Monitoring Cholesterol Levels: Measurement Error or True Change?

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Background: Cholesterol level monitoring is a common clinical activity, but the optimal monitoring interval is unknown and practice varies.

Objective: To estimate, in patients receiving cholesterol-lowering medication, the variation in initial response to treatment, the long-term drift from initial response, and the detectability of long-term changes in on-treatment cholesterol level ("signal") given short-term, within-person variation ("noise").

Design: Analysis of cholesterol measurement data in the LIPID (Long-Term Intervention with Pravastatin in Ischaemic Disease) study.

Setting: Randomized, placebo-controlled trial in Australia and New Zealand (June 1990 to May 1997).

Patients: 9014 patients with past coronary heart disease who were randomly assigned to receive pravastatin or placebo.

Measurements: Serial cholesterol concentrations at randomization, 6 months, and 12 months, and then annually to 5 years.

Results: Both the placebo and pravastatin groups showed small increases in within-person variability over time. The estimated within-person SD increased from 0.40 mmol/L (15 mg/dL) (coefficient of variation, 7%) to 0.60 mmol/L (23 mg/dL) (coefficient of variation, 11%), but it took almost 4 years for the long-term variation to exceed the short-term variation. This slow increase in variation and the modest increase in mean cholesterol level, about 2% per year, suggest that most of the variation in the study is due to short-term biological and analytic variability. Our calculations suggest that, for patients with levels that are 0.5 mmol/L or more (≥19 mg/dL) under target, monitoring is likely to detect many more false-positive results than true-positive results for at least the first 3 years after treatment has commenced.

Limitations: Patients may respond differently to agents other than pravastatin. Future values for nonadherent patients were imputed.

Conclusion: The signal–noise ratio in cholesterol level monitoring is weak. The signal of a small increase in cholesterol level is difficult to detect against the background of a short-term variability of 7%. In annual rechecks in adherent patients, many apparent increases in cholesterol level may be false positive. Independent of the office visit schedule, the interval for monitoring patients who are receiving stable cholesterol-lowering treatment could be lengthened.

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Cholesterol level monitoring is a common clinical activity. Because indications for treatment have been widening over the past decade, cholesterol-lowering medications have become some of the most widely used and expensive pharmaceutical items, and cholesterol screening, treatment, and monitoring have increased. For example, lipid panels were the third highest contributors to Medicare testing growth between 2000 and 2004, with a 61% increase in volume and a 65% increase in cost (1). Previous studies have suggested that, because of measurement error, frequent monitoring is just as likely to mislead when trying to decide whether changes in treatment are needed (2).

Most lipid management guidelines clearly state the number and interpretation of initial measurements but are less specific about subsequent monitoring. The National Cholesterol Education Program in the United States suggests that " . . . patients can be monitored for response to therapy every 4 to 6 months, or more often if considered necessary," (3) whereas the Medicare guideline (4) states "The LDL [low-density lipoprotein] cholesterol or total cholesterol may be measured three times yearly after treatment goals have been achieved." In the United Kingdom, the PRODIGY (Prescribing Rationally with Decision Support in General Practice Study) guidelines (5) suggest rechecking annually. The Australian National Heart Foundation and the Cardiac Society of Australia and New Zealand guidelines suggest lipid profile measurement every 6 to 12 months (6). However, the basis for recommending these intervals is unclear, and none of the guidelines explicitly describes within-person variability or the likely rates of change in cholesterol levels over time with fixed-dose therapy.

We therefore studied the implications of different strategies for monitoring cholesterol level. Our objectives were to estimate, in patients receiving a fixed dose of cholesterol-lowering medication or placebo, 1) the extent to which the initial response to treatment varies among patients; 2) the extent to which the initial response is sustained and long-term change varies within and among patients; and 3) the detectability of these long-term changes in on-treatment cholesterol level ("signal"), given short-term, within-person variation ("noise").

