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Low-Density Lipoprotein-Dependent and -Independent Effects of Cholesterol-Lowering Therapies on C-Reactive Protein
- A Meta-Analysis

INTRODUCTION

Inflammation plays a central role in the progression and destabilization of atherosclerosis that herald cardiovascular events. Modest elevations of plasma markers of in-flammation, such as C-reactive protein (CRP), are associated with future risk of cardiovascular disease and are thought to reflect inflammation in atherosclerosis.

The 5-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) lower cardiovascular risk and have potent anti-inflammatory effects on atherosclerosis. Statins can diminish inflammation by decreasing plasma low-density lipoprotein (LDL) cholesterol and removing pro-inflammatory modified LDL from the artery wall. However, in vitro studies suggest that statins may have non-LDL anti-inflammatory effects. For example, statins also decrease cholesterol-independent isoprenoids and prevent activation of the proinflammatory rho kinase.

In clinical studies, it is difficult to tease the known lipid effects of statins from their potential nonlipid effects. Although the correlations between changes in LDL and CRP are small among individuals within any single study, the intraindividual variation in the measurement of these variables can cloud any true relationships. This variation can be reduced by examining the relationships of average changes among different groups of individuals.

In this study, a novel use of meta-analysis techniques assessed the relationship between group changes in LDL cholesterol and CRP from a variety of statin and nonstatin interventions designed to lower LDL cholesterol. Meta-analysis is usually used to assess clinical outcomes, however, in this study the techniques are used to explore mechanisms of disease to provide insights into the clinical importance of lipid and nonlipid effects of statin therapy.

OBJECTIVES

This study sought to assess the contribution of low-density lipoprotein (LDL)–dependent and LDL–independent effects of LDL-lowering therapies to changes in C-reactive protein (CRP) in healthy or stable subjects.

BACKGROUND

Correlations of change in LDL and CRP in individuals are lowered by their measurement variability. By using average changes in LDL and CRP in study groups, meta-analysis reduces this variability to better assess their correlation.

METHODS

A systematic search for randomized placebo-controlled trials reporting change in LDL and CRP with LDL-lowering interventions retrieved 23 studies with 57 groups treated with a variety of statins, nonstatin drugs, or other regimens. Meta-analysis techniques assessed the relationships between average mean differences (placebo treatment) in change in CRP and LDL.

RESULTS

The overall reduction in CRP was 28% (95% confidence interval 26% to 30%). Significantly greater CRP reduction occurred in statin and statin-ezetimibe interventions, interventions using 80 mg/day of statins, and with greater LDL lowering. Meta-regression analysis showed a strong correlation between the change in LDL and CRP ($r=0.80$, $p<0.001$). Statin therapies had no significant effect on CRP after adjusting for the change in LDL.

Meta-regression analysis was used to assess the relationship of average LDL change and the use of statin therapy to average change in CRP. On univariate analysis, there was a highly significant correlation between change in LDL and change in CRP (regression coefficient or

slope for change in LDL = 0.89, 95% CI 0.70 to 1.09, p<0.001). The variance adjusted correlation between change in LDL and change in CRP was r = 0.80 (p<0.001). On multivariate analysis, there was no significant effect of statin therapy, or any other therapy, on change on CRP after accounting for change in LDL (coefficient for LDL = 1.03, p < 0.001; statin alone therapy = 0.075, p = 0.7; statin-ezetimibe combination = 0.09, p = 0.7; ezetimibe alone = 0.02, p=0.9).

The coefficients for a model of change in CRP as a function of change in LDL, and any statin therapy were used to estimate the proportion of CRP change related to LDL change and non-LDL statin effects across a range of intensity of statin therapy (LDL reduction of 20% to 60%). In this model, 98% to 89% of the CRP reduction was related to LDL reduction and 2% to 11% of CRP change was related to statin effects independent of LDL reduction.

DISCUSSION

This analysis clearly revealed a strong relationship between the change in LDL cholesterol and change in CRP, a marker of inflammation in atherosclerosis. The principal reason that single studies rarely show a correlation between change in LDL and CRP among individual subjects is that any correlation is obscured by measurement error that is largely related to the intraindividual variation in LDL and CRP. In contrast, assessing the relationship between the average change in CRP and LDL across many studies diminishes the diluting effect of intraindividual variation to reveal a strong relationship.

