

ABSTRACT

BACKGROUND: Significantly higher cytotoxic and thrombogenic human electronegative low-density lipoprotein (LDL), or L5, has been found in patients with stable coronary artery disease and acute coronary syndrome. We hypothesized that the statin-benefit groups (SBGs) defined by the new cholesterol guideline were of higher electronegative L5. METHODS: In total, 62 hyperlipidemia patients (mean age 59.4 +/- 10.5, M/F 40/22) were retrospectively divided into SBGs (n = 44) and N-SBGs (n = 18). The levels of complete basic lipid panel, biochemical profile and electronegative L5 of each individual were obtained before and after rosuvastatin 10 mg/day for 3 months. RESULTS: After 3 months' statin therapy, significant reduction of total cholesterol, LDL-C and triglyceride were demonstrated (all p-values < 0.05), with 38.4% LDL-C reduction. The percentage of L5 was significantly reduced by 40.9% (from 4.4% to 2.6%) after statin therapy (p = 0.001). Regarding absolute L5 concentration, derived from L5% multiplied by LDL-C, there was approximate 63.8% reduction (from 6.3 mg/dL to 2.3 mg/dL) of absolute L5 (p < 0.001) after statin treatment. Notably, while plasma LDL-C levels were similar between SBGs and N-SBGs (152.8 +/- 48.6 vs. 146.9 +/- 35.0 mg/dL), the SBGs had significantly elevated L5% (5.2 +/- 7.4% vs. 2.6 +/- 1.9%, p = 0.031) and higher absolute L5 concentration (7.4 +/- 10.4 vs. 3.7 +/- 3.1 mg/dL, p = 0.036). Linear regression showed the significantly positive correlation between the plasma L5 concentration and the 10-year cardiovascular risk by pooled cohort equation (r = 0.297, p < 0.05). CONCLUSIONS: The four SBGs defined by the 2013 ACC/AHA new cholesterol guideline tend to have increased atherogenic electronegative L5. Statin therapy can effectively reduce the electronegative L5 of these four major SBGs.


ABSTRACT

BACKGROUND: Hydroxymethyl glutaryl coenzyme A reductase inhibitors, commonly called statins, are some of the most commonly prescribed medications worldwide. Evidence suggests that statin therapy has significant mortality and morbidity benefit for both primary and secondary prevention from cardiovascular disease. Nonetheless, concern has been expressed regarding the adverse effects of long term statin use. The purpose of this article was to review the current medical literature regarding the safety of statins. METHODS: Major trials and review articles on the safety of statins were identified in a search of the MEDLINE database from 1980
to 2016, which was limited to English articles. RESULTS: Myalgia is the most common side effect of statin use, with documented rates from 1-10%. Rhabdomyolysis is the most serious adverse effect from statin use, though it occurs quite rarely (less than 0.1%). The most common risk factors for statin-related myopathy include hypothyroidism, polypharmacy and alcohol abuse. Derangement in liver function tests is common, affecting up to 1% of patients; however, the clinical significance of this is unknown. Some statin drugs are potentially diabetogenic and the risk appears to increase in those patients on higher doses. Pitavastatin has not been associated with increased risk of diabetes. Statins have not been proven to increase the risk of malignancy, dementia, mood disorders or acute interstitial nephritis. However, statins do have multiple drug interactions, primarily those which interact with the cytochrome p450 enzyme group.

CONCLUSIONS: Overall, statin drugs appear to be safe for use in the vast majority of patients. However, patients with multiple medical co-morbidities are at increased risk of adverse effects from long-term statin use.


ABSTRACT

Preliminary evidence suggests that statins may prevent major perioperative vascular complications. METHODS: We randomized 648 statin-naive patients who were scheduled for noncardiac surgery and were at risk for a major vascular complication. Patients were randomized to a loading dose of atorvastatin or placebo (80 mg anytime within 18 hours before surgery), followed by a maintenance dose of 40 mg (or placebo), started at least 12 hours after the surgery, and then 40 mg/d (or placebo) for 7 days. The primary outcome was a composite of all-cause mortality, nonfatal myocardial injury after noncardiac surgery, and stroke at 30 days. RESULTS: The primary outcome was observed in 54 (16.6%) of 326 patients in the atorvastatin group and 59 (18.7%) of 316 patients in the placebo group (hazard ratio [HR] 0.87, 95% CI 0.60-1.26, P=.46). No significant effect was observed on the 30-day secondary outcomes of all-cause mortality (4.3% vs 4.1%, respectively; HR 1.14, 95% CI 0.53-2.47, P=.74), nonfatal myocardial infarction (3.4% vs 4.4%, respectively; HR 0.76, 95% CI 0.35-1.68, P=.50), myocardial injury after noncardiac surgery (13.2% vs 16.5%; HR 0.79, 95% CI 0.53-1.19, P=.26), and stroke (0.9% vs 0%, P=.25). CONCLUSION: In contrast to the prior observational and trial data, the LOAD trial has neutral results and did not demonstrate a reduction in major cardiovascular complications after a short-term perioperative course of statin in statin-naive patients undergoing noncardiac surgery. We demonstrated, however, that a large multicenter blinded perioperative statin trial
for high-risk statin-naive patients is feasible and should be done to definitely establish the efficacy and safety of statin in this patient population.


ABSTRACT

A recent analysis of a commercially insured US population found fewer cardiovascular disease (CVD) events in high-risk patients attaining low levels of low-density lipoprotein (LDL), as measured by LDL particle number (LDL-P) versus low LDL cholesterol (LDL-C). Here, we investigated the cost effectiveness of LDL-lowering therapy guided by LDL-P. Patients were selected from the HealthCore Integrated Research Database and followed for 12 to 36 months. Patients who achieved LDL-P <1,000 nmol/l were placed into the LDL-P cohort, whereas those without LDL-P tests, but who achieved LDL-C <100 mg/dl, were placed into the LDL-C cohort. CVD-related costs included all health plan paid amounts related to CVD events or lipid management. Cost effectiveness was assessed through incremental cost-effectiveness ratios, defined as difference in total costs across the cohorts divided by difference in CVD events, measured over follow-up. Each cohort included 2,094, 1,242, and 705 patients over 12-, 24-, and 36-month follow-up. Patients in the LDL-P cohort received more aggressive lipid-lowering therapy and had fewer CVD events during follow-up compared to patients in the LDL-C cohort. This led to greater pharmacy costs and lower medical costs over time. Incremental cost-effectiveness ratio estimates ranged from $23,131 per CVD event avoided at 12 months to $3,439 and -$4,555 at 24- and 36-month follow-up, suggesting a high likelihood that achieving LDL-P <1,000 nmol/l is cost effective. In conclusion, LDL-lowering therapy guided by LDL-P was demonstrated to be cost effective, with greater clinical and economic benefit seen over longer time horizons and with the increased use of generic statins.


ABSTRACT

High triglyceride (TG) levels among patients with type 2 diabetes mellitus (DM) are associated with higher medical costs. We analyzed the economic impact of TG-lowering therapies and whether the association between medical costs and therapy differed according to TG reduction.
We conducted an observational cohort study of 184,932 patients with diabetes mellitus who had a TG measurement between January 2012 and June 2013 and a second TG measurement 3 to 15 months later. We identified 4 therapy groups (statin monotherapy, TG-specific monotherapy, statin/TG-specific combination therapy, or no therapy) and stratified those groups by percent change in TG (increased \( \geq \)5%, change of \(<\leq 4.9\%\), decreased 5% to 29%, decreased \( \geq \)30%). We compared change in medical costs between the year before and after therapy, adjusted for demographic and clinical characteristics. Of the 184,932 total patients, 143,549 (77.6%) received statin monotherapy, 900 (0.5%) received TG-specific monotherapy, 1,956 (1.1%) received statin and TG-specific combination therapy, and 38,527 (20.8%) received no prescription lipid agents. After covariate adjustment, statin/TG-specific agent recipients had a mean 1-year total cost reduction of $1,110. The greatest cost reduction was seen among statin/TG-specific combination therapy patients who reduced TG levels by \( \geq \)30% (-$2,859). Statin monotherapy patients who reduced TG by \( \geq \)30% also had a large reduction in adjusted costs (-$1,079). In conclusion, we found a substantial economic benefit to treating diabetic patients with statin/TG-specific combination lipid therapy compared with monotherapy of either type or no lipid pharmacotherapy. A TG reduction of \( \geq \)30% produced a particularly large reduction in 1-year medical costs.


