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#### Target Audience

This educational activity is designed for primary care physicians, endocrinologists, cardiologists, internists, and other healthcare professionals involved in the diagnosis and management of dyslipidemia and its comorbidities.

#### Learning Objectives

With information from the latest evidence-based studies, participants should be able to:

- Ascertain whether statin-associated adverse events are proportional to LDL-C reduction.
- Evaluate the efficacy and safety of long-term statin therapy in children with familial hypercholesterolemia, as well as the relation between the age of statin initiation and carotid IMT.
- Characterize no evidence of interaction observed between clopidogrel and any type of statins when administered concomitantly to high-risk patients.

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CLINICAL INSIGHTS® IN

# LIPID Management

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## The Magnitude of Lipid Lowering Is Not Related to the Risk of Elevated Liver Enzymes, Rhabdomyolysis, and Cancer

**R**educing low-density lipoprotein cholesterol (LDL-C) has been considered as a primary choice of lipid management in reducing cardiovascular risk. Among the currently available lipid-altering medications, statins are the most effective in LDL-C lowering. Recent national guidelines also recommended the use of higher doses of statins to achieve greater LDL-C reduction. Although studies from large-scale statin trials have demonstrated that a significant improvement in cardiovascular risk reduction can be achieved by more intensive LDL-C-lowering management, concerns have been raised about statin-associated higher rates of adverse events, including increased liver enzymes and rhabdomyolysis. In addition, lower levels of cholesterol have also been associated with an increased incidence of cancer.

To determine whether statin-associated adverse events are proportional to LDL-C reduction, Alsheikh-Ali and colleagues assessed the relationship between the magnitude of LDL-C lowering and rates of elevation of liver enzymes, rhabdomyolysis, and cancer in large, randomized statin trials.

A total of 23 statin treatment arms with 309,506 person-years of follow-up were identified by MEDLINE search. Adverse events reported in these large, prospective, randomized statin trials were evaluated. LDL-C lowering was measured by percent or absolute reduction, as well as LDL-C levels achieved by statin treatment. The relationship between LDL-C lowering and rates of elevated adverse events per 100,000 person-years was assessed using weighted univariate regression.

In primary analysis, no significant relationship was observed between percent LDL-C reduction and rates of elevated liver enzymes ( $R^2 < 0.001$ ;  $P = 0.91$ ) or rhabdomyolysis ( $R^2 = 0.05$ ;  $P = 0.16$ ). Similar results were obtained when absolute LDL-C reduction or achieved LDL-C levels were considered for additional analyses.

In contrast, there was a positive and graded relationship between rates of elevated liver enzymes

and statin dose. A significantly higher rate of elevated liver enzymes for each 10% LDL-C reduction was observed when higher statin doses were used, as compared with intermediate or low doses of statins administered. Similar findings were obtained when individual statins were evaluated. For instance, the rate of elevated liver enzymes was 1.6 times greater with higher doses of simvastatin (80 and 40 mg) than with low-dose simvastatin (20 mg;  $P = 0.006$ ). The relationship between risk of rhabdomyolysis and statin dose was not evaluated because of the small number of rhabdomyolysis cases identified.

The secondary analysis in this study was to assess the relationship between LDL-C lowering and newly diagnosed cancer. Similar to the risk of liver enzymes and rhabdomyolysis, there was no significant

relationship between new cases of cancer and percent LDL-C reduction ( $R^2 = 0.09$ ;  $P = 0.92$ ) or absolute LDL-C reduction ( $R^2 = 0.05$ ;  $P = 0.23$ ). However, an unexpected and disturbing significant inverse association was observed between cancer incidence and achieved LDL-C levels ( $R^2 = 0.43$ ;  $P = 0.009$ ).

Alsheikh-Ali and associates concluded from their findings that the risk of statin-associated elevation of liver enzymes or rhabdomyolysis is not related to the magnitude of LDL-C lowering, but rather is associated with dose-specific effects. They further suggested that drug- and dose-specific effects are more important determinants of liver and muscle toxicity than magnitude of LDL-C lowering. The risk of cancer is, however, significantly related to lower achieved LDL-C levels. The investigators indicated that the finding of an inverse relationship between cancer incidence and LDL-C levels achieved by statin treatment is exploratory and hypothesis-generating, and requires further investigation.

Alsheikh-Ali AA, Maddukuri PV, Han H, Karas RH. Effect of the magnitude of lipid lowering on risk of elevated liver enzymes, rhabdomyolysis, and cancer: insights from large randomized statin trials. *J Am Coll Cardiol.* 2007;50(5):409-418.

*These researchers assessed the relationship between the magnitude of LDL-C lowering and rates of elevation of liver enzymes, rhabdomyolysis, and cancer.*

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**Post-Test Question 1**

Based on the findings of this study, which of the following statements regarding the risk of statin-associated adverse events is incorrect?

