zole safe and effective in preventing recurrence of disease?

Background A meta-analysis of long-term omeprazole trials found both 10 and 20 mg per day omeprazole regimens to be superior to either standard dose ranitidine or placebo in preventing relapse of esophagitis. The 20-mg dose omeprazole daily was significantly more effective than the 10-mg per day dose.[1]

Population studied Adults who were referred to an open-access gastroenterology clinic by their general practitioners for symptoms of gastroesophageal reflux disease (GERD) were considered for enrollment. The authors argue that this open-access scheme led to a study population that was more reflective of a primary care physician's practice, which is probably true. Exclusion criteria included esophageal stricture, duodenal or gastric ulcer, pregnancy, lactation, esophagitis unresponsive to 3 months of treatment with H2 antagonists, and suspicion of upper gastrointestinal malignancy.

Study design and validity This was a randomized double-blind placebo-controlled study of omeprazole 10 mg per day for the maintenance therapy of erosive esophagitis. All patients initially underwent endoscopy to determine disease presence and severity; only those with grade 2 disease or higher (moderate to severe esophagitis) were entered. All patients were treated with omeprazole 20 mg 4 times daily for 12 weeks; those unhealed by repeat endoscopy were treated with omeprazole 40 mg 4 times daily for 12 additional weeks. The patients were then randomized to omeprazole 10 mg 4 times daily or placebo, and monitored for return of symptoms and recurrence of disease by endoscopy. Any recurrence (by symptoms or endoscopy) was re-treated with omeprazole 20 mg 4 times daily for 12 weeks, then the maintenance therapy was restarted. Any further relapse was similarly re-treated, but maintenance was begun with open-label omeprazole at 20 mg 4 times per day for all. Intention-to-treat analysis was appropriately carried out.

Outcomes measured The primary outcome measured was relapse (symptomatic or silent) during the initial maintenance phase and during the second maintenance phase, when applicable.

Results Of the 300 people who entered the study, 263 were randomized after the initial treatment phase. Relapse rates were significantly different in the 2 groups: 40% in the omeprazole group and 85% in the placebo group (number needed to treat over 18 months to prevent 1 relapse was 2.2; 95% confidence interval [CI], 2 - 3). There were no statistically significant differences observed between the rates of silent and symptomatic relapse. The relapse rates for the second maintenance phase (n=116, 28 in omeprazole group and 88 in placebo group) were 79% for omeprazole and 91% for placebo (absolute risk ratio=12%, 95% CI, -4% to 28%, therefore not significant). Success rates of treatment with omeprazole 20 mg were consistently greater than 90% regardless of retreatment status or previous maintenance therapy. For those patients who required maintenance therapy with open-label omeprazole 20 mg 4 times daily (n=118), it remained effective (9% relapse rate by 24 months). There were no adverse events attributable to omeprazole therapy or GERD.

Recommendations for clinical practice **This study confirms that low-dose omeprazole is safe and moderately effective compared with placebo in preventing relapse of erosive esophagitis in those patients endoscopically diagnosed with moderate to severe disease. In primary care practice, however, GERD symptoms are often treated empirically, and the grade (or even the presence) of esophagitis is often not known. From this study, symptom relief alone was achieved with similar numbers needed to treat as remission of esophagitis. The authors suggest that a reasonable approach to therapy would be to start with a 10-mg maintenance dose for mild to moderate esophagitis and progress to 20-mg daily maintenance if retreatment is required. This is especially appropriate when cost is an issue, since only 40% of patients requiring maintenance therapy would benefit from the higher dosage.**

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Treating Average Cholesterol Levels in Patients with Coronary Heart Disease

The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. N Engl J Med 1998; 339:1349-57.

Clinical question **Does reduction of average cholesterol levels with pravastatin in patients with coronary heart disease (CHD) reduce mortality and cardiovascular events?**

Background HMG-CoA reductase inhibitors, or statins, have been shown to decrease overall mortality in hypercholesterolemic patients with CHD.[1] They have also decreased myocardial infarctions (MIs) and coronary deaths in patients with past MIs and average cholesterol levels.[2] However, no previous studies of these medications have demonstrated reduction in overall mortality in CHD patients with average cholesterol levels.

Population studied This multicenter trial recruited patients aged 31 to 75 years in Australia and New Zealand, all of whom had acute MI or discharge diagnosis of unstable angina between 3 and 36 months before study entry. Total cholesterol levels were between 155 and 271 mg/dL, and fasting triglyceride levels were <445 mg/dL. The median cholesterol level was 218 mg/dL, the median age 62 years, and only 17% were women. Patients were excluded if they were already taking any cholesterol-lowering agents or if they had cardiac failure, renal impairment, or hepatic disease.

Study design and validity This was a randomized double-blind trial comparing pravastatin 40 mg daily to placebo. All of the 9014 patients participated in an 8-week run-in phase during which they received dietary advice on fat-calorie reduction; this dietary counseling continued throughout the study. Lipid profiles were drawn at set intervals throughout the study, and routine clinic visits were scheduled every 6 months. Patients and clinicians were notified of results of other cholesterol-lowering trials as they were published, and participants had the option of starting open-label lipid-lowering therapy if indicated.

Outcomes measured The primary outcome was death from CHD, reviewed by a blinded outcomes-assessment committee. Secondary outcomes included death from any cause, death from any cardiovascular cause (including stroke), incidence of MI, incidence of stroke, incidence of coronary revascularization, and number of days in the hospital.

Results Patients were followed for a mean of 6.1 years. There was a 1.9% absolute risk reduction in CHD death in the pravastatin group compared with placebo (6.4% vs 8.3%; number needed to treat [NNT] = 53 for 6 years of treatment), and a 3.1% absolute risk reduction in overall mortality (11.0% vs 14.1%, NNT = 32 for 6 years of treatment). Both of these results were highly statistically significant. By the end of the study, 24% of those in the placebo arm were actually taking a cholesterol-lowering agent, but they were kept in the placebo group for analysis (indicating that this intention-to-treat analysis probably underestimates the benefit of pravastatin). Other statistically significant findings included reductions in mortality from all cardiovascular causes and the rates of MIs, revascularization, and stroke. Investigators observed no increase in adverse effects, including cancer, suicide, trauma, liver disease, or myopathy. Subgroup analysis demonstrated a significant decrease in CHD death and nonfatal MI incidence for patients both above and below total cholesterol levels of 213 mg/dL. Although there was a trend toward improvement, the study did not have enough power to show differences in these end points for the following subgroups: women, patients with diabetes, patients older than 70 years, and patients with LDL-cholesterol levels <135 mg/dL.

Recommendations for clinical practice **It has been reported that only 10% to 30% of post-MI patients in developed countries are prescribed lipid-lowering drugs. This study adds to the evidence that nearly all patients with CHD are candidates for such medication, even with average cholesterol levels. Although some of the subgroups mentioned above did not show statistically significant differences, other studies have demonstrated encouraging results. For example, a recent analysis of older patients in the Cholesterol and Recurrent Events Trial reported significant benefit of pravastatin; this group had mean total cholesterol of 208 mg/dL.[3] The authors estimated that only 4 post-MI patients aged 65 to 75 years would need to be treated with pravastatin to prevent one cardiovascular hospitalization over 5 years. Clinicians should be thinking strongly about using statins in most of their CHD patients.**

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