ABSTRACT

Coronary artery disease is the leading cause of mortality worldwide. Most acute coronary syndromes are caused by a rupture of a vulnerable atherosclerotic plaque which can be characterized by a lipid-rich necrotic core with an overlying thin fibrous cap. Many vulnerable plaques can cause angiographically mild stenoses due to positive remodelling, which is why the extent of coronary artery disease may be seriously underestimated. In recent years, we have witnessed a paradigm shift in interventional cardiology. We no longer focus solely on the degree of stenosis; rather, we seek to determine the true extent of atherosclerotic disease. We seek to identify high-risk plaques for improvement in risk stratification of patients and prevention. Several imaging methods have been developed for this purpose. Intracoronary near-infrared spectroscopy is one of the most promising. Here, we discuss the possible applications of this diagnostic method and provide a comprehensive overview of the current knowledge.


**ABSTRACT**

OBJECTIVE: To create a model of atherosclerosis using green fluorescent protein (GFP)-targeted monocytes/macrophages, allowing analysis of both endogenous GFP+ and adoptively transferred GFP+ myeloid cells in arterial inflammation. APPROACH AND RESULTS: hCD68GFP reporter mice were crossed with ApoE-/ mice. Expression of GFP was localized to macrophages in atherosclerotic plaques and in angiotensin II-induced aortic aneurysms and correlated with galectin 3 and mCD68 expression. Flow cytometry confirmed GFP+ expression in CD11b+/CD64+, CD11c+/MHC-IIHI, and CD11b+/F4/80+ myeloid cells. Adoptive transfer of GFP+ monocytes demonstrated monocyte recruitment to both adventitia and atherosclerotic plaque, throughout the aortic root, within 72 hours. We demonstrated the biological utility of hCD68GFP monocytes by comparing the recruitment of wild-type and CCR2-/ monocytes to sites of inflammation. CONCLUSIONS: hCD68GFP/ApoE-/ mice provide a new approach to study macrophage accumulation in atherosclerotic plaque progression and to identify cells recruited from adoptively transferred monocytes.


**ABSTRACT**

Overexpression of the HER2 oncogene contributes to tumor angiogenesis, which is an essential hallmark of cancer. Simvastatin has been reported to exhibit antitumor activities in several cancers; however, its roles and molecular mechanisms in the regulation of colorectal angiogenesis remain to be clarified. Here, we show that colon cancer cells express high levels of VEGF, total HER2 and phosphorylated HER2, and simvastatin apparently decreased their expression in HER2-overexpressing colon cancer cells. Simvastatin pretreatment reduced endothelial tube formation in vitro and microvessel density in vivo. Furthermore, simvastatin markedly inhibited tumor angiogenesis even in the presence of heregulin (HRG)-beta1 (a HER2 co-activator) pretreatment in HER2+ tumor cells. Mechanistic investigation showed that simvastatin significantly abrogated HER2-induced tumor angiogenesis by inhibiting VEGF secretion. Together, these results provide a novel mechanism underlying the simvastatin-induced inhibition of tumor angiogenesis through regulating HER2/VEGF axis.


ABSTRACT

BACKGROUND: To evaluate the ability of community-based exercise programmes to facilitate public participation in exercise and hence improved cardiovascular health, we assessed the respective impacts of: a continuously monitored exercise programme based within our university (study 1); a Valleys Regional Park-facilitated community-based outdoor exercise programme (study 2); a Wales National Exercise Referral Scheme-delivered exercise-referral programme (study 3). METHODS: Biomolecular (monocytic PPARgamma target gene expression), vascular haemodynamic (central/peripheral blood pressure, arterial stiffness), clinical (insulin sensitivity, blood lipids) and anthropometric (body mass index, waist circumference, heart rate) parameters were investigated using RT-PCR, applanation tonometry, chemical analysis and standard anthropometric techniques. RESULTS: In studies 1-3, 22/28, 32/65 and 11/14 participants adhered to their respective exercise programmes, and underwent significant increases in physical activity levels. Importantly, beneficial effects similar to those seen in our previous studies (eg, modulations in expression of monocytic PPARgamma target genes, decreases in blood pressure/arterial stiffness, improvements in blood lipids/insulin sensitivity) were observed (albeit to slightly differing extents) only in participants who adhered to their respective exercise programmes. While study 1 achieved more intense exercise and more pronounced beneficial effects, significant cardiovascular risk-lowering health benefits related to biomolecular markers, blood pressure, arterial stiffness and blood lipids were achieved via community/referral-based delivery modes in studies 2 and 3. CONCLUSIONS: Because cardiovascular health benefits were observed in all 3 studies, we conclude that the majority of benefits previously reported in laboratory-based studies can also be achieved in community-based/exercise-referral settings. These findings may be of use in guiding policymakers with regard to introduction and/or continued implementation of community/referral-based exercise programmes.


ABSTRACT
AIMS: Extended Release-Niacin (ERN) is the most effective agent for increasing high-density lipoprotein-cholesterol (HDL-C). Having previously identified anti-HDL antibodies, we investigated whether ERN affected the antioxidant capacity of HDL and whether ERN was associated with the production of antibodies against HDL (aHDL) and apolipoprotein A-I (aApoA-I). METHODS: Twenty-one patients older than 18 years, with HDL-C ≤ 40 mg/dL (men) or ≤ 50 mg/dL (women) were randomly assigned to receive daily ERN (n = 10) or placebo (n = 11) for two sequential 12-week periods, with 4 weeks of wash-out before cross-over. Primary outcome was change of paraoxonase-1 (PON1) activity and secondary outcomes were changes in aHDL and aApoA-I antibodies. Clinical Trial Unique Identifier: EudraCT 2006-006889-42.

RESULTS: The effect of ERN on PON1 activity was non-significant (coefficient estimate 20.83 U/L, 95% CI -9.88 to 51.53; p = 0.184). ERN was associated with an increase in HDL-C levels (coefficient estimate 5.21 mg/dL, 95% CI 1.16 to 9.25; p = 0.012) and its subclasses HDL2 (coefficient estimate 2.46 mg/dL, 95% CI 0.57 to 4.34; p = 0.011) and HDL3 (coefficient estimate 2.73 mg/dL, 95% CI 0.47 to 4.98; p = 0.018). ERN was significantly associated with the production of aApoA-I antibodies (coefficient estimate 0.25 microg/mL, 95% CI 0.09-0.40; p = 0.001). aApoA-I titres at baseline were correlated with decreased PON activity. CONCLUSIONS: The rise in HDL-C achieved with ERN was not matched by improved anti-oxidant capacity, eventually hampered by the emergence of aApoA-I antibodies. These results may explain why Niacin and other lipid lowering agents fail to reduce cardiovascular risk.


ABSTRACT

Acute coronary syndrome is a life-threatening condition of utmost clinical importance, which, despite recent progress in the field, is still associated with high morbidity and mortality. Acute coronary syndrome results from a rupture or erosion of vulnerable atherosclerotic plaque with secondary platelet activation and thrombus formation, which leads to partial or complete luminal obstruction of a coronary artery. During the last decade, scientific evidence demonstrated that, when an acute coronary event occurs, several non-culprit plaques are in a "vulnerable" state. Among the promising approaches, several investigations provided evidence of photodynamic therapy (PDT) induced stabilisation and regression of atherosclerotic plaque. Significant development of PDT strategies improved its therapeutic outcome. This review addresses PDT's pertinence and major problems/challenges toward its translation to a clinical reality. This article is protected by copyright. All rights reserved.


ABSTRACT


ABSTRACT

Untreated, severe, symptomatic aortic stenosis is associated with a dismal prognosis. The only treatment shown to improve survival is aortic valve replacement; however, before symptoms occur, aortic stenosis is preceded by a silent, latent phase characterized by a slow progression at the molecular, cellular, and tissue levels. In theory, specific medical therapy should halt aortic stenosis progression, reduce its hemodynamic repercussions on left ventricular function and remodeling, and improve clinical outcomes. In the present report, we performed a systematic review of studies focusing on the medical treatment of patients with aortic stenosis. Lipid-lowering therapy, antihypertensive drugs, and anticalcific therapy have been the main drug classes studied in this setting and are reviewed in depth. A critical appraisal of the preclinical and clinical evidence is provided, and future research avenues are presented.


ABSTRACT

Antibodies are glycoproteins with high specificity binding to multiple antigens due to the large number of structural conformations of the variable chains. Hybridoma technology (fusion of myeloma cells with immunoglobulin-producing lymphocytes) has allowed the synthesis of large quantities of unique antibodies (monoclonal [mAb]). mAbs were initially murine. Subsequently, chimeric mAbs were developed, followed by humanized mAbs and finally human mAbs. The high selectivity and good tolerance of human mAbs allows their therapeutic administration to block specific exogenous or endogenous molecules. Selective human mAbs to the catalytic domain of PCSK9 have recently been developed. These antibodies block PCSK9, favour low-density lipoprotein receptor recycling and markedly reduce circulating cholesterol. Preliminary
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Studies indicate that lowering cholesterol through anti-PCSK9 antibodies may significantly reduce the cardiovascular complications of arteriosclerosis.


