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Projected coronary heart disease risk benefit with ezetimibe

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Abstract

Low density lipoprotein (LDL) cholesterol and total cholesterol (TC) are the primary clinical parameters of interest for any cholesterol intervention. Clinicians are interested in how the reduction of these lipid parameters as well as increases in high density lipoprotein (HDL) relate to changes in coronary heart disease (CHD) risk. The objective of this analysis was to estimate the additional CHD risk reduction that could potentially be provided by co-administration of ezetimibe with statin therapy. Data from four double-blind placebo controlled clinical trials were used to predict the level of CHD risk reduction that might be achieved by co-administration of ezetimibe with statin therapy when compared to those receiving statin as monotherapy. Patients without a previous history of CHD were included in the analysis. Projected CHD risk reduction was calculated as percent change in projected CHD risk from baseline to 12 weeks based on observed lipid levels at those time points. For all the studies combined greater reductions in percent change in 5-year CHD risk were observed for patients receiving ezetimibe and statin as co-therapy, 53.4%, when compared to those receiving statin alone, 39.7%. Co-administration of ezetimibe with statin therapy provides an additional 13.7% reduction in predicted 5-year CHD risk when compared to statin monotherapy. Reductions in 5-year CHD risk for each of the statin studies ranged from 16.1% for lovastatin to 9.8% for atorvastatin. Co-administration of ezetimibe with statins could significantly reduce CHD events in patients with primary hypercholesterolemia.

Keywords: Risk appraisal function; Co-administration; Statin

1. Introduction

Numerous epidemiologic studies [1–5] and clinical trials [6–11] have confirmed that improvements in lipid parameters (i.e., reductions in LDL and total cholesterol and increases in HDL cholesterol) result in reduced CHD risk. In a meta-analysis of eight randomized clinical trials of statins, Gould et al. [12] demonstrated that every 10% points of cholesterol lowering reduces CHD mortality risk by 15% and total mortality risk by 11%. These authors concluded that the effect of statins on CHD and total mortality risk can be explained by their lipid lowering ability and appears to be directly proportional to the degree to which they lower lipids. Consequently, the ultimate goal of any lipid lowering intervention is to reduce CHD risk.

Ezetimibe is a new chemical entity that inhibits the absorption of dietary and biliary cholesterol without affecting the absorption of triglycerides or fat-soluble vitamins. Ezetimibe complements the lipid-altering effects of other therapies such as statins. Clinical studies have shown that co-administration of ezetimibe with statins could provide as much as an additional 12–14% reduction in LDL cholesterol, an additional 10–12% reduction in total cholesterol and an additional 2–5% increase in HDL cholesterol [13–16] in patients with primary hypercholesterolemia. These studies also indicate that co-administration of ezetimibe with the lowest dose of statin could provide similar reductions in LDL cholesterol when

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compared to monotherapy with the highest dose of statin [13–16].

Given the improved lipid profile that ezetimibe provides when co-administered with statins, it is of interest to evaluate how this improvement may translate into reduced CHD risk. CHD risk appraisal functions based on the Framingham Heart Study have been developed to be able to predict an individual's risk of a future CHD event [17–19]. The objective of this evaluation is to use CHD risk appraisal functions to see how the additional lipid-altering effects of ezetimibe translate into projected CHD risk reductions.

2. Methods

Data from four randomized clinical trials that evaluated the effect of co-administration of statin therapy with ezetimibe in a population of patients with primary hypercholesterolemia were used to estimate the percent change in projected 5 and 10-year CHD risk from baseline to 12 weeks [13–16]. After completing dietary stabilization, a 2–12 weeks washout period and a 4 weeks run-in-period, patients with baseline LDL cholesterol between 145 and 250 mg/dl and triglycerides ≤350 mg/dl were randomized to receive placebo, ezetimibe 10 mg, statin monotherapy with doses of 10, 20, 40 or 80 mg, or ezetimibe 10 mg co-administered with one of the doses of statin therapy. Detailed illustrations of the basic study designs are given in the primary publications [13–16]. Separate studies were conducted for lovastatin (10, 20, 40 mg) [15], pravastatin (10, 20, 40 mg) [16], simvastatin (10, 20, 40, 80 mg) [14] and atorvastatin (10, 20, 40, 80 mg) [13]. Lipid parameters were monitored for a 12-week period.

