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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:

- Outline the efficacy of statin therapy on the reduction in major vascular events in patients with diabetes
- Describe the role of extreme lipoprotein(a) levels in the prediction of risk of myocardial infarction in the general population
- Access the impact of triglyceride levels on coronary heart disease risk after an acute coronary syndrome

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**Grantor**

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**PPS Staff Disclosures**

Natasha K. McIntyre, Associate Program Manager; Elizabeth Ward, CME Director; Wade'ah Terry, CME Manager; Al Tauriello, Associate Editor; and Caroline Tredway, Editorial Director, have all indicated no relevant financial relationships.

**Off-Label Disclosure**

Some of the drug treatments discussed in this issue may note uses not approved by the Food and Drug Administration. Such uses will be noted at the end of the article.

CLINICAL INSIGHTS<sup>®</sup> IN

# LIPID Management

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## Efficacy of Statin Therapy on Major Vascular Events in Patients With Diabetes: A Meta-Analysis

Both type 1 and type 2 diabetes are associated with increased risk of atherosclerotic vascular disease. Prevention of occlusive vascular events is considered a high priority in the management of patients with diabetes. Reports from the Cholesterol Treatment Trialists' (CTT) Collaboration study indicate that lowering low-density lipoprotein cholesterol (LDL-C) by 1 mmol/L (39 mg/dL) with statin therapy decreases the risk of major vascular events in a wide range of high-risk participants. There are, however, uncertainties about the effects of statins on specific outcomes of major coronary events, and whether statin effects depends on the type of diabetes, lipid profile, history of occlusive vascular disease, or other factors in the patient.

To resolve these uncertainties, the CTT collaborators conducted a prospective meta-analysis of 14 trials of statin therapy involving only 18,686 patients with diabetes (1,466 with type 1 and 17,220 with type 2). The effects of statins on clinical outcomes per 1 mmol/L (39 mg/dL) reduction in LDL-C were evaluated.

During a mean follow-up of 4.3 years, 3,247 major vascular events were identified in patients with diabetes. A 9% proportional reduction in all-cause mortality per mmol/L reduction in LDL-C was seen in patients with diabetes (rate ratio [RR] 0.91, 99% confidence interval [CI], 0.82–1.01;  $P=0.02$ ), which was similar to the 13% reduction in those without diabetes (RR 0.87, 99% CI, 0.82–0.92;  $P<0.0001$ ). The reduction in mortality in patients with diabetes was a result of significant reduction in vascular mortality (RR 0.87, 99% CI, 0.76–1.00;  $P=0.008$ ), and

not in non-vascular mortality (RR 0.97, 99% CI, 0.82–1.16;  $P=0.70$ ).

Among patients with diabetes, a significant 21% proportional reduction in major vascular events per mmol/L reduction in LDL-C was observed (RR 0.79, 99% CI, 0.72–0.86;  $P<0.0001$ ), which was similar to the effect seen in those without diabetes (RR 0.79, 99% CI, 0.76–0.82;  $P<0.0001$ ). Similar reductions were also observed in specific outcomes of major vascular events, including myocardial infarction

or coronary death, coronary revascularization, and stroke. The reduction effect on each outcome was not dependent on the diabetic status of the patient. Moreover, the proportional reductions in major vascular events by statins were much the same among patients with diabetes, irrespective of whether there was a prior history of vascular disease or hypertension, and independent of patient's lipid profiles and other baseline risk factors. After 5 years of follow-up, 42 (95% CI 30–55) fewer patients with diabetes had major vascular events per 1,000 allocated statin therapy.

The investigators concluded that the proportional benefits of statin therapy on major vascular events were similar in a wide range of individuals with or without diabetes, and a statin regimen should be considered for all people with diabetes who are at sufficiently high risk of vascular events.

Kearney PM, Blackwell L, Collins R, et al. Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomized trials of statins: a meta-analysis. *Lancet*. 2008;371(9607):117-125.

*Reports from the CTT study indicate that lowering LDL-C by 1 mmol/L (39 mg/dL) with statin therapy decreases the risk of major vascular events in a wide range of high-risk participants.*

<sup>a</sup> Dr Libby has indicated financial relationships as noted: consultant for AstraZeneca, GlaxoSmithKline, Schering-Plough, Merck & Co., Inc., Kowa Pharmaceutical Company Ltd., Novartis AG, and Pfizer Inc. Dr Libby does not accept remuneration from drug manufacturers.

<sup>b</sup> Dr Blevins has indicated financial relationships as noted: consultant for sanofi-aventis, Merck & Co., Inc., Novo Nordisk, Eli Lilly and Company, AstraZeneca, Abbott Laboratories, Medtronic, Inc.; clinical research for Eli Lilly and Company, Amylin Pharmaceuticals, Inc., and Medtronic, Inc.