ABSTRACT

Patients with type 2 diabetes are considered to have the same cardiovascular risk as patients with ischemia. However, the degree of lipid control in diabetic and ischemic patients remains highly deficient. The availability of new agents, such as anti-PCSK9 monoclonal antibodies, could represent a notable advance in meeting this unmet need. Alirocumab and evolucumab, followed by bococizumab, are currently under the advanced phase of research. A growing database has demonstrated a relationship between glucose metabolism, body weight and PCSK9 function, but the clinical implications of this relationship have not been well defined. A broad programme of clinical trials has demonstrated that these agents decrease low-density lipoprotein cholesterol by more than 60% and also decrease apolipoprotein B and lipoprotein (a), showing a good tolerability and safety profile. In addition, post hoc analyses of phase 2 and 3 trials have observed that when these agents are associated with conventional lipid-lowering they reduce cardiovascular risk by more than 50%. Currently, 4 large clinical trials of cardiovascular prevention are underway in patients with ischemia or high cardiovascular risk. The aim of these trials is to define the role of anti-PCSK9 agents in the treatment of dyslipidemia and the prevention of cardiovascular disease in patients with ischemia and high cardiovascular risk.


ABSTRACT

The achievement of low-density lipoprotein (LDL) therapeutic targets is especially difficult in some patients at high cardiovascular risk. These patients include persons with statin intolerance and those with very high LDL cholesterol (LDLc) levels such as persons with familial hypercholesterolemia. The proportion of statin-intolerant patients is between 7% and 29%. Alternative lipid-lowering drugs (including ezetimibe) are less effective and are not free from adverse effects. Both alirocumab, with the ODYSSEY ALTERNATIVE study, and evolocumab, with
the GAUSS study, have shown strong lipid-lowering efficacy, with much greater tolerability than currently available alternatives, with the result that a larger number of patients achieve therapeutic targets. In familial hypercholesterolemia, the monogenic metabolic disease most frequently associated with high cardiovascular risk, early intervention is cost-effective. Although statins have substantially improved the prognosis of familial hypercholesterolemia, many affected individuals are far from achieving the recommended therapeutic targets. In this patient group, PCSK9 inhibition with monoclonal antibodies has also been shown to be highly effective in reducing LDLc, especially in heterozygous individuals. The studies performed to date have shown that these drugs are safe and effective and can help many patients with familial hypercholesterolemia to drastically reduce their cardiovascular risk.


ABSTRACT

PCSK9 is a protease, synthesized mainly in the liver, which promotes the hepatic degradation of the LDL receptor and consequently decreases LDL receptor density and clearance of LDL particles. Statins inhibit HMG-CoA-reductase activity, an enzyme that catalyses an important step in hepatic cholesterol biosynthesis. The decrease of the hepatic intracellular cholesterol pool produced by these drugs upregulates the activity of the SREBP2 transcription factor, which subsequently stimulates the expression of the LDL receptor gene, an effect that is followed by an increase in the serum concentration of PCSK9. This article aims to review the effects of different lipid-lowering drugs on plasma PCSK9 concentrations. Overall, statins increase blood PCSK9 levels, an effect that is enhanced by ezetimibe. In contrast, others drugs, such as fibrates and niacin, could decrease PCSK9 levels.


ABSTRACT

Proprotein convertase subtilisin/kexin type 9 (PCSK9) binds to the low-density lipoprotein receptor (LDLr) and then targets it for lysosomal degradation in cells, thus preventing LDLr from recycling back to the hepatocyte surface, with a consequent decrease in LDLr density and clearance of LDL-cholesterol (LDLc). There have been reports of both gain-of-function
mutations in the PCSK9 gene that cause a marked increase in LDLc concentrations and loss-of-function mutations, which lead to modest reductions in LDLc and low rates of coronary heart disease. The PCSK9 gene has become a promising therapeutic target to reduce blood cholesterol levels. This review discusses the most interesting recent data on PCSK9 regulation and its molecular function in cholesterol homeostasis.


ABSTRACT

BACKGROUND/OBJECTIVES: Chronic kidney disease (CKD) and cancer are both common in older patients; whether CKD increases risk for cancer is unclear. This study evaluated CKD as a risk factor for cancer mortality in a large cohort of hypertensive patients. STUDY DESIGN: We did post-hoc analyses of in-trial and post-trial data from participants in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). SETTING AND PARTICIPANTS: Participants were >/= 55 years old with hypertension and one other additional risk factor for coronary heart disease. PREDICTOR: Baseline estimated glomerular filtration rate (eGFR). OUTCOMES: Cancer mortality was ascertained by cancer-related deaths reported in national databases during and after the trial. Cox proportional hazard models were used to calculate hazard ratios (HRs) adjusted for possible confounders and were stratified by baseline GFR. RESULTS: Participants' mean age was 66.9 years. After a mean follow-up of 8.9 years, there were 2,338 reported cancer-related deaths. Participants with GFR < 45 mL/min/1.73 m2 were at increased risk of cancer mortality compared to those with GFR >/= 90 mL/min/1.73 m2 (adjusted HR 1.54 (1.22 - 1.94), p-value for trend 0.004). These findings were consistent across subgroups defined by race, gender, and diabetes. Participants with GFR < 45 mL/min/1.73 m2 were at higher risk for mortality related to colon cancer (p-value for trend 0.048, HR 2.28 (1.12 - 4.62)) and urinary tract cancer (p-value for trend 0.001, adjusted HR 2.95 (1.14 - 7.65)). LIMITATIONS: This is a post hoc analysis of clinical trial data. CONCLUSIONS: In a large cohort of hypertensive patients, GFR < 45 mL/min/1.73 m2 was associated with a higher risk of cancer-related mortality.


ABSTRACT
Preeclampsia is a multisystem disorder that affects 3% to 5% of pregnant women and remains a significant source of short-term and long-term maternal and neonatal mortality and morbidity. Many professional societies recommend the use of low-dose aspirin to prevent preeclampsia in high-risk women. Owing to the similarities in pathophysiology between preeclampsia and atherosclerotic cardiovascular disease, and the encouraging data from preclinical and pilot clinical studies, pravastatin has been proposed for preventing preeclampsia. However, before statin administration becomes part of routine clinical practice, a large, well-designed, and adequately powered randomized-controlled trial is needed.


**ABSTRACT**

BACKGROUND: Elevated levels of total cholesterol and low-density lipoprotein play an important role in the development of atheromas and, therefore, in cardiovascular diseases. Cholesterol biosynthesis follows a circadian rhythm and is principally produced at night (between 12:00 am and 6:00 am). The adjustment of hypolipaemic therapy to biologic rhythms is known as chronotherapy. Chronotherapy is based on the idea that medication can have different effects depending on the hour at which it is taken. Statins are one of the most widely used drugs for the prevention of cardiovascular events. In usual clinical practice, statins are administered once per day without specifying the time when they should be taken. It is unknown whether the timing of statin administration is important for clinical outcomes. OBJECTIVES: To critically evaluate and analyse the evidence available from randomised controlled trials regarding the effects of chronotherapy on the effectiveness and safety of treating hyperlipidaemia with statins. SEARCH METHODS: We searched the CENTRAL, MEDLINE, Embase, LILACS, ProQuest Health & Medical Complete, OpenSIGLE, Web of Science Conference Proceedings, and various other resources including clinical trials registers up to November 2015. We also searched the reference lists of relevant reviews for eligible studies. SELECTION CRITERIA: We included randomised controlled trials (RCTs), enrolling people with primary or secondary hyperlipidaemia. To be included, trials must have compared any chronotherapeutic lipid-lowering regimen with statins and any other statin lipid-lowering regimen not based on chronotherapy. We considered any type and dosage of statin as eligible, as long as the control and experimental arms differed only in the timing of the administration of the same statin. Quasi-randomised studies were excluded. DATA COLLECTION AND ANALYSIS: We used the standard methodological procedures expected by Cochrane. We extracted the key data from studies in relation to participants, interventions, and outcomes for safety and efficacy. We calculated odds ratios (OR) for dichotomous data and mean differences (MD) for continuous...
data with 95% confidence intervals (CI). Using the GRADE approach, we assessed the quality of the evidence and we used the GRADEpro Guideline Development Tool to import data from Review Manager to create 'Summary of findings' tables. MAIN RESULTS: This review includes eight RCTs (767 participants analysed in morning and evening arms). The trials used different lipid-lowering regimens with statins (lovastatin: two trials; simvastatin: three trials; fluvastatin: two trials; pravastatin: one trial). All trials compared the effects between morning and evening statin administration. Trial length ranged from four to 14 weeks. We found a high risk of bias in the domain of selective reporting in three trials and in the domain of incomplete outcome data in one trial of the eight trials included. None of the studies included were judged to be at low risk of bias. None of the included RCTs reported data on cardiovascular mortality, cardiovascular morbidity, incidence of cardiovascular events, or deaths from any cause. Pooled results showed no evidence of a difference in total cholesterol (MD 4.33, 95% CI -1.36 to 10.01), 514 participants, five trials, mean follow-up 9 weeks, low-quality evidence), low-density lipoprotein cholesterol (LDL-C) levels (MD 4.85 mg/dL, 95% CI -0.87 to 10.57, 473 participants, five trials, mean follow-up 9 weeks, low-quality evidence), high-density lipoprotein cholesterol (HDL-C) (MD 0.54, 95% CI -1.08 to 2.17, 514 participants, five trials, mean follow-up 9 weeks, low-quality evidence) or triglycerides (MD -8.91, 95% CI -22 to 4.17, 510 participants, five trials, mean follow-up 9 weeks, low-quality evidence) between morning and evening statin administration. With regard to safety outcomes, five trials (556 participants) reported adverse events. Pooled analysis found no differences in statins adverse events between morning and evening intake (OR 0.71, 95% CI 0.44 to 1.15, 556 participants, five trials, mean follow-up 9 weeks, low-quality evidence). AUTHORS’ CONCLUSIONS: Limited and low-quality evidence suggested that there were no differences between chronomodulated treatment with statins in people with hyperlipidaemia as compared to conventional treatment with statins, in terms of clinically relevant outcomes. Studies were short term and therefore did not report on our primary outcomes, cardiovascular clinical events or death. The review did not find differences in adverse events associated with statins between both regimens. Taking statins in the evening does not have an effect on the improvement of lipid levels with respect to morning administration. Further high-quality trials with longer-term follow-up are needed to confirm the results of this review.


