



CLINICAL INSIGHTS® IN LIPID Management

VOLUME 1, NUMBER 8 • FEBRUARY 2008

Release Date: February 8, 2008

Valid Through: August 8, 2008

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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:

- Discuss the benefits of pravastatin therapy in women with hypercholesterolemia
- Describe the association between socioeconomic position and inflammatory burden among different race/ethnic groups
- Identify the age-specific associations of total cholesterol with ischemic heart disease, stroke, and other vascular mortality

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Grantor

The CCMD™ is supported by educational grants from Pfizer Inc, AstraZeneca, Reliant Pharmaceuticals, Inc., Abbott Laboratories, and Takeda Pharmaceuticals North America, Inc.

This activity is supported by an educational grant from Takeda Pharmaceuticals North America, Inc.

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Natasha K. McIntyre, Associate Program Manager; Elizabeth Ward, CME Director; Al Tauriello, Associate Editor; Wade'ah Terry, CME Program Manager; 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. Articles containing such uses will be noted at the end of the article.

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MEGA: Pravastatin Therapy Reduces Cardiovascular Risk Among Women With Hypercholesterolemia

Statins have been demonstrated to significantly reduce the risk of cardiovascular disease (CVD), yet their ability to prevent cardiovascular events in women has not been established.

Mizuno and associates assessed the effect of diet plus pravastatin therapy on the primary prevention of cardiovascular events in women using data obtained from the Management of Elevated cholesterol in the primary prevention Groups of Adult Japanese (MEGA) study, a large-scale primary prevention trial with pravastatin. In this study, 5,356 postmenopausal women and 2,476 men with hypercholesterolemia (total cholesterol, 5.7–7.0 mmol/L [222–273 mg/dL]) and no history of coronary heart disease (CHD) or stroke were randomized to diet or diet plus pravastatin 10 mg/day to 20 mg/day.

The mean follow-up was 5.3 years. During this time, cardiovascular events occurred 2 to 3 times more often in men than in women. Further, among women, there were reductions in the risk of CHD (25%), stroke (37%), CHD plus cerebral infarction (26%), cerebral infarction plus transient ischemic attack (23%), and all CVD (28%) in the diet plus pravastatin treatment group compared with the diet alone group. Such differences between the treatment groups did not reach statistical significance; however, the overall risk reductions among women were similar to those among men. Among participants treated with diet plus pravastatin, the observed risk reduction for

women compared with men was 25% versus 35% for CHD, 26% versus 41% for CHD plus cerebral infarction, 37% versus 34% for stroke, and 41% versus 19% for total mortality.

The incidence of cardiovascular events in this study increased with age, and diet plus pravastatin treatment was more effective at reducing this incidence in older women.

Remarkably, among women ≥60 years of age, those treated with diet plus pravastatin demonstrated substantially higher risk reductions for CHD (45%), CHD plus cerebral infarction (50%), and stroke (64%) than did women treated with diet alone. The effectiveness of pravastatin among younger women could not be determined in this study because of the small proportion (22%) of women <55 years of age.

These findings suggest that pravastatin therapy in women with hypercholesterolemia, but no history of CVD, offers

benefits similar to those achieved in men. Additionally, these benefits might be more apparent in older women. A limitation of this study is the involvement of Japanese individuals—a group whose CVD risk is low compared with other populations. The study investigators recommended that pravastatin therapy should be considered an option for the primary prevention of cardiovascular events in women with hypercholesterolemia.

Mizuno K, Nakaya N, Ohashi Y, et al. Usefulness of pravastatin in primary prevention of cardiovascular events in women. Analysis of the Management of Elevated cholesterol in the primary prevention Groups of Adult Japanese (MEGA study). *Circulation*. 2008;117(4):494-502.

Investigators recommend that pravastatin therapy be considered an option for the primary prevention of CV events in women with hypercholesterolemia.

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Post-Test Question 1

The results of this study suggest that pravastatin therapy in women with elevated cholesterol, but no history of cardiovascular disease, has preventative benefits lesser than those seen in men treated with this medication.

