

Pravastatin's Efficacy in the Elderly at High Risk for Vascular Disease

Shepherd J, Blauw GJ, Murphy MB, et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. *Lancet* 2002;360:1623–30.

Study Overview

Objective. To determine whether pravastatin is effective at reducing coronary and cerebrovascular morbidity and mortality in elderly patients with or at increased risk of developing cardiovascular disease and stroke.

Design. Double-blind randomized controlled trial. All analyses were by intention-to-treat.

Setting and participants. 2804 men and 3000 women were recruited for the trial. Patients were aged 70 to 82 years, lived in 1 of 3 European countries, and had a history of or risk factors for vascular disease. Patients with poor cognitive function or who failed to comply with a placebo regimen during a 4-week lead-in period were excluded. Patients were randomized to either 40 mg of pravastatin daily (intervention) or to placebo (control).

Main outcome measurements. The primary outcome was the combined endpoint of death from coronary artery disease, nonfatal myocardial infarction, and nonfatal or fatal stroke. Magnitude of benefit in relation to degrees of baseline risk factors was also examined. Transient ischemic attacks (TIA), disability, and cognitive decline also were assessed.

Main results. 2891 patients were randomized to the intervention group and 2913 to the control group. Patients were followed for an average of 3.2 years. Pravastatin lowered low-density lipoprotein cholesterol concentrations by 34% and reduced the incidence of the primary endpoint of myocardial infarction and stroke by 14% (hazard ratio [HR], 0.85 [95% confidence interval [CI], 0.74–0.97]; $P = 0.014$). Mortality from coronary artery disease fell by 24% ($P = 0.043$) in the intervention group. In the subgroup analysis, stroke risk was not significantly affected, but a trend suggests that the risk for TIA was (HR, 0.75 [95% CI, 0.55–1.00]; $P = 0.051$). Benefit of pravastatin was most significant for patients with the lowest tertile of high-density lipoprotein cholesterol concentrations. The study found an increased incidence of new cancer diagnosis in the pravastatin group (HR, 1.25 [95% CI, 1.04–1.51]; $P = 0.020$), but a meta-analysis

incorporating results from all pravastatin and other statin trials showed no overall increase in cancer risk. The intervention had no significant effect on cognitive function or disability. Rates of adverse drug events were similar in the intervention and control groups.

Conclusion. Pravastatin given for 3 years reduced the risk of coronary artery disease and was well tolerated in the elderly population.

Commentary

Since elderly patients are more vulnerable to the potential side effects of medications [1], clinicians taking care of them need to exercise caution in deciding whether the benefits of a medication justifies its risks. The PROSPER trial was designed to address that specific issue for patients at high risk of developing another cardiovascular or cerebrovascular event: can the benefits of statin drugs seen in the middle-aged population be replicated in the elderly within a meaningful follow-up period? Are the risks of pravastatin acceptable in the elderly population?

The answer to both questions is yes. The results from this well-designed double-blind randomized controlled trial supplement the existing subgroup analyses that have suggested that statin medications are efficacious in the elderly population [2,3]. This benefit of pravastatin, which was well tolerated, became evident within just 3 years of follow-up. Since the average 75-year-old woman is expected to survive a further 12.08 years and her male counterpart an additional 9.39 years [4], most septuagenarians at risk for vascular disease would benefit by taking pravastatin.

Several caveats, however, should be born in mind when we apply the results of the PROSPER trial to the geriatric population. The PROSPER trial recruited patients between age 70 and 82 years, and it is unclear whether the benefit and risk profile of pravastatin translates readily to the high-risk elderly patients in their 80s or 90s. While the effect of pravastatin was not statistically different for groups with or without preexisting vascular disease or between men and women, the subgroup analyses suggest that pravastatin's benefit may be attenuated when used for primary prevention

and for women. Further research may be required to clarify these issues.

Applications for Clinical Practice

The cardiovascular protective effect of pravastatin is significant in the septuagenarian patient at increased risk of further cardiovascular events. These benefits are seen within 3 years of taking the medication. Therefore, clinicians should not exclude these patients from taking pravastatin for primary and secondary prevention of cardiovascular events based on age alone, unless the patients' comorbidities put their expected survival significantly below 3 years.

—Review by Eric G. Poon, MD

References

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