See also:

Print
Editors' Notes 657

Web-Only
Appendix
Appendix Table
Conversion of graphics into slides
Audio summary

METHODS

We used data from the LIPID (Long-Term Intervention with Pravastatin in Ischaemic Disease) trial (June 1990 to May 1997). The LIPID trial was a randomized trial of 9014 patients with acute coronary syndromes diagnosed 3 to 36 months previously who had been randomly assigned to 40 mg of pravastatin or matching placebo and had been followed for an average of 6.0 years (7). Before randomization, patients entered an 8-week placebo run-in phase. For patients to qualify for the study, their plasma total cholesterol levels 4 weeks before randomization had to be between 4.0 and 7.0 mmol/L (155 and 271 mg/dL), and the fasting triglyceride level had to be less than 5 mmol/L (<443 mg/dL). Lipid concentrations (including concentrations of LDL cholesterol, high-density lipoprotein cholesterol, and triglycerides) were measured at randomization, 6 and 12 months later, and then every 12 months for 5 years. We recorded information on adherence to treatment and uptake of other cholesterol-lowering medications. A single laboratory measured all cholesterol concentrations, eliminating differences among laboratories as a source of variation.

Estimation for each of the 3 objectives required different methods.

Variation in Initial Response to Treatment

Patients receiving placebo will show some variation in apparent response that will be attributable to short-term variation. A greater variation of change in total cholesterol level in the pravastatin group indicates some variation in the true response. Therefore, we used the difference in the variance of change from baseline to 6 months between the pravastatin and placebo groups to estimate the variation in true response to treatment with pravastatin.

Variation in Long-Term Change within and among Patients

After initial response to therapy, the apparent changes in cholesterol level measurements over time comprise 3 components: 1) the average, true, long-term change in cholesterol level of the whole group, which we estimated from the group average at each time point; 2) short-term variability, which is a combination of analytic variability and week-to-week biological fluctuation around a stable average; and 3) long-term variability, which is a variation in true, long-term change among individuals (as would be seen with the theoretical average of a large number of measurements per individual).

To estimate short-term variability, we used 2 methods. First, we used the cholesterol concentrations during the run-in period (excluding the first measurement), measured only 4 weeks apart, to provide a direct estimate of short-term (4-week) variability. Second, we used a linear extrapolation backward from the longer-term measurements ("variogram" method) (8), to estimate what the apparent variance would be at time 0.

We estimated the long-term variability with a linear mixed-effects model and a direct method. Details and equations are provided in the **Appendix** (available at www.annals.org). The next sections outline the statistical methods, assumptions, and problems.

Modeled Method of Estimation

We estimated the components of variance by using a mixed longitudinal model, which assumed that each patient had a linear increase over time but that the rate of increase varied between patients. Specifically, if each patient i has a rate of increase β_i over time and these rates follow a normal distribution $N(\beta, \sigma_1^2)$, the model was:

$$CHOL_{it} = T_i + \beta_1 t + \omega_{it}$$

with T_i again being the true cholesterol measurement at baseline, and ω_{it} being the error terms for $t = 1, 2, \ldots n_i$, which are independent from each other even for the same patient. The **Appendix** (available at www.annals.org) gives more details and equations.

Direct Method of Estimation

The direct method to estimate long-term variability uses the variance of the differences between the baseline value and each subsequent time point, calculated as:

(cholesterol level at time i − cholesterol level at baseline)

in which the times i are 6 months to 5 years after the stable baseline (which we have taken as 6 months after treatment for the pravastatin group). By subtracting the short-term variability (described in the previous section) from this variability of the change, we estimated the additional long-term variability. In general, the direct method and the modeled method gave similar estimates, but the latter esti-

Context

What is the optimal monitoring interval for patients taking cholesterol-lowering medication?

Contribution

This analysis of data from a trial that compared pravastatin with placebo in patients with coronary disease found that the signal–noise ratio in cholesterol monitoring was weak. Short-term variability of measurement was about −0.80 to 0.80 mmol/L (−31 to 31 mg/dL). Calculations suggested that frequent follow-up of patients with values 0.5 mmol/L (19 mg/dL) or more under target detected many more false-positive results than truly elevated cholesterol values.