- a. True
- b. False

Commentary

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The Management of Elevated cholesterol in the primary prevention Group of Adult Japanese (MEGA) study is the first large outcomes trial of statins involving a Japanese population and stands as the landmark primary prevention trial in Asia—as significant as WOSCOPS and AFCAPS/Tex-CAPS were in the west. While it is specific to the Japanese population, MEGA has important implications for the care of men and women worldwide. While it is well-known that statins reduce the risk of cardiovascular disease (CVD), controversy exists regarding the role of statins in the primary prevention of CVD for both Asians and women.

Prior to MEGA, there were no randomized, controlled trials of statins targeting the primary or secondary prevention of coronary heart disease (CHD) in Asians. The lower incidence of heart disease in Asians, as well as the safety concerns regarding statins, made it difficult to extrapolate the desired results from western populations, which necessitated a trial focused on this group. Local investigators hypothesized that less aggressive cholesterol-lowering therapy might be sufficient to reduce CHD risk during primary prevention. In fact, compared with western primary prevention trials, such as WOSCOPS, AFCAPS/TexCAPS, ALLHAT-LLT, and ASCOT-LLA, the patients enrolled in the MEGA trial experienced much smaller reductions in low-density lipoprotein cholesterol (LDL-C), but saw a significant decrease in CHD events overall.

Further, irrespective of race, few primary prevention studies have been conducted involving a substantial enough proportion of women to determine the impact of statins on this population. The MEGA study had more women (68% of patients) than any previous statin trial; had patients with a relatively low 10-year risk; used a lower dose of pravastatin than typically prescribed; and, although it did not produce a dramatic difference in LDL-C, it did show marked reductions in CHD events—particularly in women of advanced years. In this subanalysis of the MEGA study, Japanese women randomized to diet alone or diet plus low-dose pravastatin provided a similar, although not statistically significant reduction in events as compared with men. Of note, statistically significant improvements in outcomes were observed in women ≥ 55 years of age.

This study supports the notion that statins are beneficial in the primary prevention of cardiovascular events, particularly in those with a higher baseline risk, and that even modest reductions in LDL-C can have a significant impact on CHD for men and women.

Greater Inflammatory Burden Linked to Lower Socioeconomic Position

In industrialized countries, cardiovascular events and subclinical atherosclerosis are more prevalent among individuals in lower than higher socioeconomic groups. The basis for such differences is under investigation. Accumulating evidence has revealed that inflammation is important in the development of atherosclerosis.

Recently, Ranjit and colleagues examined the associations of educational level and household income with the inflammatory markers interleukin-6 (IL-6) and C-reactive protein (CRP) in the Multi-Ethnic Study of Atherosclerosis (MESA). This longitudinal study of risk factors for subclinical atherosclerosis and its progression included 6,814 men and women (45–84 years of age) who were free of clinical cardiovascular disease at baseline.

This cross-sectional analysis involved baseline MESA data that were adjusted for infection and medication use, psychosocial factors, behaviors, adiposity, and diabetes mellitus. In addition, education and household income data were available for 6,791 and 6,541 participants, respectively.

After adjusting for age and sex, low income

was significantly associated with higher IL-6 concentrations among all race/ethnic groups. For whites, Chinese, blacks, and Hispanics, percent differences in IL-6 concentrations associated with a 1 standard deviation (SD) lower income were 9% (95% confidence interval [CI], 7–11; $P < 0.0001$), 6% (95% CI, 1–10; $P = 0.022$), 8% (95% CI, 4–11; $P < 0.0001$), and 8% (95% CI, 3–13; $P = 0.002$), respectively. However, low income was significantly associated with higher CRP concentrations among whites (percent difference in CRP level associated with a 1 SD lower income, 9% [95% CI, 5–13; $P < 0.0001$]).

