REGRESSION OF ATHEROSCLEROSIS: WHERE ARE WE NOW, AND WHERE ARE WE GOING?

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INTRODUCTION

Atherosclerosis is a chronic inflammatory disorder, and lipoproteins are believed to play a critical role in its initiation and progression. Increased levels of atherogenic lipoproteins (low-density lipoprotein [LDL], intermediate-density lipoprotein [IDL], very-low-density lipoprotein [VLDL] remnants, lipoprotein(a) [Lp(a)]), which all contain apolipoprotein (apo) B, are associated with increased development and progression of atherosclerosis. In contrast, high levels of high-density lipoprotein (HDL) are associated with less atherosclerosis, and HDL is thought to play a critical role in reverse cholesterol transport. Therapies that alter lipoprotein metabolism can affect the progression, stabilization, and regression of atherosclerosis, and these effects can be studied by a number of imaging modalities.

QUANTITATIVE CORONARY ANGIOGRAPHY

In the past, studies using quantitative coronary angiography (QCA) have shown chat LDL cholesterol (LDL-C) reduction with statins decreased progression of coronary atherosclerosis and decreased new lesion developmem.[1] The Lipoprotein and Coronary Atherosclerosis Study (LCAS), which was conducted at The Methodist Hospital and St. Luke's Episcopal Hospital in Houston, included 340 patients with evaluable angiography. Patients randomized to fluvastatin were shown to have significantly less angiographic progression, assessed by within-patient per-lesion change in minimum lumen diameter of qualifying lesions, than patients randomized to placebo.[2]

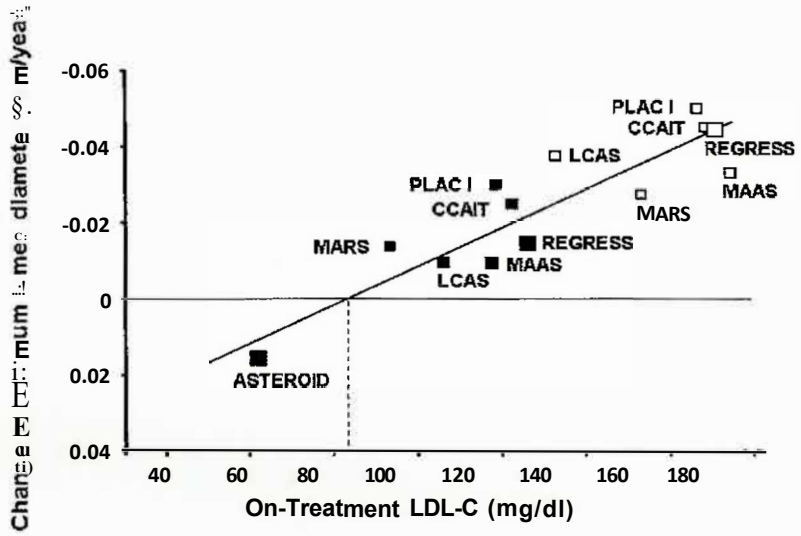

Figure 1. Relation between low-density lipoprotein cholesterol (LOl.:C) achieved and progression of coronary atherosclerosis assessed by quantitative coronary angiography in statin trials.[3,4]

A recently published substudy of A Study to Evaluate the Effect of Rosuvastatin on lntravascular Ultrasound-Derived Coronary Atheroma Burden (ASTEROID) assessed whether rosuvastatin could regress coronary atherosclerosis measured by quantitative coronary angiography.[3] ASTEROID treated 507 coronary disease patients with rosuvastatin 40 mg/d for 24 months. Mean±SD percent diameter stenosis decreased from 37.3±8.4% (median, 35.7%; range, 26–73%) to 36.0± 10.1 % (median, 34.5%; range, 8-74%; p<0.001). Minimum lumen diameter increased from 1.65 ±0.36 mm (median, 1.62 mm; range, 0.56-2.65 mm) to 1.68±0.38 mm (median, 1.67 mm; range, 0.76-2.77 mm; p<0.001). While previous QCA studies showed slowed progression ofatherosclerosis with statin monotherapy, this study demonstrated that rosuvastatin treatment for 24 months to achieve average LDL-C levels well below 70 mg/di, accompanied by significant increases in HDL-C, produced regression of atherosclerosis. The evidence from QCA studies shows that lower LDL-C appears to be better with regard to stopping progression and enhancing regression (Figure 1).[3,4]

INTRAVASCULAR ULTRASOUND

Because angiography images the lumen, early atherosclerosis, characterized by compensatory enlargement of the affected artery, may be underestimated by measures of minimum lumen

diameter and percent diameter stenosis. lntravascular ultrasound (IVUS) has been used in a number of lipid therapy trials since it allows quantitative imaging of the coronary vessel wall and measurement of atherosclerotic disease burden rather than measuring encroachment on the lumen.