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## Post-Test Question 1

Based on the findings of this study, proportional reduction in major vascular events per mmol/L reduction in LDL-C by statin therapy among patients with diabetes was:

- 60%
- 40%
- 21%
- 9%

## Commentary

THOMAS C. BLEVINS, MD, Director, Texas Diabetes & Endocrinology. Faculty Member, Committee on Cardiovascular and Metabolic Disease™ (CCMD™).

The number of people with diabetes is growing relentlessly. It is associated with an increased risk of vascular disease and is considered a coronary heart disease (CHD) equivalent. Preventing vascular events in patients with diabetes is a healthcare priority. It is safe to say that in clinical practice we see more patients with CHD risk equivalence, such as diabetes, than patients who have documented CHD.

This meta-analysis by the Cholesterol Treatment Trialists' Collaborators analyzed the outcomes in 14 statin trials that included only patients with diabetes or a subgroup of patients with diabetes. Some of the more familiar trials included the Heart Protection Study (~6,000 patients with diabetes) and the CARDS trial (~3,000 patients with diabetes).<sup>1,2</sup> They found a 9% reduction in all-cause mortality in patients treated with statins per the modest reduction of 1 mmol/L (39 mg/dL) in low-density lipoprotein cholesterol (LDL-C) and a 21% reduction in major vascular events (including myocardial infarction, CHD death, coronary revascularization, and stroke) per mmol/L reduction in LDL-C. The benefit of statin therapy in people with diabetes was observed irrespective of whether vascular disease was present or absent at baseline, and was independent of a patient's lipid profile and other baseline risk factors. Benefits were also seen in patients in the lowest tertile of baseline LDL-C, and larger reductions in LDL-C were associated with greater proportional reductions in major vascular events.

This study lends yet more strength to the current guidelines for statin therapy in diabetes.<sup>3</sup> Further, I agree with the author's conclusion of this paper: "Statin therapy [in diabetes] is only likely to be inappropriate when there are compelling reasons to avoid such treatment..." In other words, all patients with diabetes stand to benefit and are candidates for statin therapy except those with contraindications. Further, it appears that there is *no* controversy regarding the benefit of statins in reducing events in our growing number of patients with diabetes, and we should continue to educate these patients on this topic.

1. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. *Lancet*. 2003;361(9374):2005-2016.

2. Colhoun HM, Betteridge DJ, Durrington PN, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicenter randomised placebo-controlled trial. *Lancet*. 2004;364(9435):685-696.

3. American Diabetes Association. Standards of medical care in diabetes—2008. *Diabetes Care*. 2008;31(suppl 1):S12-S54.

## Extreme Lipoprotein(a) Levels Predict Risk of MI in the General Population: the Copenhagen City Heart Study

Lipoprotein(a) (Lp[a]), which is composed of a low-density lipoprotein (LDL) bound to plasminogen-like apolipoprotein(a), is associated with increased risks of atherosclerosis, myocardial infarction (MI), and ischemic heart disease (IHD). The use of lipoprotein(a) as a risk factor for MI and IHD in clinical practice, however, has not been established.

In the present study, Kamstrup and colleagues proposed to test the hypothesis of using extreme Lp(a) levels to predict the risks of MI and IHD in the general population. The Copenhagen City Heart Study, a prospective study of the Danish general population, included 9,330 men and women. The study involved measuring Lp(a) levels at baseline shortly after sampling, correcting for regression dilution bias, and calculating hazard ratios. In addition, absolute risk estimates for MI and IHD as a function of extreme Lp(a) levels in the general population was also evaluated.

During 10 years of follow-up, 498 participants developed MIs. A stepwise increment in risks of

MI and IHD with increasing levels of Lp(a) was observed in both men and women. In women, multifactorial adjusted hazard ratios for MI for elevated Lp(a) levels were 1.1 (95% confidence interval [CI], 0.6 to 1.9) for 5 to 29 mg/dL (22nd to 66th percentile), and 3.6 (95% CI, 1.7 to 7.7) for >120 mg/dL (>95th percentile) versus levels <5 mg/dL (<22nd percentile). Equivalent values in men were 1.5 (0.9 to 2.3) and 3.7 (1.7 to 8.0). Thus, a 3- to 4-fold increase in risk of MI can be predicted from extreme Lp(a) levels (>95th percentile) in both genders.

The increase in absolute 10-year risks of MI and IHD with elevating Lp(a) levels is more evident in men than in women, and with smoking, hypertension, and increasing age. Absolute 10-year risks of MI were 10% and 20% in smoking, hypertensive women aged >60 years with Lp(a) levels of <5 mg/dL and ≥120 mg/dL, respectively. Equivalent values in men were 19% and 35%. In general, similar but attenuated results were observed for risk for IHD.