After adjusting for age and sex, low levels of education were significantly associated with higher IL-6 and CRP concentrations among whites and blacks. Percent differences in IL-6 concentrations associated with a 1 SD lower education were 9% (95% CI, 6–12; $P < 0.0001$) and 7% (95% CI, 3–10; $P < 0.001$) for whites and blacks, respectively. Percent differences in CRP concentrations associated with a 1 SD lower education were 14% (95% CI, 9–19;

Continued

Greater Inflammatory Burden Linked to Lower Socioeconomic Position

Continued

$P < 0.0001$) and 10% (95% CI, 3–15; $P < 0.004$) for whites and blacks, respectively.

The most influential factor for these associations, particularly among whites and blacks, was adiposity. Smaller effects were noted for psychosocial factors and behaviors in all race groups. Based on these results, the authors con-

cluded that both household income and education level are associated with inflammatory burden, but that these associations differ across race/ethnic groups.

Ranjit N, Diez-Roux AV, Shea S, et al. Socioeconomic position, race/ethnicity, and inflammation in the multi-ethnic study of atherosclerosis. *Circulation*. 2007;116(21):2383-2390.

Post-Test Question 2

Which statement most accurately reflects the results of this study:

- Only household income was associated with inflammatory burden
- Only educational level was associated with inflammatory burden
- Both household income and educational level were associated with inflammatory burden
- Neither household income nor educational level was associated with inflammatory burden

Cholesterol Levels Predict Ischemic Heart Disease Mortality But Not Stroke Mortality: The Results of a Meta-Analysis

The relationship between vascular mortality and total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) depends on age, sex, and blood pressure (BP). This collaborative meta-analysis examined the combined influence of baseline BP and TC level on vascular mortality.

Data were derived from 61 observational prospective studies and involved approximately 900,000 adults without previous disease (70% from Europe, 20% from the United States or Australia, and 10% from Japan or China). More than 55,000 vascular deaths (34,000 with ischemic heart disease [IHD], 12,000 with stroke, and 10,000 with other vascular diseases) occurred during nearly 12 million person-years at risk between the ages of 40 and 89 years (mean follow-up, 13 ± 6 years).

Among both sexes at early middle age (40–49 years), later middle age (50–69 years), and old age (70–89 years), a prolonged 1 mmol/L (39 mg/dL) lower TC concentration was associated with approximately a half (hazard ratio [HR], 0.44; 95% confidence interval [CI], 0.42–0.48), a third (HR, 0.66; 95% CI, 0.65–0.68), and a sixth (HR, 0.83; 95% CI, 0.81–0.85) lower IHD mortality, respectively. Lower TC was associated with lower IHD mortality throughout the main TC range, with no apparent TC threshold. Moreover, the proportional risk reduction decreased with increasing BP; the absolute effects of TC and BP were roughly additive in nature.

Among the various parameters involving HDL-C, the TC/HDL-C ratio was the strongest predictor of IHD mortality. Indeed, the TC/HDL-C ratio was 40% more informative than non-HDL-C and more than twice as informative as TC level.

At ages 40 to 59 years, there was a weak positive association between TC level and total stroke mortality. However, this finding might be attributed to the association of TC level with BP. A positive relation was noted only in the middle-aged group and only among those with below-average BP. At ages 70 to 89 years and, especially for individuals with systolic BP approximately >145 mm Hg, TC was negatively related to hemorrhagic and total stroke mortality. Outcomes for other types of vascular mortality were intermediate between those for IHD and stroke mortality.

TC level correlated positively with IHD mortality among both middle-aged and old-aged individuals and at all BP levels. The reason for the lack of an independent positive association between TC and stroke mortality, especially at older ages or with higher BP levels, is not known at this time. Yet, ample definitive evidence from randomized trials indicates that statin therapy, which lowers LDL-C levels, substantially reduces both coronary event rates and total stroke rates in patients with varying ages and BP levels.

Prospective Studies Collaboration. Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55,000 vascular deaths. *Lancet*. 2007;370(9602):1829-1839.

Post-Test Question 3

In this study, among both middle- and old-aged individuals and at all blood pressure levels, total cholesterol level correlated positively with which of the following?

- Ischemic heart disease (IHD) mortality
- Total stroke mortality
- Both IHD and total stroke mortality
- Neither IHD nor total stroke mortality