In the Reversal Atherosclerosis with Aggressive Lipid Lowering {REVERSAL) trial, IVUS was used to assess progression of coronary atherosclerosis in patients with angiographic evidence of coronary heart disease (CHO). Patients were randomized to treatment with intensive statin therapy (atorvastatin 80 mg) or moderate-intensity therapy (pravastatin 40 mg).5 LDL-C was reduced from a mean baseline of 150 mg/dl to 79 mg/di and 110 mg/dl in the respective treatment groups. For the 502 patients with evaluable IVUS, analysis of the primary endpoint, percent change in atheroma volume at 18-month follow-up, showed significantly less atherosclerotic progression with atorvastatin; progression was not observed in the atorvastacin group (-0.4% change in atheroma volume, p=0.98) but was observed in the pravascatin group (2.7% increase in atheroma volume, p=0.001). Each 10% reduction in LDL-C level was associated with approximately a l% reduction in atheroma volume.

In the primary analysis of ASTEROID, IVUS was used to assess the effect of rosuvastatin 40 mg/d on atherosclerosis in patients with angiographic CHD.6 All patients received rosuvasrarin; IVUS was evaluable in 349 patients. LDL-C was reduced to 61 mg/dl, and HDL-C was increased to 49 mg/di. At 24-month follow-up, percent atheroma volume - one of the primary efficacy outcomes - was reduced by a mean of 0.98% and a median of 0.79%; 64% of patients had regression by chis measure. For the second primary efficacy parameter, change in the 10-mm subsegment wich greatest baseline disease severity, atheroma volume was reduced by a mean of 6.1 mm^3 and a median of 5.6 $mm;^3$ 78.1% of patients had regression by chis measure.

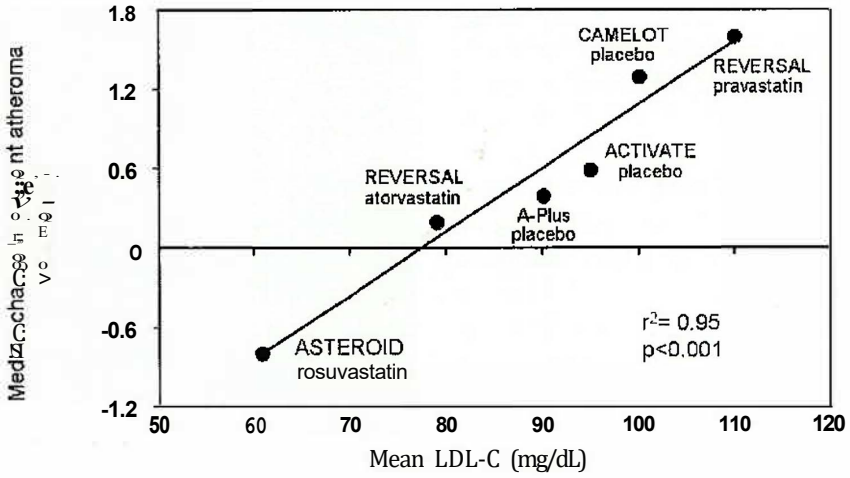

Figure 2. Relation between LDL:-C achieved and progression of coronary atherosclerosis assessed by intravascular ultrasound.6

Both QCA (see Figure l) and IVUS (Figure 2) have shown that more intensive lowering of LDL-C with statins is associated with stabilization and modest regression of plaque. Clinical event trials have also shown that more intensive LDL-C reduction with statins has led to greater event reduction.

NONINVASIVE IMAGING

Although QCA and IVUS provide valuable information, they are invasive modalities and would not be used in primary prevention of CHO or routinely in clinical practice even in patients with CHO. Noninvasive modalities such as ultrasound and magnetic resonance imaging (MRI) have been used in recent studies to image acherosclerotic plaque in patients wirhouc symptomatic atherosclerosis.