Heterogeneity of net CRP change across studies. The change in CRP was very heterogenous across studies. Average CRP change was greater for statin and statin ezetimibe therapies versus other therapies and with high dose statin therapy. However, the dose-response relationship between change in LDL and change in CRP suggests that it is the greater reduction in LDL with statin and high-dose regimens that account for the treatment differences.

LDL and non-LDL effects of statins on inflammation. In this study, the change in LDL was the predominant factor related to change in CRP. The high correlation between changes in LDL and CRP (r = 0.80) strongly support a causal link between changes in LDL and arterial inflammation in atherosclerosis, and complements histopathological studies in animals and humans using a variety of statin and nonstatin therapies. In these studies, LDL lowering dramatically reduces the content of oxidized LDL in plaque and inflammatory cell density and activity.

Although statins do have non-LDL effects that reduce inflammatory pathways in cell culture and animal experiments, in many studies these require high concentrations of statins that are several log concentrations higher than those achieved with their therapeutic use in humans. If these LDL-independent effects were clinically important (for example, the rho pathway), then statins should decrease CRP more than nonstatin therapies for a similar change in LDL.

This study provides mechanistic insights into the conclusions from an earlier meta-analysis of clinical outcomes in lipid-lowering trials, in which virtually all of the decrease in cardiovascular risk was attributable to the degree of LDL reduction. The lack of any substantial LDLindependent effect of statins on cardiovascular outcomes reflects similar findings on CRP reduction in this study. These results, along with animal and pathology studies, suggest that LDL lowering and inflammation are not separate entities. Rather, LDL lowering is likely a primary driver for the reduction in inflammation that contributes to lower cardiovascular risk.

Measuring change in inflammation in individuals. To consistently observe a change in LDL or CRP in individual patients, the change in these markers needs to be greater than the intraindividual variability. Before statins, LDL lowering was modest in the range of 5% to 15%, and often was obscured in individual patients by measurement variability. With the development of more powerful therapies, with which LDL is lowered by 50% to 60%, a response to therapy is consistently observed. The same cannot be said for CRP. The interindividual variability of CRP is similar in magnitude to the modest change in CRP, even with intensive LDL-lowering therapy. Thus, in clinical studies of statins, 27% to 46% of patients seem to increase their CRP. These are not necessarily nonresponders, but merely patients in whom the whims of variability have obscured the signal of a real change in CRP.

Although the ongoing JUPITER (Randomized Trial of Rosuvastatin in the Primary Prevention of Cardiovascular Events Among Individuals with Low Levels of LDL-C and Elevated levels of CRP) study is incorporating CRP as an independent focus of lipid-lowering therapy, this metaanalysis suggests somewhat paradoxically that LDL reduction may be a more consistent measure of a decrease in inflammation in individual patients receiving LDL lowering therapies.

CONCLUSIONS

In clinical practice, most of the anti-inflammatory effect of LDL-lowering therapies is related to the magnitude of change in LDL. The potential non-LDL effects of statins on inflammation are much smaller in magnitude.

Reference: J Am Coll Cardiol 2007;49:2003–9

Hypertriglyceridemia

THE CLINICAL PROBLEM

Hypertriglyceridemia is a common form of dyslipidemia that is frequently associated with premature coronary artery disease, which is generally defined by the occurrence of a myocardial infarction or the need for a coronary-artery procedure before 55 years of age for men and 65 years of age for women. These upper age limits might increase by 5 to 10 years in nonsmoking men and women. Whether hypertriglyceridemia causes coronary artery disease or is a marker for other lipoprotein abnormalities that cause premature coronary artery disease remains controversial. Specifically, hyper-triglyceridemia correlates strongly with the presence of small, dense particles of LDL cholesterol and reductions in the HDL_2 component of HDL cholesterol, both of which are known to be associated with premature coronary artery disease. Hypertriglyceridemia has been shown to predict coronary artery disease after adjustment for many traditional risk factors, but not after adjustment for LDL or HDL cholesterol sub-fractions.

Several common genetic disorders of hypertriglyceridemia cause premature coronary artery disease. These disorders include familial combined hyperlipidemia, the residual dyslipidemia in patients with well-controlled type 2 diabetes mellitus, and familial hypoalphalipoproteinemia.