ABSTRACT

PURPOSE OF REVIEW: HDL to promote cholesterol efflux from macrophages is a predictor of cardiovascular risk independent of HDL cholesterol levels. However, the molecular determinants of HDL cholesterol efflux capacity (CEC) are largely unknown. RECENT FINDINGS:
The term HDL defines a heterogeneous population of particles with distinct size, shape, protein, and lipid composition. Cholesterol efflux is mediated by multiple pathways that may be differentially modulated by HDL composition. Furthermore, different subpopulations of HDL particles mediate CEC via specific pathways, but the molecular determinants of CEC, either proteins or lipids, are unclear. Inflammation promotes a profound remodeling of HDL and impairs overall HDL CEC while improving ATP-binding cassette transporter G1-mediated efflux. This review discusses recent findings that connect HDL composition and CEC. SUMMARY: Data from recent animal and human studies clearly show that multiple factors associate with CEC including individual proteins, lipid composition, as well as specific particle subpopulations. Although acute inflammation remolds HDL and impairs CEC, chronic inflammation has more subtle effects. Standardization of assays measuring HDL composition and CEC is a necessary prerequisite for understanding the factors controlling HDL CEC. Unraveling these factors may help the development of new therapeutic interventions improving HDL function.


ABSTRACT


ABSTRACT

BACKGROUND: Previous studies demonstrated that lower outdoor temperatures increase the levels of established cardiovascular disease risk factors, such as blood pressure and lipids. Whether or not low temperatures increase novel cardiovascular disease risk factors levels is not well studied. The aim was to investigate associations of outdoor temperature with a comprehensive range of established and novel cardiovascular disease risk factors in two large Northern European studies of older adults, in whom cardiovascular disease risk is increased. DESIGN AND METHODS: Data came from the British Regional Heart Study (4252 men aged 60-79 years) and the Prospective Study of Pravastatin in the Elderly at Risk (5804 men and women aged 70-82 years). Associations between outdoor temperature and cardiovascular disease risk factors were quantified in each study and then pooled using a random effects model. RESULTS: With a 5 lower mean temperature, total cholesterol was 0.04 mmol/l (95% confidence interval (CI) 0.02-0.07) higher, low density lipoprotein cholesterol was 0.02 mmol/l (95% CI 0.01-0.05)
higher and SBP was 1.12 mm Hg (95% CI 0.60-1.64) higher. Among novel cardiovascular disease risk factors, C-reactive protein was 3.3% (95% CI 1.0-5.6%) higher, interleukin-6 was 2.7% (95% CI 1.1-4.3%) higher, and vitamin D was 11.2% (95% CI 1.0-20.4%) lower. CONCLUSIONS: Lower outdoor temperature was associated with adverse effects on cholesterol, blood pressure, circulating inflammatory markers, and vitamin D in two older populations. Public health approaches to protect the elderly against low temperatures could help in reducing the levels of several cardiovascular disease risk factors.


ABSTRACT

We investigated the independent and interactive impact of the common APOE genotype and marine n-3 polyunsaturated fatty acids (PUFA) on the development of obesity and associated cardiometabolic dysfunction in a murine model. Human APOE3 and APOE4 targeted replacement mice were fed either a high-fat control diet (HFD) or a HFD supplemented with 3% n-3 PUFA from fish oil (HFD + FO) for 8 wk. We established the impact of intervention on food intake, bodyweight, and visceral adipose tissue (VAT) mass; plasma, lipids (cholesterol and triglycerides), liver enzymes, and adipokines; glucose and insulin during an intraperitoneal glucose tolerance test; and Glut4 and ApoE expression in VAT. HFD feeding induced more weight gain and higher plasma lipids in APOE3 compared to APOE4 mice (P < 0.05), along with a 2-fold higher insulin and impaired glucose tolerance. Supplementing APOE3, but not APOE4, animals with dietary n-3 PUFA decreased bodyweight gain, plasma lipids, and insulin (P < 0.05) and improved glucose tolerance, which was associated with increased VAT Glut4 mRNA levels (P < 0.05). Our findings demonstrate that an APOE3 genotype predisposes mice to develop obesity and its metabolic complications, which was attenuated by n-3 PUFA supplementation.-Slim, K. E., Vauzour, D., Tejera, N., Voshol, P. J., Cassidy, A., Minihane, A. M. The effect of dietary fish oil on weight gain and insulin sensitivity is dependent on APOE genotype in humanized targeted replacement mice.


ABSTRACT
This article summarizes some of the recent and clinically relevant advances in chronic pancreatitis. These advances mainly concern the definition of the disease, the etiological diagnosis of idiopathic disease, the correlation between fibrosis degree and pancreatic secretion in the early stages of chronic pancreatitis, the treatment of the disease and of pain, the clinical relevance of pancreatic exocrine insufficiency, and the diagnosis of autoimmune pancreatitis. A new mechanistic definition of chronic pancreatitis has been proposed. Genetic testing is mainly of help in patients with relapsing idiopathic pancreatitis. A significant correlation has been shown between the degree of pancreatic fibrosis as evaluated by elastography and pancreatic secretion of bicarbonate. New data supports the efficacy of antioxidants and simvastatin for the therapy of chronic pancreatitis. The pancreatoscopy-guided intraductal lithotripsy is an effective alternative to extracorporeal shock wave lithotripsy in patients with chronic calcifying pancreatitis. The presence of pancreatic exocrine insufficiency in patients with chronic pancreatitis is associated with a significant risk of cardiovascular events. Fine needle biopsy and contrast enhanced harmonic endoscopic ultrasonography are of help for the diagnosis of autoimmune pancreatitis and its differential diagnosis with pancreatic cancer.


ABSTRACT

BACKGROUND: Drug interactions, particularly those involving warfarin, are a major clinical and public health problem. Minimizing serious bleeding caused by anticoagulants is a recent major focus of the United States (US) Department of Health and Human Services. This study quantified the risk of gastrointestinal bleeding (GIB) and intracranial hemorrhage (ICH) among concomitant users of warfarin and individual antihyperlipidemics. METHODS: The authors conducted a high-dimensional propensity score-adjusted cohort study of new concomitant users of warfarin and an antihyperlipidemic, among US Medicaid beneficiaries from five states during 1999-2011. Exposure was defined by concomitant use of warfarin plus one of eight antihyperlipidemics. The primary outcome measure was a composite of GIB/ICH within the first 30days of concomitant use. As a secondary outcome measure, GIB/ICH was examined within the first 180days of concomitant use. RESULTS: Among 236,691 persons newly-exposed to warfarin and an antihyperlipidemic, the crude incidence of GIB/ICH was 13.2 (95% confidence interval 12.7 to 13.8) per 100person-years. Users were predominantly older, female, and Caucasian. Adjusted hazard ratios (aHRs) for warfarin and individual statins were consistent with no association. Warfarin+gemfibrozil was associated with an 80% increased risk of GIB/ICH within the first month of concomitant use (aHR=1.8, 1.4 to 2.4). Warfarin+fenofibrate was
associated with a similar increased risk (aHR=1.8, 1.2 to 2.7), yet with an onset during the second month of concomitant use. CONCLUSIONS: Among warfarin-treated persons, the use of fibrates but not statins-increases the risk of hospital presentation for GIB/ICH.


