellularity will have greater probability of growing up to become obese adolescents and adults. These newborns, whose obesity is hyperplastic as well as hypertrophic, as adults will have difficulty losing weight through diet and exercise or will regain the lost weight more quickly than others without these characteristics. Accordingly, increased placental fatty acid transfer and accelerated adipocyte generation may explain not only neonatal obesity, but some aspects of the adult obesity epidemic also. It is therefore recommended that prevention of fetal fat cell hyperplasia, by lowering maternal plasma lipids in mid and late pregnancy, should be attempted in pregnancies at risk for macrosomia.


ABSTRACT
BACKGROUND It is unclear whether high-dose atorvastatin pretreatment benefits acute coronary syndrome (ACS) patients undergoing percutaneous coronary intervention (PCI). To clarify this issue, we performed a meta-analysis of the published literature. MATERIAL AND METHODS Randomized controlled trials (RCTs) assessing high-dose atorvastatin pretreatment in ACS patients undergoing PCI were enrolled. Short-term major adverse cardiac events (MACEs), changes in serum high-sensitivity C-reactive protein (hs-CRP), peak creatine kinase-myocardial band (CK-MB) level, and thrombolysis in myocardial infarction (TIMI) grade 3 flow after PCI were studied as clinical outcomes. RESULTS Seventeen RCTs including 10 072 patients were retrieved. High-dose atorvastatin showed greater benefits in reducing the incidence of short-term MACEs (OR 0.72; 95% CI: 0.56 to 0.94; P=0.01) and hs-CRP level (SMD -1.59; 95% CI: -2.38 to -0.80; P<0.0001) among ACS patients after PCI. No significant difference was found between
the 2 groups in terms of peak CK-MB (SMD -0.34; 95% CI: -0.79 to 0.10; P=0.13) or final TIMI flow grade 3 (OR 1.31; 95% CI: 0.73 to 2.36; P=0.36) after PCI. High-dose atorvastatin therapy also was not associated with alanine aminotransferase (ALT) elevation (OR 1.95; 95% CI: 0.95 to 4.03; P=0.07). CONCLUSIONS The results of this meta-analysis suggest that high-dose atorvastatin pretreatment reduces the incidence of short-term MACEs and hs-CRP level without increasing drug-induced hepatotoxicity in ACS patients after PCI.


ABSTRACT


ABSTRACT

Although ticagrelor has been demonstrated to possess an antiatherosclerosis (AS) effect, its underlying mechanism remains unclear. In the present study, it was investigated whether ticagrelor reduces oxidized lowdensity lipoprotein (oxLDL)induced endothelial cell apoptosis, an initial step for the development of AS, and alleviates AS in apolipoproteinEdeficient (ApoE/) mice by inhibiting the expression of proprotein convertase subtilisin/kexin type 9 (PCSK9). The human endothelial cell line EAhy926 was treated with oxLDL, oxLDL + ticagrelor (40 micromol/l) and oxLDL + ticagrelor (60 micromol/l) for 24 h. Cell apoptosis was detected using Annexin Vfluorescein isothiocyanate/propidium iodide staining. The expression levels of PCSK9, apoptosisassociated proteins and signaling pathways were determined by reverse transcriptionquantitative polymerase chain reaction and western blotting. ApoE/ mice fed a highfat diet were used to induce an AS model. After 20 weeks, ApoE/ mice were randomly assigned to receive saline or ticagrelor intragastrically for 10 days. The formation of atherosclerotic plaques was detected by hematoxylin and eosin staining. The expression of PCSK9 in the arterial tissues was measured by immunohistochemistry. The results demonstrated that treatment with ticagrelor was able to decrease oxLDLinduced apoptosis in a concentrationdependent manner (40 micromol/l vs. oxLDL, 17.58+/-2.66 vs. 27.25+/-5.54%; 60 micromol/l vs. oxLDL, 12.26+/-1.54 vs. 27.25+/-5.54%). The mRNA and protein expression level of PCSK9 significantly decreased following treatment with ticagrelor, accompanied with upregulation of Bcell lymphoma (Bcl) 2 and downregulation of Bcl2 associated X, apoptosis regulator, caspase3, p38, phosphorylated(p) p38, pjun Nterminal kinases (JNK), pextracellular signalregulated kinases and the ratio of pJNK to JNK. Histological analysis of arterial tissues revealed ticagrelor markedly decreased the atherosclerotic plaque area and inhibited the expression of PCSK9. The present results suggested that ticagrelor may alleviate AS via downregulation of PCSK9mediated endothelial cell apoptosis, which may be JNKdependent.