Table 1. Effects of Selected Drugs on Triglyceride and Cholesterol Levels.*

Drug	Triglyceride	LDLCholesterol	HDLCholesterol
Alcohol	Increased	No effect	Increased
Estrogens, estradiol	Increased	Decreased	Increased
Androgens, testosterone	Increased	Increased	Decreased
Progestins	Decreased	Increased	Decreased
Glucocorticoids	Increased	No effect	Increased
Cyclosporines	Increased	Increased	Increased
Tacrolimus	Increased	Increased	Increased
Thiazide diuretics	Increased	Increased	Decreased
Beta-blockers	Increased	No effect	Decreased
Sertraline	Possible Increased	Increased	No effect
Protease inhibitors	Increased	No effect	No effect
Valproate and related drugs	Increased	No effect	Decreased
Isotretinoin	Increased	No effect	Decreased

* Alcohol, estrogens, estradiol, glucocorticoids, thiazide diuretics, beta-blockers, sertraline, protease inhibitors, valproate and related drugs, and isotretinoin can cause severe hypertriglyceridemia and the chylomicronemia syndrome in patients with a familial form of hypertriglyceridemia. LDL denotes low-density lipoprotein, and HDL high-density lipoprotein.

Each of these disorders shares features of the metabolic syndrome. Disorders associated with premature coronary artery disease are common: familial combined hyperlipidemia and familial hypoalphalipoproteinemia each affect about 1% of the general population, and type 2 diabetes affects more than 5%. Together, these three disorders have been purported to account for up to 50% of premature coronary artery disease events. These diagnoses therefore warrant aggressive interventions to reduce the cardiovascular risk. In contrast, one other inherited form of hypertriglyceridemia- monogenic familial hyper-triglyceridemia - is not associated with premature coronary artery disease; this disorder also affects up to 1% of the population and must be distinguished from the other disorders in making treatment decisions.

Obesity (in particular, central obesity) is associated with increased triglyceride levels and decreased HDL cholesterol levels. Central obesity paired with insulin resistance is probably a major factor contributing to the dyslipidemia associated with type 2 diabetes, familial combined hyperlipidemia, and familial hypoalphalipoproteinemia. The metabolic syndrome is associated with an increased risk of coronary artery disease even among people who do not have diabetes, but it is unclear whether this is the case when familial combined hyperlipidemia and familial hypoalphalipoproteinemia are absent.

Other abnormalities leading to secondary hypertriglyceridemia include untreated or uncontrolled diabetes, treatment with several medications (Table-1), and alcohol consumption. More complex forms of secondary hypertriglyceridemia develop with hypothyroidism, end-stage renal disease, the nephrotic syndrome, and human immunodeficiency virus infection; these disorders are not covered in this article. Patients with triglyceride levels above 2000 mg per deciliter (22.6 mmol per liter) almost always have both a secondary and a genetic form of hypertriglyceridemia.

STRATEGIES AND EVIDENCE

Evaluation

The evaluation of patients with hypertriglyceridemia should initially focus on whether there is a family history of the condition or a personal or family history of premature coronary artery disease; in addition, potential secondary causes (e.g., medications or untreated diabetes) should be identified. The presence of premature coronary artery disease in a first-degree relative (parent or sibling) or in a sibling of a parent suggests familial combined hyperlipidemia or familial

hypoalphalipoproteinemia and indicates the need to consider drug therapy. Xanthomas are usually not present in mild-to-moderate hypertriglyceridemia; when present, they do not help distinguish the various hypertriglyceridemic disorders. The body-mass index should be calculated, and waist circumference measured. The combination of an elevated triglyceride level and a large waist circumference may be a better marker of insulin resistance and the risk of coronary disease than hypertriglyceridemia alone; the presence of a large waist circumference (defined in European Americans as a value greater than 40 in. [101.6 cm] for men and 35 in. [88.9 cm] for women) may help to distinguish familial hypertriglyceridemia (which is not associated with central adiposity or an increased cardiovascular risk) from familial combined hyperlipidemia or familial hypoal-phalipoproteinemia.

Usually, a fasting lipid profile is the only laboratory work needed to evaluate lipids in a patient with elevated triglyceride levels and premature coronary artery disease. Although nonfasting triglyceride levels have recently been associated with coronary heart disease, the measurement of nonfasting triglyceride levels is not currently recommended because no standard values have been developed and because most of the variation in postprandial triglyceride levels is determined by the fasting level. Patients with familial combined hyperlipidemia may have elevated or normal LDL cholesterol levels. HDL cholesterol levels are reduced in both familial combined hyperlipidemia and familial hypoalphalipoproteinemia.