Implication

Consider testing adherent patients with well-controlled cholesterol levels every 3 to 5 years rather than every few months or annually.

—The Editors

Table 1. **Average Total Cholesterol Concentrations in the Placebo and Pravastatin Groups in the LIPID Study at Randomization (Baseline), 6 Months, 3 Years, and 5 Years***

Treatment Group	Patients, *n*†	Mean Cholesterol Level (SD) [Interquartile Range]	
		mmol/L	*mg/dL*
Placebo			
Baseline	4502	5.65 (0.81) [5.1–6.2]	218 (31) [197–239]
6 months	4307	5.67 (0.84) [5.1–5.6]	219 (32) [197–216]
3 years	3881	5.60 (0.87) [5.0–6.2]	216 (34) [193–239]
5 years	3602	5.73 (0.90) [5.1–6.3]	221 (35) [197–243]
Pravastatin			
Baseline	4512	5.65 (0.82) [5.1–6.2]	218 (32) [197–239]
6 months	4318	4.49 (0.81) [3.9–5.0]	173 (31) [151–193]
3 years	3979	4.51 (0.86) [3.9–5.0]	174 (33) [151–193]
5 years	3735	4.63 (0.88) [4.0–5.1]	179 (34) [154–197]

* LIPID = Long-Term Intervention with Pravastatin in Ischaemic Disease.
† Includes both deaths and crossovers; patients were censored from the time of death or crossover.

mate seemed to increase too slowly at first and too rapidly later. Alternative functional relationships may be needed.

Censored Values

Few patients were lost to follow-up. However, to estimate the change for those who were receiving stable treatment, a key issue was patients who withdrew or started taking a nonstudy cholesterol-lowering treatment. To estimate the change, we used 3 methods. First, when patients discontinued or started taking alternative cholesterol-lowering medication, we "censored" the data and replaced values thereafter with the last value carried forward for each subsequent measurement. Second, we excluded patients who stopped or began taking the study medication. These 2 methods have small (and opposing) biases, so we examined any discrepancy between the methods. Third, we performed an extrapolation based on a weighted sum of the group trend and the individual patient's own trend.

Detectability of Long-Term Changes ("Signal") Given Within-Person Variation ("Noise")

Finally, we aimed to estimate true- and false-positive rates: the number of patients whose "true" cholesterol level would or would not exceed an acceptable threshold. After a treated patient's cholesterol level has stabilized, 2 elements may lead to a true increase in cholesterol level: the average change of the whole group over time and the real variation around the average change. To estimate these, we used the average change (0.03 mmol/L [1 mg/dL] per year) and the true within-person variability (estimated as described previously), and—for time points of 1, 3, and 5 years—a normal distribution to estimate the proportion whose true value would or would not have changed beyond that acceptable threshold. For those below or above the target value, we calculated the error rate on the basis of the short-term variability.

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RESULTS

At baseline, 9014 patients with a median age of 62 years (83% male) and an average pretreatment cholesterol level of 5.65 mmol/L (SD, 0.82; range, 3.0 to 9.2 mmol/L) (218 mg/dL [SD, 32; range, 116 to 355 mg/dL]) were randomly assigned to pravastatin or placebo. **Table 1** shows the cholesterol levels over time. Only 1 patient was lost to follow-up, but by year 5, about 5% and 6% of patients had died in the pravastatin and placebo groups, respectively.

Of the patients randomly assigned to pravastatin, 6%, 11%, and 19% had permanently stopped taking the study drug after 1 year, 3 years, and at the end of the study, respectively. Of those assigned to placebo, 3%, 9%, and 24% had begun open-label therapy with a cholesterol-lowering drug after 1 year, after 3 years, and at the end of the study, respectively. For patients discontinuing study medication, cholesterol levels after that time point were based on the last value (see "Censored Values" in the Methods section).