Carotid Ultrasound

Imirna-rnedia thickness of the carotid arteries (CIMT) has been correlated with development of future cardiovascular evencs.7 In the Measuring Effects on Intima-Media Thickness: an Evaluation of Rosuvastatin (METEOR) study, B-mode ultrasound was used to assess change in CIMT with rosuvastatin 40 mg versus placebo; the study was conducted in subjects with either age as the only risk factor (mean age 57 years) or a 10-year Framingham risk score <10%, modestly increased CIMT thickening (1.2-3.S mm), and elevated LDL-C (mean 154 mg/dl).8 Mean LDL-C was reduced from 155 mg/di to 78 mg/dl with rosuvastatin. The change in maximum CIMT for 12 carotid sites as assessed by standard B-mode ultrasound showed significant progression in the placebo group (0.0131 mm/year) bur no progression in the rosuvastatin group, indicating that rosuvastatin slowed progression of CIMT compared to placebo in a low-risk, middle-aged population with mild atherosclerosis.

In the Ezetimibe and Simvascarin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE) trial, B-mode ultrasonographic imaging of CIMT and femoral IMT was used to evaluate the effect of the cholesterol absorption inhibitor ezetimibe on atherosclerosis.9 Ultrasound was performed at baseline and 24-month follow-up in 720 patients with familial hypercholesterolemia who were randomized to receive simvastatin 80 mg/d with either placebo or ezetimibe 10 mg/d; 642 patients had evaluable ultrasound assessments. The primary endpoint of mean (±SE) change in CIMT increased by 0.0058±0.0037 mm in the simvastatin-only group and

by 0.0111±0.0038 mm in the simvastatin-plus-ezetimibe group (p=0.29). Although greater reductions in LDL-C and C-reactive protein (CRP) were obtained with combination therapy, combined creatment with simvastatin and ezetimibe did not result in a signif.. icant difference in CIMT compared with simvastatin alone. However, it should be noted that the CIMT was thinner in this trial compared with previous trials and that there was very little change in either group.

Ongoing Clinical Trials at the Center for Cardiovascular Disease Prevention

- **Atherosclerosis Underlying Devdopment Assessed by Intima-Media Thickness in Patients on Rimonabant (AUDITOR).** AUDITOR is a multicenter, double-blind, randomized, placebo-controlled trial that is evaluating the effect of rimonabant, a selective antagonise of CB1 cannabinoid receptors, on carotid atherosclerosis assessed by ulrrasound. The primary endpoint is the change in CIMT at 2.5-year follow-up.
- **Evaluation of Choline Fenofibrate (ABT-335) on Carotid IMT in Patients with T_{ype} IIa and Type IIb Dyslipidernia in the Residual Risk in Addition to Atorvastarin Therapy (FIRS'D.** FIRST is a phase III, multicenter, randomized, double-blind, placebo-controlled trial of ABT-335, a peroxisome proliferator-activated receptor-a (PPAR-a) agonist and a choline salt formulation of fenofibric acid. ABT-335 is more water soluble and has greater bioavailability than fenofibrate; fenofibrate decreases triglycerides and increases HDL-C. The objective of che study is ro evaluate the effect of ABT-335 135 mg or placebo in addition to atorvastatin therapy on CIMT in patients with mixed dyslipidemia. The primary endpoint is the rate of change from baseline of mean posterior wall CIMT of the lefc and right common carotid arteries.

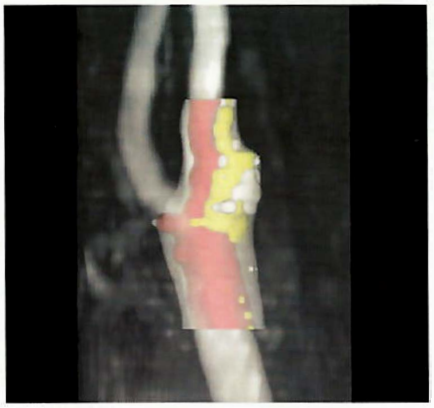

Figure 3. - Three-dimensional MRI image of carotid artery measuring volume of the arterial wall and lipid-rich necrotic core.

Magnetic Resonance Imaging

High-resolution MRI can be used co study the components of plaque as well as plaque volume. Software is used by investigators at the Center for Cardiovascular Disease Prevention ro assess quantitatively che volume of the arterial wall and the volume of the lipid-rich necrotic core (Figure 3).