- The risk of statin-associated elevation of liver enzymes and rhabdomyolysis is not significantly related to the percent reduction of LDL-C
- The risk of cancer is inversely associated with LDL-C levels achieved by statin treatment
- The risk of elevated liver enzymes is negatively associated with statin dose administration
- The risk of statin-associated elevation of liver enzymes and rhabdomyolysis is not significantly related to achieved LDL-C levels

**COMMENTARY**

JOHN C. LaROSA, MD, President of SUNY Downstate Medical Center, Brooklyn, New York. Education Council Member, Committee on Cardiovascular and Metabolic Diseases™ (CCMD™)

*In this meta-analysis of several large statin trials published through the end of 2005, the authors examine side effects of both statin dose and LDL lowering. The latter is measured by absolute and percent drop in LDL cholesterol (LDL-C), as well as by achieved LDL-C levels. Rhabdomyolysis cases were too infrequent for study. Elevated liver enzymes were more related to statin doses than to LDL-C changes. New cancer cases, however, were most closely related to achieved LDL-C levels. No single form of cancer predominated.*

*This finding is in keeping with older observational studies showing an association between naturally very-low cholesterol levels and increased cancer risk. The clinical significance of this finding is unclear. It could be because of a chance observation, the result of surviving atherosclerosis long enough to develop cancer (although the average length of the trials was only about 5 years), or some unknown drug-induced biologic effect that adversely affected cell biology. Observations like this, however, can only be hypothesis-generating. They have no direct clinical application. They should not be a cause for restricting LDL-lowering therapy, which has now been conclusively demonstrated to lower both morbidity and mortality from atherosclerotic vascular disease.*

**No Evidence of Interaction Between Clopidogrel and Statin: the CHARISMA Trial**

Clopidogrel, an antiplatelet agent, is often coadministered with statins to patients with atherosclerosis. Clopidogrel and several statins—in particular, lipophilic statins—also share the same metabolic pathway and are predominantly metabolized by cytochrome P450 3A4 isoenzyme (CYP3A4). Therefore, any negative interaction between clopidogrel and statin may adversely affect the management of cardiovascular disease. For instance, statins may reduce the metabolism of clopidogrel to its active metabolite and thus diminish the clinical efficacy of clopidogrel. In that conflicting data have been reported from previous investigations regarding the possibility of this interaction, Saw and colleagues aimed to evaluate the potential impact of clopidogrel and statin interaction in a randomized placebo-controlled trial with long-term follow-up.

The Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial was a prospective, multicenter, double-blind, randomized placebo-controlled trial comparing long-term treatment of 75 mg/day clopidogrel versus placebo in patients at high risk for cardiovascular events. All patients were ≥45 years old and received low-dose aspirin. The primary efficacy end point was the first occurrence of myocardial infarction, stroke, or cardiovascular death at median follow-up of 28 months. A secondary analysis was performed by evaluating the interaction of clopidogrel versus placebo according to 2 types of statin administration at baseline: statins that are predominantly metabolized by CYP3A4 (including CYP3A4-MET, atorvastatin, lovastatin, and simvastatin) and others that are not CYP3A4 metabolized (including non-CYP3A4-MET, pravastatin, and fluvastatin). The primary safety end point was major bleeding.

Of 15,603 patients enrolled in the CHARISMA trial, 10,078 received a statin at baseline (8,245 CYP3A4-MET, 1,748 non-CYP3A4-MET) and 5,496 had no history of statin therapy before randomization. A total of 7,802 and 7,801 patients were randomized to clopidogrel and placebo, respectively.

Study results showed that 6.8% of the patients on clopidogrel sustained the primary end point compared with 7.3% with placebo (hazard ratio [HR] 0.93;  $P=0.23$ ). These results were similar among patients with either type of statin administration at baseline, CYP3A4-MET (5.9% clopidogrel, 6.6% placebo, HR 0.89;  $P=0.18$ ) or non-CYP3A4-MET (5.7% clopidogrel, 7.2% placebo, HR 0.78;  $P=0.19$ ). Additionally, there was no significant interaction between statin types and randomized treatment ( $P=0.69$ ). A similar primary efficacy end point was also observed when patients were treated with atorvastatin ( $n=4,127$ ) (5.7% clopidogrel, 7.1% placebo, HR 0.80;  $P=0.06$ ) or pravastatin ( $n=1,440$ ) (5.1% clopidogrel, 7.0% placebo, HR 0.72;  $P=0.13$ ) together with clopidogrel. Moreover, there was no difference in the primary safety end point of major bleeding among all study groups.

Saw and associates concluded that no evidence of interaction was observed between clopidogrel and any type of statins, CYP3A4-MET or non-CYP3A4-MET, when they were administered concomitantly to patients with high risk of cardiovascular events.