## Extreme Lipoprotein(a) Levels Predict Risk of MI in the General Population: the Copenhagen City Heart Study

The authors concluded that extreme Lp(a) levels are an important risk factor for MI and IHD in both genders. It predicts a 3- to 4-fold increase in risk of MI in the general population, and absolute 10-year risks of 20% and 35% in high-risk women and men, respectively.

Kamstrup PR, Benn M, Tybjaerg-Hansen A, et al. Extreme lipoprotein(a) levels and risk of myocardial infarction in the general population: the Copenhagen City Heart Study. *Circulation*. 2008;117(2):176-184.

### Post-Test Question 2

Based on the data in the Copenhagen City Heart Study, which of the following statements regarding the extreme Lp(a) levels is *false*?

- Extreme Lp(a) levels predict a 3- to 4-fold increase in risk of MI in the general population
- Extreme Lp(a) levels do not predict absolute 10-year risks of MI
- A stepwise increase in risk of MI is associated with increasing levels of Lp(a)
- Extreme Lp(a) levels predict risk of IHD in the general population

## Impact of Low TG Levels on CHD Risk After Acute Coronary Syndrome: the PROVE IT-TIMI 22 Trial

It is widely accepted that combined hyperlipidemia—elevated low-density lipoprotein cholesterol (LDL-C) and triglycerides (TG)—increases coronary heart disease (CHD) risk to a significantly greater extent than either high LDL-C or TG alone. Further, the PROVE IT-TIMI (Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction) 22 trial showed that LDL-C <70 mg/dL is associated with greater CHD event reduction than LDL-C <100 mg/dL after an acute coronary syndrome (ACS). The purpose of the present study was to assess whether low on-treatment levels of TG (<150 mg/dL), when added to low LDL-C (<70 mg/dL), have a better control than low LDL-C alone in reducing CHD events in patients after ACS.

The study population originated from the PROVE IT-TIMI 22 trial. A total of 4,162 patients hospitalized for ACS were randomly assigned to receive intensive therapy (atorvastatin 80 mg daily) or standard therapy (pravastatin 40 mg daily). The relationship between on-treatment levels of TG and LDL-C and the composite end point of death, myocardial infarction (MI), and recurrent ACS was assessed 30 days after initial presentation, with a mean follow-up period of 2 years.

Patients achieving low on-treatment TG (<150 mg/dL) had fewer CHD events (13.2%)

than those with higher TG ( $\geq 150$  mg/dL; 17.6%) in a univariate analysis (hazard ratio [HR] 0.73, 95% confidence interval [CI] 0.62 to 0.87;  $P < 0.001$ ) or after multifactorial adjustment (HR 0.80, 95% CI 0.66 to 0.97;  $P = 0.025$ ). Further reduction in CHD risk was observed when both low on-treatment TG and LDL-C <70 mg/dL were achieved (HR 0.72, 95% CI 0.54 to 0.94;  $P = 0.017$ ).

Each 10-mg/dL decrement in on-treatment TG was associated with a 1.4% to 1.6% reduction in the incidence of death, MI, and recurrent ACS after adjustment of covariates. A 41% reduction in CHD risk was observed when three parameters—low on-treatment TG and LDL-C and C-reactive protein (<2 mg/L)—were achieved in patients receiving statin therapy after ACS (HR 0.59, 95% CI 0.41 to 0.83;  $P = 0.002$ ).

Miller and colleagues concluded that low on-treatment TG was associated with a lower risk of recurrent CHD events independent of the LDL-C level, and suggested that achieving low TG (<150 mg/dL) may be an additional important therapeutic parameter beyond low LDL-C (<70 mg/dL) in patients after ACS.

Miller M, Cannon CP, Murphy SA, et al; PROVE IT-TIMI 22 Investigators. Impact of triglyceride levels beyond low-density lipoprotein cholesterol after acute coronary syndrome in the PROVE IT-TIMI 22 trial. *J Am Coll Cardiol*. 2008;51(7):724-730.

### Post-Test Question 3

Based on the results in the PROVE IT-TIMI 22 trial, what levels of TG and LDL-C had significant impacts on the reduction in CHD events in patients receiving statin therapy after ACS?

- TG <150 mg/dL, LDL-C <70 mg/dL
- TG <150 mg/dL, LDL-C  $\geq 70$  mg/dL
- TG  $\geq 150$  mg/dL, LDL-C <70 mg/dL
- TG  $\geq 150$  mg/dL, LDL-C  $\geq 70$  mg/dL