Review of *The Lipid Research Clinics Coronary Primary Prevention Trial Results*

Grace Yi Chen

In the first article, the author first introduced the background and design of the multicenter, randomized, double-blind Lipid clinical trial called Research Clinics Coronary Primary Prevention Trial (LRC-CPPT). The goal is to test the efficacy of cholesterol lowering in reducing risk of coronary heart disease (CHD) in asymptomatic middle-aged men with primary hypercholesterolemia. The treatment group received a drug called cholestyramine resin which is approved for general use of reducing total cholesterol (TOTAL-C) and low-density lipoprotein cholesterol (LDL-C) levels. The control group received a placebo and people in both groups had a moderate cholesterol-lowering diet. All participants are followed for an average of 7.4 years, and they attended clinics every two months. In the end, people in the treatment group had larger average TOTAL-C and LDL-C reductions than those in the placebo group. The treatment group had statistically significant 19% reduction in risk of the primary end point CHD death at 5% one-sided level. For the second article, the study team focused on the treatment and control group separately as an observational longitudinal study. Only in the treatment group, there was a statistically significant decrease of TOTAL-C or LDL-C levels associated with reduction in CHD risk at 0.001 significance level. These two articles concluded strong evidence for a causal relationship between lipids level and risk of CHD. The reduction of CHD incidence in the treated group is influenced by reduction of TOTAL-C and LDL-C levels.

I think these two articles are good overview of this clinical trial in detail. CHD is a complicated disease and could have many risk factors, but the study team designed and implemented the trial carefully. For example, in the eligibility criteria and randomization section, the study team targeted at asymptomatic middle-aged men with primary hypercholesterolemia since this group should be at higher risk of CHD. The study team also used stratified randomized design to control for potential confounders like smoking, blood pressure level etc. In addition, I find the observed reduction in primary endpoint and reduction of TOTAL-C in treated group are quite different from the expected values. That would be better if our expected and the observed values are similar since the power and sample size calculation of the study are based on our expected values from historical studies. For the conclusion part, I see the authors are trying to generalize the result of this study to other age group and women arguing that the expected benefit should be considerable. I could understand it since this is a large study and it is hard to replicate it in other groups. However, I am not sure whether this conclusion could be easily extrapolated since the evidence of this study is not strong (19% risk reduction significant at 5% one-sided level) and there is no benefit in the overall mortality endpoint.

Questions:

1. In the second part, is using the percent change in LDL-C ratio in the regression model a good way to evaluate the relationship between CKD incidence and LDL-C reduction level?
2. Since there is no benefit in the overall mortality endpoint, I am wondering is it because of the drug long term adverse event or anything else?

3. I read another article and it mentioned that the original design is to compare the primary endpoint based on statistical significance at 0.01 level. Why there is a change in the actual analysis?