ABSTRACT

Objective Recently, tenofovir disoproxil fumarate (TDF)-related side effects, such as renal nephrotoxicity and reduction of bone mineral density, have been reported. Consequently, increased switching from fixed-dose tablet TDF and emtricitabine (TDF/FTC) to abacavir and lamivudine (ABC/3TC) has occurred. Interestingly, while TDF has a lipid-lowering property, one of the ABC-related side effects is hyperlipidemia. Therefore, such switching could cause lipid elevation. To evaluate the change in lipid levels associated with switching from TDF/FTC to ABC/3TC in virologically-suppressed human immunodeficiency virus (HIV)-infected patients.

Methods This is a retrospective, single-center study. We included the HIV-infected patients whose therapy included a drug switch from TDF/FTC to ABC/3TC between September 2009 and December 2012 at Ryukyu University Hospital. The exclusion criteria were HIV-RNA >40 copies/mL on the switching day, and a documented therapy change to a lipid-lowering agent or any other antiretroviral agents within 3 months before or after switching. We compared the low-density lipoprotein (LDL), high-density lipoprotein (HDL), total cholesterol (TC), and triglyceride (TG) levels before switching to three months after. Results A total of 18 patients met the inclusion criteria. The LDL, HDL, and TC levels significantly increased three months following the switch (p<0.05), with median (interquartile range) values of 17 (7, 32), 6 (2, 13), and 27 (10, 45) mg/dL, respectively. The TG values did not markedly change. Conclusion Switching from TDF/FTC to ABC/3TC resulted in significantly increased LDL, HDL, and TC levels.


ABSTRACT
ABSTRACT

Patients undergoing coronary angiography for suspected coronary heart disease who are found to have coronary atherosclerotic disease with <50% diameter stenosis may carry a risk of adverse cardiac events similar to that in patients with single-vessel obstructive disease. Yet clinical practice guidelines offer no direction for managing symptomatic patients with nonobstructive coronary atherosclerosis because current diagnostic criteria for coronary heart disease are not met. Accordingly, secondary preventive measures are not endorsed, and their role is not defined in this setting. Available data suggest that we are missing the opportunity to provide effective preventive measures in millions of patients with nonobstructive coronary heart disease. The emergence of noninvasive coronary angiography in patients with suspected coronary heart disease provides the opportunity to transition from a categorical perspective on the presence or absence of coronary heart disease to accepting the risk continuum from atherosclerosis and its implications for diagnosis and management.

ABSTRACT

BACKGROUND: Costs and uncertainty about the benefits of nonstatin therapies limit their use. OBJECTIVES: The authors sought to identify patients who might benefit from the addition of a nonstatin to background statin therapy. METHODS: We performed systematic reviews of subgroup analyses from randomized trials and observational studies with statin-treated participants to determine estimated 10-year absolute risk of atherosclerotic cardiovascular disease (ASCVD) and to define high-risk and very high-risk patients. We used the relative risk
reductions for the addition of a nonstatin to lower low-density lipoprotein (LDL-C) used to determine the number needed to treat (NNT) to prevent 1 ASCVD event over 5 years for each patient group and to allow comparisons with 5-year cost analyses. RESULTS: The 10-year ASCVD risk is at least 30% (very high risk) for statin-treated participants with clinical ASCVD and comorbidities, and 20% to 29% (high risk) for those with ASCVD without comorbidities or who have heterozygous familial hypercholesterolemia. Adding ezetimibe to reduce low-density LDL-C by 20% would provide a 5-year NNT \( \leq 50 \) for very high-risk patients with LDL-C \( \geq 130 \) mg/dl or for high-risk patients with LDL-C \( \geq 190 \) mg/dl, and an NNT \( \leq 30 \) for very high-risk patients with LDL-C \( \geq 160 \) mg/dl. Adding a PCSK9 monoclonal antibody to lower LDL-C by at least 50% would provide an NNT \( \leq 50 \) for very high-risk and high-risk patients with LDL-C \( \geq 70 \) mg/dl, and an NNT \( \leq 30 \) for very high-risk and high-risk patients with an LDL-C \( \geq 130 \) mg/dl.

CONCLUSIONS: Adding ezetimibe or PCSK9 monoclonal antibodies to maximally tolerated statin therapy may be cost effective in very high-risk and high-risk patients, depending on baseline LDL-C levels.


ABSTRACT

Accumulating evidence implicates endoplasmic reticulum (ER) stress as a mediator of impaired lipid metabolism, thereby contributing to fatty liver disease and atherosclerosis. Previous studies demonstrated that ER stress can activate the sterol regulatory element-binding protein-2 (SREBP2), an ER localized transcription factor that directly upregulates sterol-regulatory genes, including PCSK9. Given that PCSK9 contributes to atherosclerosis by targeting low-density lipoprotein (LDL) receptor (LDLR) degradation, our present study investigates a novel mechanism by which ER stress plays a role in lipid metabolism by examining its ability to modulate PCSK9 expression. Herein, we demonstrate the existence of two independent effects of ER stress on PCSK9 expression and secretion. In cultured HuH7 and HepG2 cells, agents or conditions that cause ER Ca2+ depletion, including thapsigargin (TG), induced SREBP2-dependent upregulation of PCSK9 expression. In contrast, a significant reduction in the secreted form of PCSK9 protein was observed in the media from both TG- and tunicamycin (TM)-treated HuH7 cells, mouse primary hepatocytes and in the plasma of TM- treated C57BL/6 mice. Furthermore, TM significantly increased hepatic LDLR expression and reduced plasma LDL concentrations in mice. Based on these findings we propose a model in which ER Ca2+ depletion promotes the activation of SREBP2 and subsequent transcription of PCSK9. However, conditions that cause ER stress irregardless of their ability to dysregulate ER Ca2+ inhibit PCSK9 secretion, thereby reducing PCSK9-mediated LDLR degradation and promoting LDLR-dependent
hepatic cholesterol uptake. Taken together, our studies provide evidence that the retention of PCSK9 in the ER may serve as a potential strategy for lowering LDL cholesterol levels.


ABSTRACT

In spite of the unequivocal efficacy of statins in reducing primary and secondary cardiovascular events, the use of these drugs in a considerable number of patients is limited because of statin intolerance, mainly statin-associated muscle symptoms (SAMS). SAMS encompass a broad spectrum of clinical presentations, including mild muscular aching and other types of myalgias, myopathy with the significant elevation of creatine kinase, and the rare but life-threatening rhabdomyolysis. Among several pathophysiologic mechanisms of SAMS, mitochondrial dysfunction is thought to be one of the main one. Curcumin is the polyphenolic ingredient of Curcuma longa L., which has various pharmacological properties against a vast range of diseases. Curcumin has several mechanisms of actions relevant to the treatment of SAMS. These effects include the capacity to prevent and reduce delayed onset muscle soreness by blocking the nuclear factor inflammatory pathway, attenuation of muscular atrophy, enhancement of muscle fibre regeneration following injury, and analgesic and antioxidant effects. Curcumin can also increase the levels of cyclic adenosine monophosphate, which leads to an increase in the number of mitochondrial DNA duplicates in skeletal muscle cells. Finally, owing to its essential lipid-modifying properties, curcumin might serve as an adjunct to statin therapy in patients with SAMS, allowing for effective lowering of low-density lipoprotein cholesterol and possibly for statin dose reduction. Owing to the paucity of effective treatments, and the safety of curcumin in clinical practice, proof-of-concept trials are recommended to assess the potential benefit of this phytochemical in the treatment of SAMS.


ABSTRACT

BACKGROUND: As a systemic disease, atherosclerosis commonly affects intracranial and extracranial carotid arteries simultaneously which is defined as co-existing plaques. Previous studies demonstrated that co-existing atherosclerotic diseases are significantly associated with
ischemic cerebrovascular events. The aim of this study was to investigate the characteristics of co-existing intracranial and extracranial carotid atherosclerotic plaques and their relationships with recurrent stroke by using 3D multi-contrast magnetic resonance (MR) vessel wall imaging.

**METHODS:** Patients with recent cerebrovascular symptoms in anterior circulation and at least one carotid plaque were recruited. All patients underwent cardiovascular magnetic resonance (CMR) for brain and intracranial and extracranial arteries. Presence/absence of atherosclerotic plaque at each arterial segment was identified. The maximum wall thickness (Max WT), length, stenosis of each plaque was measured. The presence/absence of calcification, lipid-rich necrotic core (LRNC), and intraplaque hemorrhage (IPH) was assessed. Cerebral old and acute infarcts in anterior circulation were evaluated.