Ongoing Clinical Trials at the Center for Cardiovascular Disease Prevention

- **Effect of Lipid Modification on Peripheral Arterial Disease after Intervention Trial (ELIMIT).** The hypothesis in ELIMIT is that an aggressive regimen of lipid-modifying therapy will inhibit the progression of atherosclerosis in femoral arteries and reduce the incidence of restenosis in femoral arteries following endovascular intervention through decreasing thrombosis and inflammation. This prospective, randomized, double-blind, placebo-controlled, intention-to-treat clinical trial will recruit 100 patients with symptomatic femoral artery occlusive disease in one leg. The patients will be randomized co either standard medical care or aggressive lipid modification therapy {simvastatin 40 mg, extended-release niacin 1,500 mg, and ezetimibe 10 mg) that increases HDL-C (target >40 mg/di) and decreases LDL-C (target <80 mg/di) and triglycerides (target <150 mg/di). Patients will be followed for two years, and the primary outcome of the trial is to determine the effect of aggressive lipid modification on progression of atherosclerosis and restenosis of femoral arceries assessed by MRI.
- Dal-P1aque. Positron emission tomography/computed tomography (PET/CT) and MRI will be used to evaluate the effect of dalcetrapib, a new cholesteryl ester transfer protein (CETP) inhibicor that increases HDL-C, on carotid plaque in patients with CHO. This phase 116, double-blind, randomized, placebo-controlled, multicenter study has a 24-month follow-up. The primary endpoints are the inflammatory activity of plaque after six months of treatment with dalcetrapib, assessed by PET/CT, and plaque size and burden after 12 months of treatment, assessed by MRI.

CONCLUSION

Imaging trials have proven useful in studying the effects of statin therapy on the progression, stabilization, and regression of atherosclerosis. Evaluation of newer therapies that produce greater effects on HDL-C and triglycerides will involve multimodal imaging to examine changes in plaque burden and plaque composition along with clinical outcome srudies of much greater size and duration.

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NEWS

DEBAKEY HEART CENTER UPDATE

METHODIST BEGINS NOVEL STEM CELL TRIAL FOR HEART FAILURE

The Methodist Hospital in Houston, Texas is the first site in the nation to enroll patients in a new study that uses a patient's own stem cells to treat heart failure.

Surgeons at the Methodist DeBakey Heart & Vascular Center will inject stem cells derived from a patient's own bone marrow directly into the beating heart to treat dilated cardiomyopathy (DCM).

"Some patients have such severe heart failure that their only current option is a heart transplant," said Dr. Brian Bruckner, cardiac surgeon at the Methodist DeBakey Heart & Vascular Center in Houston. "We hope that stem cells will stimulate angiogenesis, the growth of new blood vessels, in diseased heart tissue, and return patients to a much better quality of life without a transplant."

In the operating room, Dr. Bruckner makes three small incisions and then administers approximately 30 injections of highly-concentrated stem cells into the left side of the patient's heart.

There are currently 5.5 million people in the United States suffering from chronic heart failure. A subset of these patients has DCM, a chronic heart disease in which the patient's heart can not pump effectively enough to deliver blood and oxygen to the vital organs in the body. Patients with DCM typically experience severe limitations to physical activity and shortness of breath.

"Without a new approach to treatment of these patients, they will continue to decline and less than 40 percent will survive five years," said Bruckner, principle investigator for the trial. "We hope this trial will provide a completely new and viable treatment for them."

Dr. Michael Reardon, chief of cardiac surgery at Methodist, and Dr. Matthias Loebe, transplant surgeon at Methodist, are co-investigators on the trial.

About the trial

The IMPACT-DCM trial is a randomized, controlled, prospective, open-label, Phase I study that will seek to enroll 20 patients with ischemic dilated cardiomyopathy (DCM) and 20 patients with non-ischemic DCM at five clinical sites in the United States. The trial is sponsored by Aastrom Biosciences, Inc.

Participants must have a left ventricular ejection fraction of less than or equal to 25 percent (60-75 percent is typical for a healthy person) and meet certain other eligibility criteria.

All patients in each group will receive standard medical care and 75 percent of the patients will be treated with cardiac repair cells (CRC), a mixture of stem cells and progenitor cells derived from the patient's own blood marrow, through direct injection into the heart muscle during a minimally-invasive procedure in the operating room.

While the primary objective of this study is to assess the safety of CRCs in patients with DCM, efficacy measures including left ventricular ejection fraction and other cardiac function parameters as well as heart failure stage will be monitored. Patients will be followed for 12 months post treatment.