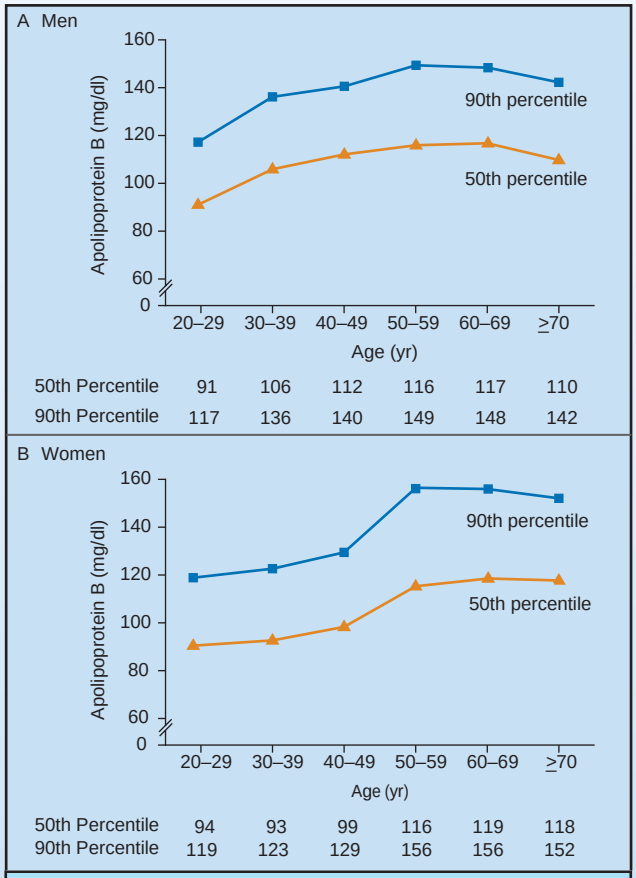

Figure 1. Apolipoprotein B Levels According to Age and Sex. Patients with the metabolic syndrome who have elevated levels of apolipoprotein B (>90th percentile for age) have familial combined hyperlipidemia and should receive aggressive lipid-lowering therapy. The data, which are based on a total of 11,483 participants in the third National Health and Nutrition Examination Survey (1988–1991), are from Carr and Brunzell.

Small, dense LDL particles are also present in both familial combined hyperlipidemia and familial hypoalphalipoproteinemia and, as noted above, have been associated with premature coronary artery disease. In patients with elevated triglyceride levels in the absence of a personal or family history of clinical atherosclerosis, the measurement of apolipoprotein B levels may help to distinguish familial combined hyperlipidemia from familial hypertriglyceridemia. In both disorders, the level of apolipoprotein B can be used to estimate the total number of LDL particles (large and small). Apolipoprotein B levels are higher in familial combined hyperlipidemia and lower in familial hypertriglycieridemia. The nomograms for apolipoprotein B (Figure-1), developed from the third National Health and Nutrition Examination Survey, can be used to define elevated apolipoprotein B as an age- and sex-adjusted value above the 90th percentile. The current National Cholesterol Education Program recommends the measurement of non-HDL cholesterol (which consists of total cholesterol minus HDL cholesterol and includes triglyceride-rich lipoprotein cholesterol) instead of apolipoprotein B. Even though non-HDL cholesterol is a better predictor of cardiovascular risk than LDL cholesterol, several studies have suggested that apolipoprotein B may be an even better predictor than non-HDL cholesterol. Although data from an international study indicate that the ratio of apolipoprotein B to apolipoprotein A-I is highly predictive of early coronary artery disease, the added value of apolipoprotein A-I measurements in refining risk estimates is unclear; consequently, apolipoprotein A-I levels are not routinely measured in clinical practice.