**RESULTS:** Fifty-eight patients (mean age: 58.0 +/- 8.5 years old, 34 males) were recruited. Of the 58 patients, co-existing intracranial and extracranial carotid artery plaques were found in 45 patients (77.6%), of which 7 (15.6%) had first time acute stroke and 26 (57.8%) had recurrent stroke. For these 33 patients with stroke, the number of intracranial plaques (OR = 11.26; 95% CI, 1.27-100; p = 0.030) and co-existing intracranial and extracranial carotid artery plaques (OR = 2.42; 95% CI, 1.04-5.64; p = 0.040) was significantly associated with recurrent stroke. After adjusting for traditional risk factors, the number of co-existing plaques was still significantly correlated with recurrent stroke (OR = 3.31; 95% CI, 1.09-10.08; p = 0.035). No correlations were found between recurrent stroke and Max WT, length, stenosis, and compositions of plaques.

**CONCLUSIONS:** Co-existing intracranial and extracranial carotid artery plaques are prevalent in symptomatic patients and the number of co-existing plaques is independently associated with the risk of recurrent stroke.


**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=27901325

**ABSTRACT**

Although stopping smoking, lowering blood pressure and reducing lipid levels will reduce global stroke risk and cardiovascular mortality, these remain leading causes of death and disability especially in ageing populations. Further prevention strategies are needed and, in the first part of this review, we explore the potential benefits of appropriate screening for carotid artery disease to reduce stroke and identify those who may have related cardiac disease. Although whole-population carotid screening is an inefficient and costly means of identifying candidates with tight carotid stenosis who might warrant intervention, it can identify many people with lower levels of stenosis who may benefit from cardiovascular risk reducing medications. Longer-term benefits and cost-effectiveness of any targeted screening programme needs further evaluation. Patients with carotid stenosis are known to be at increased risk of stroke and vascular death. Whilst randomised clinical trials and guidelines have reported stroke hazards
and benefits of interventional treatment for carotid stenosis, uncertainty remains about their optimal medical management. In the second part of this review we discuss Level I evidence for medical and surgical treatment of asymptomatic carotid stenosis, reasons for the current lack of consensus on interventional management of these patients and future studies which may help to clarify which groups will (and which will likely not) benefit from interventions.


ABSTRACT

Familial Hypercholesterolaemia (FH) is a monogenic autosomal dominant disorder affecting 1 in 500 individuals. We report a case of 32-year-old female with FH, previously not on any treatment, who presented with recurrent bilateral Middle Cerebral Artery (MCA) territory strokes and dyspnoea on exertion due to severe panvascular disease involving descending aorta, innominate, subclavian, common carotid, internal carotid and coronary vessels. Her complete clinical work up was done and was started on lipid lowering drug treatment and low calorie diet. She underwent simultaneous bilateral carotid stenting followed by coronary artery bypass surgery at a later date. In the present scenario we want to emphasize the importance of early detection and treatment of individuals with FH, failing of which results in premature and accelerated atherosclerosis causing multisystemic vascular disease with significant morbidity and mortality. Screening of first degree relatives is important owing to the autosomal dominant inheritance pattern of the FH.


ABSTRACT

BACKGROUND: Cardiovascular disease occurs at lower incidence in premenopausal females compared with age-matched males. This variation may be linked to sex differences in inflammation. We prospectively investigated whether inflammation and components of the inflammatory response are altered in females compared with males. METHODS: We performed 2 clinical studies in healthy volunteers. In 12 men and 12 women, we assessed systemic inflammatory markers and vascular function using brachial artery flow-mediated dilation (FMD). In a further 8 volunteers of each sex, we assessed FMD response to glyceryl trinitrate (GTN) at baseline and at 8 hours and 32 hours after typhoid vaccine. In a separate study in 16
men and 16 women, we measured inflammatory exudate mediators and cellular recruitment in cantharidin-induced skin blisters at 24 and 72 hours. RESULTS: Typhoid vaccine induced mild systemic inflammation at 8 hours, reflected by increased white cell count in both sexes. Although neutrophil numbers at baseline and 8 hours were greater in females, the neutrophils were less activated. Systemic inflammation caused a decrease in FMD in males, but an increase in females, at 8 hours. In contrast, GTN response was not altered in either sex after vaccine. At 24 hours, cantharidin formed blisters of similar volume in both sexes; however, at 72 hours, blisters had only resolved in females. Monocyte and leukocyte counts were reduced, and the activation state of all major leukocytes was lower, in blisters of females. This was associated with enhanced levels of the resolving lipids, particularly D-resolvin. CONCLUSIONS: Our findings suggest that female sex protects against systemic inflammation-induced endothelial dysfunction. This effect is likely due to accelerated resolution of inflammation compared with males, specifically via neutrophils, mediated by an elevation of the D-resolvin pathway. TRIAL REGISTRATION: ClinicalTrials.gov NCT01582321 and NRES: City Road and Hampstead Ethics Committee: 11/LO/2038. FUNDING: The authors were funded by multiple sources, including the National Institute for Health Research, the British Heart Foundation, and the European Research Council.


ABSTRACT

Oxidized high-density lipoprotein (ox-HDL), unlike native HDL that exerts antiatherogenic effects, plays a proatherogenic role. However, the underlying mechanisms are not completely understood. This study was designed to explore the inductive effect of ox-HDL on endoplasmic reticulum (ER) stress-C/EBP homologous protein (CHOP)-mediated macrophage apoptosis and its upstream mechanisms. Our results showed that ox-HDL could be ingested by macrophages, causing intracellular lipid accumulation. Like tunicamycin (an ER stress inducer), ox-HDL induced macrophage apoptosis with concomitant activation of ER stress pathway, including nuclear translocation of activating transcription factor 6, phosphorylation of protein kinase-like ER kinase and eukaryotic translation initiation factor 2alpha, and upregulation of glucose regulated protein 78 and CHOP, which were inhibited by 4-phenylbutyric acid (PBA, an ER stress inhibitor) and CHOP gene silencing. Additionally, diphenyleneiodonium (DPI, an oxidative stress inhibitor), probucol (a reactive oxygen species scavenger) and toll-like receptor 4 (TLR4) silencing reduced ox-HDL-induced macrophage apoptosis, oxidative stress and CHOP upregulation. Moreover, HDL isolated from patients with metabolic syndrome induced macrophage apoptosis, oxidative stress and CHOP upregulation, which were blocked by PBA and DPI. These data indicate that ox-
HDL may activate ER stress-CHOP-induced apoptotic pathway in macrophages via enhanced oxidative stress, and that this pathway may be mediated by TLR4.


ABSTRACT


ABSTRACT


ABSTRACT

Importance: On the basis of observational studies, the use of thiazide diuretics for the treatment of hypertension is associated with reduced fracture risk compared with nonuse. Data from randomized clinical trials are lacking. Objective: To examine whether the use of thiazide diuretics for the treatment of hypertension is associated with reduced fracture risk compared with nonuse. Design, Setting, and Participants: Using Veterans Affairs and Medicare claims data, this study examined hip and pelvic fracture hospitalizations in Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial participants randomized to first-step therapy with a thiazide-type diuretic (chlorthalidone), a calcium channel blocker (amlodipine besylate), or an angiotensin-converting enzyme inhibitor (lisinopril). Recruitment was from February 1994 to January 1998; in-trial follow-up ended in March 2002. The mean follow-up was 4.9 years. Posttrial follow-up was conducted through the end of 2006, using passive surveillance via national databases. For this secondary analysis, which used an intention-to-treat approach, data were analyzed from February 1, 1994, through December 31, 2006. Main Outcomes and Measures: Hip and pelvic fracture hospitalizations. Results: A total of 22180 participants (mean [SD] age, 70.4 [6.7] years; 43.0% female; and 49.9% white non-Hispanic, 31.2% African American, and 19.1% other ethnic groups) were followed for up to 8 years (mean [SD], 4.9 [1.5]
years) during masked therapy. After trial completion, 16622 participants for whom claims data were available were followed for up to 5 additional years (mean [SD] total follow-up, 7.8 [3.1] years). During the trial, 338 fractures occurred. Participants randomized to receive chlorthalidone vs amlodipine or lisinopril had a lower risk of fracture on adjusted analyses (hazards ratio [HR], 0.79; 95% CI, 0.63-0.98; P = .04). Risk of fracture was significantly lower in participants randomized to receive chlorthalidone vs lisinopril (HR, 0.75; 95% CI, 0.58-0.98; P = .04) but not significantly different compared with those randomized to receive amlodipine (HR, 0.82; 95% CI, 0.63-1.08; P = .17). During the entire trial and posttrial period of follow-up, the cumulative incidence of fractures was nonsignificantly lower in participants randomized to receive chlorthalidone vs lisinopril or amlodipine (HR, 0.87; 95% CI, 0.74-1.03; P = .10) and vs each medication separately. In sensitivity analyses, when 1 year after randomization was used as the baseline (to allow for the effects of medications on bone to take effect), similar results were obtained for in-trial and in-trial plus posttrial follow-up. Conclusions and Relevance: These findings from a large randomized clinical trial provide evidence of a beneficial effect of thiazide-type diuretic therapy in reducing hip and pelvic fracture risk compared with treatment with other antihypertensive medications. Trial Registration: clinicaltrials.gov Identifier: NCT00000542.