Saw J, Brennan DM, Steinhubl SR, et al, for the CHARISMA Investigators. Lack of evidence of a clopidogrel-statin interaction in the CHARISMA trial. *J Am Coll Cardiol.* 2007;50(4):291-295.

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#### **Post-Test Question 2**

Based on the findings in the CHARISMA trial, the primary efficacy end point with clopidogrel or placebo in patients with CYP3A4-MET statin administration was:

- a. 5.9% with clopidogrel, 6.6% with placebo
- b. 5.9% with clopidogrel, 2.6% with placebo
- c. 2.9% with clopidogrel, 6.6% with placebo
- d. None of the above

#### **COMMENTARY**

PATRICK McBRIDE, MD, MPH, Professor of Medicine & Family Medicine; Associate Dean for Students and Associate Director, Preventive Cardiology Program, University of Wisconsin School of Medicine and Public Health in Madison, Wisconsin. Faculty Member, Committee on Cardiovascular and Metabolic Diseases™ (CCMD™).

*This important study demonstrates that clopidogrel is both safe and effective with statins, regardless of statin metabolism. This study from the important CHARISMA trial provides the vital information that for patients at high risk for atherothrombotic events, the combination of statins and clopidogrel had no effect on the benefits or risk of clopidogrel. Even for statins that were metabolized by the cytochrome P450 system, no differences in the effectiveness of clopidogrel was noted in the crucial outcomes of combined myocardial infarction, stroke, and cardiovascular death. There were no differences in bleeding in any of the treatment groups compared to placebo.*

*This provides randomized clinical trial evidence that the patients still received the benefits of clopidogrel without a difference in side effects or any negative outcomes. Although this study was a post-hoc analysis, it is important to many patients who are at high-risk and the physicians who care for them. This study is reassuring, uses important endpoints, and is definitive, despite earlier small studies suggesting concerning interactions.*

## **Early Initiation of Statin Treatment in Children with Familial Hypercholesterolemia: the Younger, the Better**

Familial hypercholesterolemia (FH), a common monogenetic disorder, is characterized by severely elevated low-density lipoprotein cholesterol (LDL-C) from birth. It affects approximately 1 in 500 individuals and causes premature atherosclerosis and cardiovascular disease. Children with FH are often associated with increased carotid intima-media thickness (IMT). It was suggested that initiation of statin treatment at a young age in children with FH would delay the onset of cardiovascular events in adolescence. Rodenburg and colleagues, investigators of the current study, have previously demonstrated in a randomized placebo-controlled trial that 2-year pravastatin treatment reduced the progression of carotid IMT in 8- to 18-year-old children with FH.

To further evaluate the efficacy and safety of long-term statin therapy in children with FH, as well as the relation between the age of statin initiation and carotid IMT, the investigators conducted this follow-up study on children who initially participated in the placebo-controlled trial.

All 214 children who participated in the original placebo-controlled study were eligible for the follow-up study. Despite previous treatment with statin or placebo, all children received pravastatin 20 or 40 mg, depending on their age (<14 years, 20 mg; ≥14 years, 40 mg). The duration of follow-up was at least 2 years after completion of the original placebo-controlled study. Mean duration of statin treatment was 4.5 years (range: 2.1 to 7.4 years). Blood samples were taken on a regular basis for lipids and safety parameters, and a carotid IMT measurement was performed after an average

treatment period of 4.5 years. Follow-up data for 186 children were available for the statistical analyses.

Multivariate analyses revealed that age at statin initiation was an independent predictor for carotid IMT after follow-up on statin treatment, with adjustment for potential confounders, such as carotid IMT at initiation of statin treatment, sex, and duration of treatment. Early initiation of statin treatment was associated with a subsequently lesser IMT. Carotid IMT after follow-up is predicted to increase 0.003 mm for each year in FH patients if statin therapy is postponed.

None of the subjects had cardiovascular complaints or a cardiovascular event during the follow-up. Moreover, no serious laboratory adverse events were reported during follow-up, and statin treatment had no untoward effects on sexual maturation or growth in young children and adolescents.

Rodenburg and associates concluded that early initiation of statin therapy in children with FH delayed the progression of carotid IMT and might be beneficial in the prevention of atherosclerosis in later life. The finding of favorable safety further supported the concept of early initiation of statin treatment in childhood. The investigators recommended that statin treatment be initiated for all children older than 8 years when FH is diagnosed.

Rodenburg J, Vissers MN, Wiegman A, et al. Statin treatment in children with familial hypercholesterolemia: the younger, the better. *Circulation*. 2007;116(6):664-668.

#### **Post-Test Question 3**

Based on this study, at which of the following stages are children with FH recommended to be initiated with a statin therapy?

- a. At birth
- b. Children older than 8 years once FH is diagnosed
- c. Wait till adulthood
- d. Wait till adolescence