Five and 10-year projected CHD risk were estimated using a risk appraisal function developed by Andersen et al. [17–18] from data collected by the Framingham Heart Study. The risk equation is based on an accelerated failure time model that can estimate primary CHD risk for a period of 4–12 years. Separate equations were developed for males and females. Variables in the models include age, current smoking, diabetes, diastolic or systolic blood pressure, presence of left-ventricular hypertrophy and ratio of total cholesterol to HDL cholesterol.

For each patient in the four randomized clinical trials, the 5- and 10-year CHD risk estimates were calculated at baseline and at 12 weeks. For the 12-week calculation all model parameters except the total cholesterol to HDL cholesterol ratio were held at their baseline values. Patients with missing model parameters at baseline or 12 weeks were excluded from the analysis. In addition, patients with a history of CHD were excluded because the risk equations are relevant only for patients who are CHD-free.

Percent change in CHD risk was summarized in each study for patients receiving ezetimibe plus statins and for those receiving statin monotherapy by pooling across statin dose groups. Pooled estimates of CHD risk were also computed across all four studies. Patients receiving placebo or ezetimibe monotherapy were excluded from the analysis. The difference in mean percent change in CHD risk between the statin + ezetimibe and statin monotherapy groups and its corresponding 95% confidence interval was calculated for each study and the pooled studies.

3. Results

A total of 1861 patients across the four clinical studies received either statin monotherapy, or statin plus ezetimibe 10 mg. Of the 1861 patients, 152 patients were excluded because they had a previous history of CHD and 18 patients were excluded because of missing endpoint data or for missing data for one or more of the model parameters. Consequently, 1691 patients ($n = 840$, ezetimibe + statin, $n = 851$ statin monotherapy) were included in the analysis of projected CHD risk. Baseline demographics and lipid parameters are summarized in Table 1. The summary of the pooled baseline demographics and lipid parameters suggested that there were no differences between those receiving ezetimibe and those who did not. Patients receiving ezetimibe experienced an additional 9–12% reduction in their baseline TC:HDL cholesterol ratio compared to those receiving statin monotherapy (Table 2). Mean baseline CHD risk ranged from 4.0 to 5.3% for 5 years and 10.3 to 12.0% for 10 years across the four studies (Table 3).

The percent reduction in baseline primary CHD risk for patients receiving statin and ezetimibe was significantly greater than for those receiving statin monotherapy (Table 3). This result was consistent across the four statin studies. Patients treated with lovastatin and ezetimibe were projected

Table 1
Baseline lipid profile and other demographics pooled across studies

Baseline lipid profile	Ezetimibe + statin, $n = 840$	Statin Monotherapy, $n = 851$
Total cholesterol (mg/dl)	264.4 (25.1)	265.3 (25.4)
HDL Cholesterol (mg/dl)	51.3 (12.4)	51.5 (11.7)
LDL Cholesterol (mg/dl) calculated	178.5 (20.8)	179.6 (21.3)
Ratio TC:HDL cholesterol	5.4 (1.2)	5.4 (1.2)
Other baseline characteristics		
Age	57.0 (S.D. = 11.6)	55.5 (S.D. = 12.1)
Gender – male (%)	41.1	39.7
SBP (mmHg)	128.9 (16.1)	128.7 (16.2)
DBP (mmHg)	80.5 (9.2)	79.5 (9.0)
Diabetes (%)	4.9	4.9
ECG-LVH (%)	0.4	0.4
Smoking (%)	10.8	13.4
Statin therapies		
Lovastatin (%)	21.1	23.0
Simvastatin (%)	29.4	28.8
Pravastatin (%)	22.3	22.0
Atorvastatin (%)	27.3	26.2