Likewise, measurement of the size or density of LDL particles is currently considered a research tool and is not recommended in routine care. Measurement of Lp(a) lipoprotein levels does not help to distinguish forms of hypertriglyceridemia, but it may be useful in assessing the relative risk of atherosclerosis among patients who have hypertriglyceridemia in combination with other lipid or nonlipid cardiovascular risk factors. However, data that support the routine measurement of Lp(a) lipoprotein levels in patients with normal lipid levels are lacking. Similarly, there are no data to support routine assessment

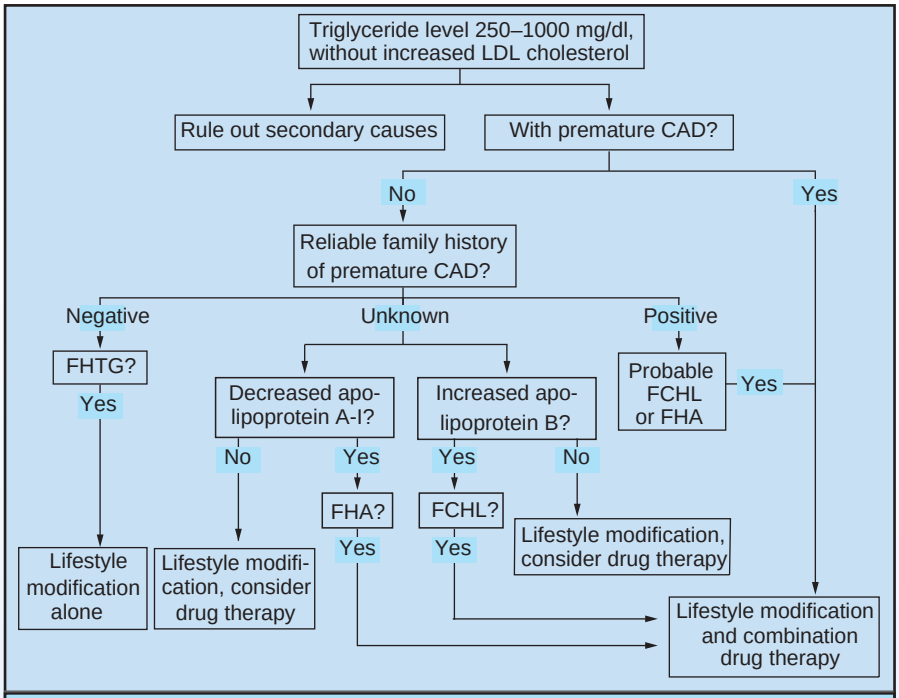

Figure 2. Algorithm for the Diagnosis and Management of Moderate Hypertriglyceridemia.
After secondary causes of hypertriglyceridemia have been ruled out, patients who do not have clinical premature coronary artery disease (CAD) should undergo evaluation, including family history, apolipoprotein B levels, and possibly apolipoprotein A-I levels, to distinguish genetic disorders associated with a risk of premature CAD (familial combined hyperlipidemia [FCHL] and familial hypoalphalipoproteinemia [FHA]) from a genetic disorder that is not associated with an increased risk of premature CAD (familial hypertriglyceridemia [FHTG]). The ultimate diagnosis dictates the form of therapy required. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129.

for subclinical vascular disease (by means of coronary calcium scanning or other types of imaging) in patients with asymptomatic hypertriglyceridemia.

Management

After treatment of secondary disorders and removal of offending medications, lifestyle modification and drug treatment should be considered in a patient with hypertriglyceridemia who is considered to be at risk for premature coronary artery disease (Figure-2). A major question in management is whether therapy should be directed solely toward reduction of triglyceride levels or toward the modification of associated abnormalities of intermediate-density lipoprotein, LDL, and HDL cholesterol. Triglyceride levels greater than 1000 to 1500 mg per deciliter (11.3 to 16.9 mmol per liter) require treatment with fibrates to reduce the risk of pancreatitis. The benefit of treating mild-to-moderate elevations in triglyceride levels is less clear.

Lifestyle Modification

Weight loss results in a mild-to-moderate decrease in triglyceride levels (about 22%) and an increase in HDL cholesterol (about 9%), largely because of an increase in HDL_2 cholesterol (about 43%). The level of small, dense LDL particles may decrease by as much as 40%. Although losing large amounts of weight and maintaining that weight loss are difficult, even moderate weight loss may result in reductions in triglyceride levels and may be maintained with regular aerobic exercise.

Aerobic exercise of moderate intensity with high frequency (about 4 hours per week) has been associated with maintenance of improved cardiorespiratory fitness. It has also been associated with a decrease in intraabdominal fat, an increase in HDL cholesterol levels if those levels were low, and a small decrease in triglyceride levels.

