

## Frequent Cholesterol Monitoring Prone to Error and May Be Unnecessary

Glasziou PP, Irwig L, Heritier S, et al; LIPID Study Investigators. Monitoring cholesterol levels: measurement error or true change? *Ann Intern Med* 2008;148:656–61.

### Study Overview

**Objective.** To determine the variability in cholesterol levels over time and whether this variability can be attributed to measurement error or true change.

**Design.** Post hoc analysis of a randomized, double-blind, placebo-controlled trial.

**Setting and participants.** 9014 patients with coronary heart disease were enrolled in the Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) trial in New Zealand and Australia (June 1990–May 1997). Patients were included if they had an acute coronary syndrome 3 to 36 months before the trial began, a total cholesterol level of 155 to 271 mg/dL, and a triglyceride level < 443 mg/dL. Participants were randomized to pravastatin 40 mg or placebo and followed for a mean of 6 years. Serum lipid levels (low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides) were measured at randomization, 6 and 12 months, and annually thereafter for 5 years.

**Main outcome measures.** Within-person and within-group variation in cholesterol levels over the short and long term. Variation in true response to pravastatin was measured using the difference in variance of change in cholesterol levels from baseline to 6 months between the pravastatin and placebo groups. Calculations of short-term variability in cholesterol levels were based on measurements obtained during a 4-week placebo run-in period and linear extrapolation from long-term values. Long-term variability was based on cholesterol measurements starting from 6 months post-randomization (initial assessment of response to therapy) to 5 years.

**Main results.** Most patients were male (83%), and the mean age was 62 years. Pretreatment total cholesterol was 218 mg/dL (range, 116–355 mg/dL). Only 1 patient was lost to follow-up; 5% and 6% of patients died during follow-up in the pravastatin and placebo groups, respectively. 19% of patients in the pravastatin group permanently discontinued therapy by the end of the trial, while 24% of patients in

the placebo group had begun open-label treatment with a cholesterol-lowering medication. Mean initial response to pravastatin therapy was a reduction of 45 mg/dL in total cholesterol (range of true change, 16–73 mg/dL). The coefficient of variation (the estimate for short-term, within-person variation) was 7%, with a 95% confidence interval of –31 to 31 mg/dL on a single total cholesterol measurement. Cholesterol levels increased slowly over time; however, it took over 3 years for long-term variability to exceed short-term variability. As a result, measurement error was more likely to cause significant changes in total cholesterol (eg, more false-positives) than true changes (eg, fewer true-positives) until 3 years after treatment initiation.

**Conclusion.** Frequent monitoring of cholesterol might reflect measurement error rather than true changes. As a result, less frequent testing of cholesterol levels may be warranted (eg, every 3–5 years instead of annually) in patients with levels at goal.

### Commentary

Treatment guidelines recommend frequent monitoring of lipid levels for patients on lipid-lowering therapy. The National Cholesterol Education Program guidelines recommend testing lipid levels every 4 to 6 months after therapy has been established [1]. However, these recommendations do not state how long to continue monitoring, and data supporting these recommendations are limited.

The time and expense associated with frequent cholesterol testing and unnecessary changes to treatment are not trivial. Laboratory testing in Medicare has risen substantially from 2000 to 2004, and lipid testing was a significant contributor to this increase [2]. New guidelines for aggressive control of lipids, with an optional low-density lipoprotein cholesterol goal of 70 mg/dL or less for patients with a history of myocardial infarction, also compel physicians to more frequently respond to marginal increases in cholesterol levels. An understanding of measurement error in lipid testing is thus critical for determining how often to assess lipid levels and how to respond to changes in levels. This study by Glasziou et al provides insight into this dilemma and

calls into question the frequent testing recommended by guidelines. One prior study reported a high degree of variability in cholesterol measurements but did not analyze the data in a way that could guide testing intervals [3].

This study has several limitations. First, the study analyzes data from only 1 clinical trial and is a post hoc analysis of the results of a trial that was designed to address cholesterol treatment efficacy rather than measurement error. Additionally, the study sample is almost exclusively male (no race breakdown is reported) and, therefore, results may not be generalizable to a more diverse population. Despite this lack of diversity, short-term variability in cholesterol measurement as reported in this study is consistent with results of several other studies [4,5].

Second, this study had significant crossover between groups despite a small number of patients lost to follow-up. Approximately the same percentage of participants began open-label treatment with a cholesterol-lowering medication in the placebo group as discontinued treatment with pravastatin in the intervention group. The authors examined the impact of these changes in several ways, including censoring follow-up for patients who changed designated therapy and carrying the last measurement forward, excluding from analysis all participants who did not continue the designated therapy, and imputing missing data resulting from these treatment changes. Analysis with each of these methods did not substantially alter the results.

Lastly, information is lacking on the influence of cholesterol testing on compliance with medication therapy. While Glasziou and colleagues assert the use of additional methods for monitoring adherence beyond cholesterol measurement, the influence of these methods cannot be easily discounted.

Further research on frequency of cholesterol monitoring should directly address the role of testing on adherence.

### **Applications for Clinical Practice**

Measurement error dominates true changes in cholesterol levels until at least 3 years after initial assessment of treatment response. As a result, clinicians should consider testing cholesterol levels less frequently after initially assessing response to cholesterol-lowering medication. Guidelines also may need to be updated to reflect the uncertainty of frequent short-term testing.

—Review by Jason P. Block, MD, MPH

### **References**

1. National Heart, Lung, and Blood Institute. Third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). Bethesda (MD): U.S. Department of Health and Human Services; 2001.
2. Hogan C. Trends in Medicare carrier-paid laboratory testing services. Available at [www.clinical-labs.org/documents/Hoganfinalreport\\_000.pdf](http://www.clinical-labs.org/documents/Hoganfinalreport_000.pdf). Accessed 30 May 2008.
3. Irwig L, Glasziou P, Wilson A, Macaskill P. Estimating an individual's true cholesterol level and response to intervention. *JAMA* 1991;266:1678–85.
4. Thompson SG, Pocock SJ. The variability of serum cholesterol measurements: implications for screening and monitoring. *J Clin Epidemiol* 1990;43:783–9.
5. Rotterdam EP, Katan MB, Knuiman JT. Importance of time interval between repeated measurements of total or high-density lipoprotein cholesterol when estimating an individual's baseline concentrations. *Clin Chem* 1987;33:1913–5.

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