

Post-Test Question 1

In this analysis comparing subjects from the ERA trial with those from FOS, which lipids were stronger predictors of CHD in postmenopausal women than TG or HDL-C?

- a. TG-rich lipoproteins
- b. HDL subpopulations
- c. Both TG-rich lipoproteins and HDL subpopulations
- d. Neither TG-rich lipoproteins nor HDL subpopulations

Commentary

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Coronary heart disease (CHD) is the leading cause of mortality for women in the United States, with the prevalence rising with increasing age. Whether the CHD predominance in menopausal women reflects older age, hormonal status, or both remains unresolved. Further, women who sustain coronary events have less favorable outcomes than men. Given this adverse substrate, new data that target risk attributes—and thereby potential preventive interventions—offer promise of improved cardiovascular health for women and warrant detailed examination.

Lamon-Fava and colleagues examined plasma levels of high-density lipoprotein (HDL) subpopulations and remnant lipoproteins in menopausal women with documented CHD (in the Estrogen Replacement and Atherosclerosis study) and without clinical evidence of CHD (in the Framingham Offspring Study). They found that subpopulations of TG-rich and HDL lipoproteins better predicted CHD in postmenopausal women than did total TG and HDL concentrations. Levels of remnant lipoproteins and plasma pre β 1 HDL particle concentration were positively associated, and α 2 HDL particle concentrations were inversely associated, with coronary atherosclerosis as determined by quantitative coronary angiography in women with documented CHD.

Several variables must be addressed from these findings. First, the status of the coronary arteries in women without documented CHD was not explicitly defined. More importantly, coronary angiography may not fully assess the atherosclerotic burden for women, as it documents only the extent of luminal narrowing of the epicardial coronary arteries.

Further to be addressed is whether similar lipid associations occur in premenopausal women with CHD: Are they present across the lifespan, or might there be hormonal interaction? Are there comparable differences between premenopausal women with and without CHD, in addition to the predictive value of these lipid moieties for the extent of coronary atherosclerosis? These probes, if further validated, offer exciting implications for targeting specific therapies.

Secondary Prevention of CV Events With Bezafibrate Therapy Among Patients With Established CHD

The Bezafibrate Infarction Prevention (BIP) trial evaluated the effect of increasing high-density lipoprotein cholesterol (HDL-C) and decreasing triglyceride (TG) levels on cardiac risk in patients with established coronary heart disease (CHD) and normal or slightly elevated total cholesterol (TC) levels. Despite substantial lipid-modifying effects with bezafibrate, there was a relatively small, statistically nonsignificant 7.3% reduction in the rate of major cardiovascular (CV) events after a mean follow-up period of 6.2 years. The researchers hypothesized that this outcome was attributed to the unbalanced use of non-study lipid-lowering drugs (LLDs).

In the BIP trial, 3,090 patients were randomized to either bezafibrate 400 mg/day ($n=1,548$) or placebo ($n=1,542$). Participants were aged 45 to 74 years, had a history of myocardial infarction (MI) and/or angina, and a lipid profile consisting of TC between 180 mg/dL and 250 mg/dL, low-density lipoprotein cholesterol (LDL-C) ≤ 180 mg/dL (≤ 160 mg/dL for patients aged <50 years), HDL-C ≤ 45 mg/dL, and TG ≤ 300 mg/dL. Almost 80% of patients had a history of MI, and 10% had treated diabetes.

Goldenberg and associates performed a post hoc analysis of the long-term cardiovascular benefits of bezafibrate therapy among patients with CHD enrolled in the BIP trial. The adjusted risk

for the combined endpoint of cardiac death or nonfatal MI was assessed after discontinuation of the study medication. Patients were observed for CV events for an additional period, extending the total follow-up time to a mean 8.2 years. This analysis was performed on an intention-to-treat basis.

During the extended follow-up period, the combined endpoint occurred in 17.8% (276/1,548) of the bezafibrate group and 20.3% (313/1,542) of the placebo group ($P=0.09$). Survival curves revealed that, after a total follow-up of 9 years, the cumulative probability of the combined endpoint was 19.7% in the bezafibrate group and 23.8% in the placebo group, representing a significant 17.6% reduction in the rate of cardiac death or non-fatal MI ($P=0.03$).

Non-study LLDs were administered during the extended follow-up period to a significantly greater proportion of the placebo group than the bezafibrate group (57% vs 53%, respectively; $P=0.02$). Interaction-term analysis that adjusted for unbalanced non-study LLD use indicated that the benefit of bezafibrate therapy was pronounced without or before treatment with non-study LLDs initiated during follow-up (18% risk reduction; $P=0.03$) and attenuated after therapy with non-study LLDs initiated during the follow-up period (hazard ratio, 1.05; $P=0.85$). Moreover, when