Although a decrease in dietary fat can lead to weight loss (and associated reductions in triglyceride levels), diets that are low in fat but high in carbohydrates may result in reductions in both LDL and HDL cholesterol. Because replacing saturated fat with monounsaturated fat leads to a smaller decrease in HDL cholesterol than replacing saturated fat with carbohydrates, a reasonable approach is to reduce foods rich in saturated fat and replace them with complex carbohydrates and monounsaturated and polyunsaturated fats. It is also advisable to avoid simple sugars, particularly fructose, which has been associated with postprandial hypertriglyceridemia. Fructose is present in many carbonated beverages and fruit juice mixes, and high-fructose corn syrup is added to many prepared foods as a preservative and sweetener. For patients with exercise limitations, the combination of a diet low in saturated fat and a regimen of walking on a daily basis is a lifestyle change that can usually be maintained.

Supplementation with n-3 fatty acids may lower triglyceride levels and, according to some data, reduce cardiovascular events. However, a meta analysis of trials did not show a significant reduction in cardiovascular events or mortality with dietary or pharmacologic n-3 fatty acid supplementation.

Table 2. Pharmacologic Treatment for Hypertriglyceridemia.

Drug Class	Decrease in Triglycerides (%)	Maintenance Regimen	Contraindications	Side Effects	Selective Decrease in Small, Dense LDL Cholesterol	Selective Increase in HDL_2 Cholesterol
Nicotinic acid	17–26	1500–2000 mg once a day	Hypersensitivity, hepatic dysfunction	Flushing, pruritus, nausea, hepatitis (at higher doses), activation of migraine (rare)	Yes	Yes
Fibrates	18–45	Gemfibrozil, 600 mg twice a day; Fenofibrate, 145 mg once a day	Hypersensitivity, hepatic dysfunction, end stage renal disease	Myositis, cholelithiasis	Yes	No
Statins	5	Multiple agents	Hypersensitivity, pregnancy, breast-feeding	Myalgia, influenza-like syndrome, rhabdomyolysis (rare), weakness	No	No
Nicotinic acid and statin	36	Same as for individual agents	Same as for individual agents	Same as for individual agents	Yes	Yes

Cigarette smoking is associated with an earlier occurrence of coronary artery disease, by about 10 years. Discontinuation of smoking is associated with improvement in lipid levels despite the weight gain that often follows cessation.

Alcohol intake is associated with a reduced risk of atherosclerotic cardiovascular disease but also leads to an increase in blood pressure and in the risk of hemorrhagic stroke. Modest alcohol intake (two drinks per day for men and one drink per day for women) is considered acceptable in people who do not have a predisposition for alcohol abuse. Patients with severe hypertriglyceridemia (triglyceride levels above 2000 mg per deciliter) associated with alcohol use should abstain. The limited effect in patients with triglyceride levels below 500 mg per deciliter (5.6 mmol per liter) should not preclude moderate alcohol intake.

Medication

As noted above, no set targets for triglyceride levels are clearly warranted other than to reduce the risk of pancreatitis. Generally, medications are considered in patients with hypertriglyceridemia who have a personal or family history of premature coronary disease. When medications are used, those that specifically decrease the level of small, dense LDL particles and raise the level of HDL_2 particles are preferred (Table-2).

In patients with, or at risk for, premature coronary artery disease, statins are generally considered the first drug of choice to lower LDL cholesterol. Nicotinic acid therapy, often combined with a statin, may be an alternative first choice in patients at risk for premature coronary artery disease. Nicotinic acid decreases the level of small, dense LDL particles and raise the level of HDL_2 particles (Table-2). In the Coronary Drug Project, nicotinic acid resulted in a 15% reduction in the risk of myocardial infarction among men with hypercholesterolemia who had atherosclerosis and decreased total mortality by 10% at 15 years. In the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER) 2 trial, it was also shown to prevent the progression of carotid artery disease in patients with atherosclerosis who were already receiving statin therapy.