ABSTRACT

BACKGROUND: Statin treatment and variants in the gene encoding HMG-CoA reductase are associated with reductions in both the concentration of LDL cholesterol and the risk of coronary heart disease, but also with modest hyperglycaemia, increased bodyweight, and modestly increased risk of type 2 diabetes, which in no way offsets their substantial benefits. We sought to investigate the associations of LDL cholesterol-lowering PCSK9 variants with type 2 diabetes and related biomarkers to gauge the likely effects of PCSK9 inhibitors on diabetes risk.

METHODS: In this mendelian randomisation study, we used data from cohort studies, randomised controlled trials, case control studies, and genetic consortia to estimate associations of PCSK9 genetic variants with LDL cholesterol, fasting blood glucose, HbA1c, fasting insulin, bodyweight, waist-to-hip ratio, BMI, and risk of type 2 diabetes, using a standardised analysis plan, meta-analyses, and weighted gene-centric scores. FINDINGS: Data were available for more than 550,000 individuals and 51,623 cases of type 2 diabetes. Combined analyses of four independent PCSK9 variants (rs11583680, rs11591147, rs2479409, and rs11206510) scaled to 1 mmol/L lower LDL cholesterol showed associations with increased fasting glucose (0.09 mmol/L, 95% CI 0.02 to 0.15), bodyweight (1.03 kg, 0.24 to 1.82), waist-to-hip ratio (0.006, 0.003 to 0.010), and an odds ratio for type diabetes of 1.29 (1.11 to 1.50).
Based on the collected data, we did not identify associations with HbA1c (0.03%, -0.01 to 0.08), fasting insulin (0.00%, -0.06 to 0.07), and BMI (0.11 kg/m2, -0.09 to 0.30). INTERPRETATION: PCSK9 variants associated with lower LDL cholesterol were also associated with circulating higher fasting glucose concentration, bodyweight, and waist-to-hip ratio, and an increased risk of type 2 diabetes. In trials of PCSK9 inhibitor drugs, investigators should carefully assess these safety outcomes and quantify the risks and benefits of PCSK9 inhibitor treatment, as was previously done for statins. FUNDING: British Heart Foundation, and University College London Hospitals NHS Foundation Trust (UCLH) National Institute for Health Research (NIHR) Biomedical Research Centre.


ABSTRACT
The essential oils (EOs) of Lippia alba, an herb extensively used as a folk medicine in Latin America, are today promoted as an effective means of eliminating problems caused by hyperlipemia. We hypothesized that L.alba EOs inhibited cholesterol and triacylglycerols synthesis and decreased the intracellular depots of those lipids (lipid droplets), mechanisms involving the induction of a hypolipidemic response. Our aim was, therefore, to evaluate the hypolipogenic capability of the EOs of four L. alba chemotypes on liver-derived (HepG2) and non-liver (A549) human cell lines and to identify the potential biochemical targets of those chemotypes, particularly within the mevalonate pathway (MP). [14C]Acetate was used as radioactive precursor for assays. Lipid analyses were performed by thin-layer and capillary gas chromatography, lipid droplets analyzed by fluorescence microscopy, and HMGCR levels determined by Western blot. In both cell lines, all four chemotypes exerted hypocholesterogenic effects within a concentration range of 3.2-32 microg/mL. Nonsaponifiable lipids manifested a decrease in incorporation of [14C]acetate into squalene, lanosterol, lathosterol, and cholesterol, but not into ubiquinone, thus suggesting an inhibition of enzymes in the MP downstream from farnesyl pyrophosphate. The tagetenone chemotype, the most efficacious hypocholesterogenic L. alba EO, lowered HMGCR protein levels; inhibited triacylglycerols, cholesteryl esters, and phospholipids synthesis; and diminished lipid droplets in size and volume. These results revealed that L. alba EOs inhibited different lipogenic pathways and such lipid-lowering effects could prove essential to prevent cardiovascular diseases.


ABSTRACT

BACKGROUND Plasma cholesteryl ester transfer protein (CETP) activity is often decreased in patients with hypothyroidism, whereas less is known about the phospholipid transfer protein (PLTP). We aimed to evaluate simultaneously serum CETP and PLTP activity in patients diagnosed with hypothyroidism. MATERIAL AND METHODS The selection criteria for control group members (without thyroid dysfunction) in this case to case study were levels of total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol (HDL-C), and triglycerides similar to those in study group patients (101 patients diagnosed with hypothyroidism). Serum CETP and PLTP activities were measured by homogenous fluorometric assays using synthetic donor particle substrates. RESULTS Serum CETP and PLTP activities in hypothyreotic patients were lower (p<0.001) compared with those in healthy subjects. This lowering was associated with significant changes in HDL-C subclasses: decrease in HDL2- and increase in HDL3 cholesterol levels. Multiple linear regression analyses adjusted for age, sex, body mass index, smoking habits, and alcohol drinking showed a strong association between hypothyroidism and activity of lipid transfer proteins. A linear inverse relationship between thyroid-stimulating hormone (TSH) and CETP (r=-0.21; p<0.01) and between TSH and PLTP (r=-0.24; p<0.001) was shown. There also was a positive correlation (p<0.001) between CETP and HDL2 cholesterol (r=0.27) and between PLTP and HDL2 cholesterol (r=0.37). A negative correlation between CETP and HDL3 cholesterol (r=-0.22: p<0.01) and between PLTP and HDL3 cholesterol (r=-0.24; p<0.001) has been demonstrated as well. CONCLUSIONS The decreased HDL2 and increased HDL3 cholesterol levels in subjects with hypothyroidism are consequences of decreased activity of lipid transfer proteins. These changes are early symptoms of lipid disturbances in hypothyroidism.


ABSTRACT


ABSTRACT
Adding Benecol - plant stanol ester spread - to statins enhances their lipid lowering effects.


ABSTRACT

BACKGROUND: Epidemiologic data suggest cholesterol-lowering drugs may prevent the progression of prostate cancer, but not the incidence of the disease. However, the association of combination therapy in cholesterol reduction on prostate or any cancer is unclear. In this study, we compared the effects of the cholesterol lowering drugs simvastatin and ezetimibe alone or in combination on the growth of LAPC-4 prostate cancer in vivo xenografts. METHODS: Proliferation assays were conducted by MTS solution and assessed by Student's t-test. 90 male nude mice were placed on a high-cholesterol Western-diet for 7 days then injected subcutaneously with 1 x 105 LAPC-4 cells. Two weeks post-injection, mice were randomized to control, 11 mg/kg/day simvastatin, 30 mg/kg ezetimibe, or the combination and sacrificed 42 days post-randomization. We used a generalized linear model with the predictor variables of treatment, time, and treatment by time (i.e., interaction term) with tumor volume as the outcome variable. Total serum and tumor cholesterol were measured. Tumoral RNA was extracted and cDNA synthesized from 1 ug of total RNA for quantitative real-time PCR.

RESULTS: Simvastatin directly reduced in vitro prostate cell proliferation in a dose-dependent, cell line-specific manner, but ezetimibe had no effect. In vivo, low continuous dosing of ezetimibe, delivered by food, or simvastatin, delivered via an osmotic pump had no effect on tumor growth compared to control mice. In contrast, dual treatment of simvastatin and ezetimibe accelerated tumor growth. Ezetimibe significantly lowered serum cholesterol by 15%, while simvastatin had no effect. Ezetimibe treatment resulted in higher tumor cholesterol. A sixfold induction of low density lipoprotein receptor mRNA was observed in ezetimibe and the combination with simvastatin versus control tumors. CONCLUSIONS: Systemic cholesterol lowering by ezetimibe did not slow tumor growth, nor did the cholesterol independent effects of simvastatin and the combined treatment increased tumor growth. Despite lower serum cholesterol, tumors from ezetimibe treated mice had higher levels of cholesterol. This study suggests that induction of low density lipoprotein receptor is a possible mechanism of resistance that prostate tumors use to counteract the therapeutic effects of lowering serum cholesterol. Prostate (c) 2016 Wiley Periodicals, Inc.