ABSTRACT
Familial hypercholesterolaemia (FH) is a dominantly inherited disorder of low-density lipoprotein (LDL) catabolism, which if untreated causes lifelong elevated LDL-cholesterol (LDL-c), accelerated atherosclerosis and premature cardiovascular disease. Recent evidence suggests the prevalence of heterozygous FH is approximately 1:220, making FH the most common autosomal dominant condition. Lowering LDL-c with statin and lifestyle therapy reduces the risk of cardiovascular events. Furthermore, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors significantly lower LDL-c in addition to statin therapy, and early outcome data suggest improved vascular outcomes with these agents in FH patients in addition to statins. However, the vast majority of people with FH still remain undiagnosed. The onus is on clinicians to identify kindreds with FH, as PCSK9 inhibitors, although expensive, are funded for patients with FH in Australia. Multiple strategies for detecting FH have been proposed. The detection of index cases can be achieved through applying electronic screening tools to general practice databases, universal screening of children during immunisation, and targeted screening of patients with premature cardiovascular disease. Advances in genomic technology have decreased costs of genetic testing, improved the understanding of the pathogenesis of FH and facilitated cascade screening. However, awareness of FH amongst clinicians and the general public still requires optimisation. This review outlines recent advances in FH detection, including emerging strategies and challenges for the next decade.


ABSTRACT
Background: Many patients at high cardiovascular risk do not reach targets for low-density lipoprotein cholesterol (LDL-C) and blood pressure (BP). Depression is a frequent comorbidity in these patients and contributes to poor medication adherence. Objective: The aim of this study was to elucidate the associations between adherence to lipid-and BP-lowering drugs, the diagnosis of depression, and the control of LDL-C and BP. Patients and methods: This study was conducted as multicenter, single-visit cross-sectional study in Germany. Adherence was assessed by the Morisky Medication Adherence Scale-8 (MMAS-8), and depression was assessed as documented in the patient chart. Results: A total of 3,188 ambulatory patients with hypercholesterolemia (39.8%), stable coronary artery disease (CAD; 7.4%), or both (52.9%) were included. Patients had a history of myocardial infarction (30.8%), diabetes (42.0%), were smokers (19.7%), and 16.1% had the investigator-reported diagnosis of depression. High or moderate adherence to lipid-lowering medication compared to low adherence was associated with lower LDL-C levels (105.5+/−38.3 vs 120.8+/−42.4 mg/dL) and lower BP (systolic BP 133.4+/−14.5 vs 137.9+/−13.9 mmHg, diastolic BP 78.3+/−9.6 vs 81.8+/−9.6 mmHg) and with a higher proportion of patients achieving the guideline-recommended LDL-C (16.9% vs 10.1%) and BP target (52.2% vs 40.8%, all comparisons P<0.0001). Adherence was worse in patients with depression. Correspondingly, patients with depression showed higher LDL-C levels, higher BP, and a lower probability of achieving the LDL-C and BP goal. Medication adherence correlated
between BP- and lipid-lowering medications. Conclusion: Self-reported medication adherence can be easily obtained in daily practice. A low adherence and the diagnosis of depression identify patients at risk for uncontrolled LDL-C and BP who likely benefit from intensified care.


**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=30587999

**ABSTRACT**

Background: This study evaluated the proportion of patients with atherosclerotic cardiovascular disease (ASCVD) and probable heterozygous familial hypercholesterolemia (HeFH) achieving >/=50% reduction in low-density lipoprotein cholesterol (LDL-C) or reaching the LDL-C </=70 mg/dL threshold, after initiating or modifying statin, and/or ezetimibe therapy. Materials and methods: Adult ASCVD patients with baseline LDL-C >70 mg/dL (index) and a subset of patients with probable HeFH (proxied by LDL-C >/=190 mg/dL) were identified between January 1, 2012, and August 31, 2014, from the IQVIA electronic medical record database. Patients were followed for 12 months pre-index to examine baseline lipid-lowering therapy (LLT) use, and 12 months post-index to evaluate treatment modifications and post-treatment LDL-C levels, stratified by type of treatment received and LDL-C levels at baseline. Results: Of the sample of ASCVD patients who initiated treatment post-index (n=111,147), only 7.6% patients achieved a >/=50% reduction from baseline LDL-C and 19.1% of patients reached the LDL-C </=70 mg/dL threshold. Among treated ASCVD patients who modified therapy post-index (n=75,523), 5.6% achieved a >/=50% reduction in LDL-C, and proportion of patients achieving LDL-C </=70 mg/dL ranged from 6.9% to 26.7%, depending on the baseline LDL-C levels. Approximately 50% of the untreated probable HeFH patients (n=3,064) initiated LLT; however, the mean (SD) post-treatment LDL-C remained high (136.2 [47.8] mg/dL), with only 4.4% reaching LDL-C </=70 mg/dL. Of the treated probable HeFH patients (n=1,073), 41.5% modified treatment; 22.1% achieved a >/=50% reduction in LDL-C and 1.1% reached LDL-C </=70 mg/dL. Conclusion: This study found that most patients had suboptimal LDL-C responses after initiating or modifying standard LLT (statin and/or ezetimibe). More frequent and aggressive lipid management, including increasing statin intensity and alternative therapies, may be needed in patients with ASCVD and probable HeFH to reduce their cardiovascular risk.