Nicotinic acid in combination with other drugs has been shown to be effective in reducing the progression of atherosclerosis in patients with hypertriglyceridemia who are at risk for premature coronary artery disease. For example, in a randomized study involving patients with atherosclerosis, low HDL cholesterol levels, and borderline-high triglyceride levels, the combination of nicotinic acid and simvastatin was associated with a slight regression of coronary stenoses, whereas placebo or antioxidant vitamins were associated with progression. However, neither medication was studied alone, and there were few clinical end points. In another study, involving men with elevated apolipoprotein B levels, nicotinic acid in combination with colestipol reduced the frequency of progression of atherosclerosis as compared with placebo. Nicotinic acid is available in crystalline form and extended-release form. Flushing may be a bothersome side effect, but its frequency may be minimized by education about use.

Fibrates also lower triglyceride levels, but the results of randomized trials have been equivocal in terms of major outcomes, generally showing decreases in the rates of nonfatal myocardial infarction but not in the rates of fatal

coronary events or total mortality. In the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial, the use of gemfibrozil resulted in a significant decrease in the primary outcome of coronary heart disease and nonfatal myocardial infarction, but not in the secondary outcome of fatal myocardial infarction or death from any cause. In a World Health Organization trial, the use of clofibrate in men with hypercholesterolemia resulted in a reduction in the rate of nonfatal myocardial infarction, but there was no decrease in the rate of fatal myocardial infarction or total mortality. Such findings raise questions about the use of a fibrate as a first-line drug for mild-to-moderate hypertriglyceridemia. Gastrointestinal side effects were also common with this therapy; similar findings were reported in another randomized trial of gemfibrozil.

Treatment in Patients with Diabetes

Use of statin therapy to lower LDL cholesterol levels is recommended for adults with type 2 diabetes mellitus who are considered to be at increased risk for coronary artery disease according to the criteria of the American Diabetes Association and the National Cholesterol Education Program. In patients with type 2 diabetes, the combination of statins and fibrates has often been used to treat hypertriglyceridemia. However, in the Fenofibrate Intervention and Event Lowering in Diabetes Trial, use of fenofibrate did not result in a significant reduction in the primary outcome - nonfatal myocardial infarction or fatal coronary heart disease - in patients with type 2 diabetes. A reduction in the rate of nonfatal myocardial infarction was offset by a slight increase in the rate of fatal myocardial infarction.

It has been suggested that nicotinic acid, which may interfere with glucose control, not be used as a first-line drug for the treatment of hypertriglyceridemia in patients with diabetes. However, several trials have demonstrated that nicotinic acid therapy can be used in patients whose diabetes is well controlled, with little effect on glucose levels.

AREAS OF UNCERTAINTY

Without knowledge of the family history, it may be challenging to differentiate patients who are at increased risk for premature coronary artery disease from those who are not. Apolipoprotein B levels, and often LDL cholesterol levels, tend to be higher in familial combined hyperlipidemia than in familial hypoalphalipoproteinemia or familial hypertriglyceridemia, and levels of small, dense LDL particles tend to be lower in familial hypertriglyceridemia than in the other two conditions, but there is considerable overlap among all three. Until the basic biochemical defects for each of the genetic forms of hypertriglyceridemia are defined, decisions about the use of drugs to prevent premature coronary artery disease must be based on the presence or absence of a family history of pre-mature atherosclerosis and dyslipidemia. Once premature coronary artery disease has developed, secondary prevention with lipid-lowering therapy is indicated, and there is no need to differentiate among the types of hypertriglyceridemia. The optimal pharmacologic approach in patients with premature coronary artery disease remains uncertain, including whether it is preferable to start with a statin or to begin with nicotinic acid and add a statin as needed. The role of fibrates also remains unclear.

GUIDELINES

The National Cholesterol Education Program has specific recommendations for target LDL cholesterol levels, but not for target triglyceride levels. Treatment with fibrates is recommended for patients with triglyceride levels over 1000 mg per deciliter in order to decrease the risk of triglyceride-induced pancreatitis. After the target level for LDL cholesterol has been reached, the program recommends lowering triglyceride levels if they are above 200 mg per deciliter (2.6 mmol per liter), although there are no data to support this recommendation.