ABSTRACT

Statins, 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitors have been shown to improve diabetic nephropathy. However, whether they provide protection via Histone deacetylases (HDAC) inhibition is not clear. We conducted a comparative evaluation of Atorvastatin (AT) versus the non-statin cholesterol-lowering drug, Ezetimibe (EZT) on severity of diabetic nephropathy. Streptozotocin-treated male Wistar rats were fed a cholesterol-supplemented diet and gavaged daily with vehicle, AT or EZT. Control rats received normal diet and gavaged vehicle (n = 8-9/group). Diabetes increased blood glucose, urine albumin-to-creatinine ratio (ACR), kidney pathology and HDAC activity, and reduced renal E-cadherin levels. Both AT and EZT reduced circulating cholesterol, attenuated renal pathology, and did not lower blood glucose. However, AT was significantly more effective than EZT at reducing kidney pathology and HDAC activity. Chromatin immunoprecipitation revealed a significantly higher association of acetylated H3 and H4 with the E-cadherin promoter in kidneys from AT-, relative to EZT- or vehicle-treated rats. Moreover, we demonstrated a direct effect of AT, but not EZT, on HDAC-inhibition and, H3 and H4- acetylation in primary glomerular mesangial cells. Overall, both AT and EZT attenuated diabetic nephropathy; however, AT exhibited greater efficacy despite a similar reduction in circulating cholesterol. HDAC-inhibition may underlie greater efficacy of statins in attenuating kidney injury.


ABSTRACT

Inflammation, lipotoxicity and mitochondrial dysfunction have been implicated in the pathogenesis of obesity-induced insulin resistance and type 2 diabetes. However, how these factors are intertwined in the development of obesity/insulin resistance remains unclear. Here, we examine the role of mitochondrial fat oxidation on lipid-induced inflammation in skeletal muscle. We used skeletal muscle-specific Cpt1b knockout mouse model where the inhibition of mitochondrial fatty acid oxidation results in accumulation of lipid metabolites in muscle and elevated circulating free fatty acids. Gene expression of pro-inflammatory cytokines, chemokines, and cytokine- and members of TLR-signalling pathways were decreased in Cpt1bm/- muscle. Inflammatory signalling pathways were not activated when evaluated by multiplex and immunoblot analysis. In addition, the inflammatory response to fatty acids was reduced in primary muscle cells derived from Cpt1bm/- mice. Gene expression of Cd11c, the M1 macrophage marker, was decreased; while Cd206, the M2 macrophage marker, was increased in skeletal muscle of Cpt1bm/- mice. Finally, expression of pro-inflammatory markers
was decreased in white adipose tissue of Cpt1bm-/mice. We show that the inflammatory response elicited by elevated intracellular lipids in skeletal muscle is repressed in Cpt1bm-/mice, strongly supporting the hypothesis that mitochondrial processing of fatty acids is essential for the lipid-induction of inflammation in muscle.


ABSTRACT

In patients with atrial fibrillation, oral anticoagulation with oral thrombin inhibitors (OTIs), in contrast to vitamin K antagonists (VKAs), associates with a modest increase in acute coronary syndromes (ACSs). Whether this observation is causatively linked to OTI treatment and, if so, whether OTI action is the result of a lower antithrombotic efficacy of OTI compared to VKA or reflects a yet undefined prothrombotic activity of OTI remain unclear. We analyzed platelet function in patients receiving OTI or dose-adapted VKA under static and flow conditions. In vivo, we studied arterial thrombosis in OTI-, VKA-, and vehicle-treated mice using carotid ligation and wire injury models. Further, we examined thrombus formation on human atherosclerotic plaque homogenates under arterial shear to address the relevance to human pathology. Under static conditions, aggregation in the presence of ristocetin was increased in OTI-treated blood, whereas platelet reactivity and aggregation to other agonists were only marginally affected. Under flow conditions, firm platelet adhesion and thrombus formation on von Willebrand factor, collagen, and human atherosclerotic plaque were increased in the presence of OTI in comparison to VKA. OTI treatment was associated with increased thrombus formation in injured carotid arteries of mice. Inhibition or ablation of GPIbalpha-thrombin interactions abolished the effect of OTI on thrombus formation, suggesting a mechanistic role of the platelet receptor GPIbalpha and its thrombin-binding site. The effect of OTI was also abrogated in the presence of aspirin. In summary, OTI treatment has prothrombotic activity that might contribute to the increase in ACS observed clinically in patients.


ABSTRACT

Large-scale randomised controlled trials, carried out in the context of secondary cardiovascular prevention, have shown that statins are superior to placebo: these drugs were shown to decrease cardiovascular events and total mortality. A further set of clinical trials compared high intensity to low/standard intensity LDL cholesterol lowering in the same setting (using either
statins or a statin/ezetimibe association). In this case, a decrease in LDL cholesterol and a concomitant significant reduction in cardiovascular events were seen with intensive therapy, however with no change in total mortality. This phenomenon we may term the LDL cholesterol mortality paradox. It could be due either to the prevention (by high-intensity therapy) of episodes not severe enough to lead to the death of patients, or to high-intensity therapy leading to the death of some patients at the same time as preventing the death of others, with a null aggregate effect. Several types of adverse effects have been seen with statin therapy, such as a possible increased incidence of Diabetes mellitus and of myopathy. The decision to start high-intensity LDL cholesterol lowering (rather than low- or moderate-intensity statin treatment) should be evaluated on a case-by-case basis, taking into consideration the overall aspects of each patient, including the patient’s preferences. High-intensity LDL cholesterol lowering, up to the present moment, has failed to produce a change in overall prognosis (total mortality), and should not therefore be mandatory in secondary cardiovascular prevention. It remains to be seen if a similar LDL cholesterol mortality paradox occurs with new drugs targeting plasma lipids.


ABSTRACT

Atherosclerosis is a widespread disease that accounts for nearly 3-quarters of deaths due to cardiovascular disease. Ultrasound elastography might be able to reliably identify characteristics associated with vulnerable plaques. There is a need for the evaluation of elastography and its ability to distinguish between vulnerable and stable plaques. The aim of this paper is to provide an overview of the literature on vascular elastography. A systematic search of the available literature for studies using elastography for assessing atherosclerotic plaques was conducted using the MEDLINE, Embase, Cochrane Library and Web of Science databases. A standardized template was used to extract relevant data following the PRISMA 2009 checklist. 20 articles were included in this paper. The studies were heterogeneous. All studies reported that elastography was a feasible technique and provided additional information compared to B-mode ultrasound alone. Most studies reported higher strain values for vulnerable plaques. Ultrasound elastography has potential as a clinical tool in the assessment of atherosclerotic plaques. Elastography is able to distinguish between different plaque types, but there is considerable methodological variation between studies. There is a need for larger studies in a clinical setting to determine the full potential of elastography.
In the treatment of dyslipidemias about 5-6 years back a new class of drugs emerged, CETP (cholesteryl ester transfer protein)-inhibitors. Their benefit was due to an increase of HDL-cholesterol (HDL-C) serum levels. This treatment mode was supported by epidemiological and clinical studies, as people with high serum HDL-C levels suffered less from cardiovascular (CV) events. Three studies with CETP inhibitors (ILLUMINATE with torcetrapib, dal-OUTCOMES with dalcetrapib and ACCELERATE with evacetrapib) were unfortunately negative, and torcetrapib was even harmful to patients due to an increase of aldosterone serum levels. Treatment with dalcetrapib was safe, but without benefit. Similar it was with evacetrapib. There is still running also a study with anacetrapib (REVEAL), but a benefit is here not expected. Evacetrapib and anacetrapib in comparison to dalcetrapib can reduce serum LDL-cholesterol (LDL-C) much more, and similar results were found also in another CETP-inhibitor TA-8995 (TULIP study). Authors try to explain why there is no benefit with CETP-inhibitors (dysfunctional HDL particle, another effective mechanism than reverse cholesterol transport). A genetic analysis in dalcetrapib studies (dal-OUTCOMES and dal-PLAQUE-2) showed, that a cardiovascular benefit from this treatment is concentrated only to a subgroup of patients with a genotype AA in the gene ADCY9 on 16th chromosome. In the population there are about 20% of people with this AA genotype. A clinical study DAL-301 will test this data in a near future. Framingham Offspring study showed that the association of "HDL-C serum level - CV risk in the future" is greatly influenced by serum levels of LDL-C and triglycerides (if these are increased, than the CV future prediction with HDL-C levels is lost). HDL particles are complex and we do not know which subtype of HDL particles is for cardiovascular prognosis important. The research here continues.Key words: acute coronary syndrome - CETP-inhibitors - dalcetrapib - dysfunctional HDL particles - dyslipidemia - HDL-cholesterol - pharmacogenomics of ADCY9 gene.