CONCLUSIONS AND RECOMMENDATIONS

A first step in evaluating patients with hypertriglyceridemia is to obtain an extensive family history, sometimes having the patient do homework to establish the presence of atherosclerosis in one or more family members, the age at onset, and, if an affected first-degree relative has died, the age at and cause of death; a family history will often identify other relatives who might need lipid lowering therapy. A family history of premature coronary artery disease would suggest familial combined hyperlipidemia or familial hypoalphalipoproteinemia. If a patient has many adult relatives with hypertriglyceridemia but without clinical evidence of atherosclerosis, successful treatment of the hypertriglyceridemia and low HDL cholesterol level might be accomplished with lifestyle modifications alone, including a reduced-calorie diet that is low in saturated fat and a program of regular aerobic exercise. If the patient has or is at apparent risk for premature coronary artery disease on the basis of the family history and appears to have familial combined hyperlipidemia or familial hypoalphalipoproteinemia, pharmacologic therapy should be considered in addition to lifestyle modification. Although the optimal therapy is uncertain, in such cases I would favor combined treatment with nicotinic acid and a statin.

Reference :

1. Brunzell JD, Hypertriglyceridemia, N Engl J Med 2007;357:1009-17.

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Cardiology News

Oral Contraceptives Linked to Increased Carotid Plaque

The use of a combination oral estrogen-progestin contraceptive by otherwise healthy young women increases the prevalence of carotid and femoral artery plaques by 20% to 30% for every 10 years of use, the results of a population-based European study show. Investigators conducted a study using a random sample of 2,524 apparently healthy women between the ages of 35 and 55 years old (median age 45.7 years), 81% of whom had taken oral contraceptives for at least 1 year. The median oral contraceptive exposure was 13 years. Women underwent ultrasound imaging studies of their carotid and femoral arteries. Oral contraceptive use increased blood pressure between 4 and 9 mmHg, and there was a trend toward a reduction in HDL cholesterol and an increase in LDL cholesterol. In light of widespread (greater than 80%) and usually prolonged (longer than 10 years) oral contraceptive use, these results suggest that oral contraceptive use could be an important factor in the global atherosclerotic burden. However, women should not discontinue use of the pill solely on the basis of these findings.

American Heart Association's Scientific Sessions 2007

TNF Inhibitor/Methotrexate Combo Cardioprotective in RA

The combination of methotrexate and a tumor necrosis factor (TNF)-inhibitor reduces by 80% the risk of acute myocardial infarction in patients with rheumatoid arthritis. The number one reason for excess mortality in patients with rheumatoid arthritis is heart attacks. Heart attacks in rheumatoid arthritis are caused by systemic inflammation throughout the body. Researchers showed that by suppressing systemic inflammation strongly with a combination of TNF inhibitor-methotrexate therapy, there is a strong beneficial positive effects on inflammation not only in the joints but in the coronary arteries, presumably, which leads to lower heart attacks and deaths from heart attacks.

Annual meeting of the American College of Rheumatology

OTC Naproxen Doesn't Interfere With Aspirin's Cardioprotection

An over-the-counter dose of naproxen sodium does not appear to diminish the antiplatelet effect of low-dose aspirin therapy. According to the investigators, all subjects demonstrated a 99% level of thromboxane (an indicator of platelet inhibition) inhibition after the first 5 days of aspirin therapy alone and the addition of naproxen to low-dose aspirin therapy did not alter the antiplatelet effect seen with aspirin alone. However, in an exploratory analysis of subjects who discontinued naproxen but continued aspirin for 2 days, the majority had serum thromboxane levels of 95% or greater. The effects of discontinuing naproxen after concomitant enteric-coated aspirin therapy need further evaluation.

Annual meeting of the American College of Rheumatology

Longer Term Survival After MI With Cardiogenic Shock Encouraging

Patients with ST-segment elevation myocardial infarction (STEMI) complicated by cardiogenic shock are at very high short-term risk of death. However, those who do survive have a long-term mortality closer to STEMI patients without cardiogenic shock. The researchers also found that predictors of long-term mortality were similar between groups. Patients aged more than 75 years old were at greatest risk. Among other strong predictors were diabetes mellitus, hypertension and previous myocardial infarction. Percutaneous revascularization during the initial hospitalization was associated with a reduced risk of death. The favorable long-term outlook in MI patients with cardiogenic shock, say the investigators was not anticipated.

J Am Coll Cardiol 2007;50:1752-1758.

Editorial Note

Dear Doctor,
We are happy to present the 11th issue of "Insight Heart". It is a small endeavor to provide you compiled & updated information on cardiovascular diseases and its management. This issue is focused on "***Hypertriglyceridemia***". We will appreciate your thoughtful comments to enrich the publication.
Thanks and regards.