Variation in Initial Response to Treatment

At 6 months, patients in the pravastatin group had a slightly greater variation of change in total cholesterol level (0.56 $mmol^2/L^2$ [21.8 mg^2/dL^2]) than those in the placebo group (0.42). This difference in variation (0.14) is due to the variation in true response to treatment with pravastatin. Therefore, the SD of variation in true change was 0.37 mmol/L (14 mg/dL). Because the average initial decrease

in total cholesterol level of the pravastatin group was 1.16 mmol/L (45 mg/dL), the range of true decrease from pravastatin treatment is 1.16 ± 0.74—that is, a 95% range of true response from 0.42 to 1.90 mmol/L (16 to 73 mg/dL).

Variation in Long-Term Change within and among Patients

Average Long-Term Change in Total Cholesterol Level

Although the difference in cholesterol levels between the pravastatin and placebo groups changed little (**Table 1**), both groups showed a small increase. For the pravastatin group, the average increase was 0.14 mmol/L (5.4 mg/dL) from 6 to 60 months, or an average of about 0.7% per year.

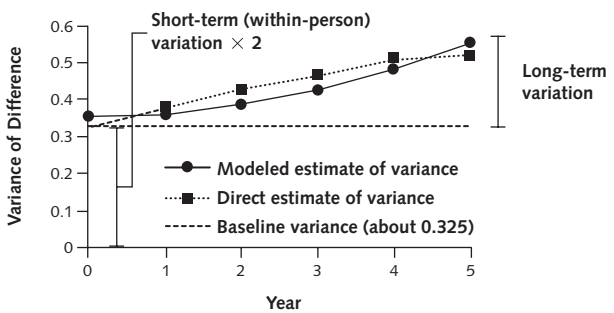
Short-Term, Within-Person Variation

During the prerandomization phase of the LIPID study, the variance of difference between pairs of cholesterol level measurements was 0.27 and 0.36 $mmol^2/L^2$ for the placebo group ($n = 206$) and the pravastatin group ($n = 203$), respectively. This variance of difference is twice that of an individual measurement. Therefore, the SD for the short-term variability of a single measurement is 0.38 and 0.42 mmol/L for the placebo group and the pravastatin group, respectively (the square root of one half the variance of difference). For the average of these (0.40 mmol/L [15 mg/dL]), this is a coefficient of variation of 0.40 divided by 5.65, which equals 7%. The 95% CI on a single cholesterol level measurement would be −0.80 to 0.80 mmol/L (−31 to 31 mg/dL).

Variation in Long-Term, True Change

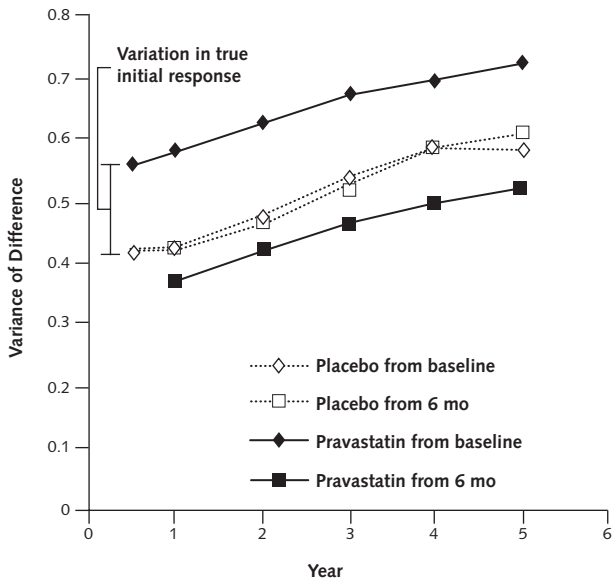
Figure 1 shows the modeled and direct estimates of the variance of change in total cholesterol levels for the pravastatin group. In **Figure 1**, we can partition the increase in variances over time into a component occurring because of the constant short-term variation and the increasing long-term variation. The variogram method of a linear backward extrapolation estimates the baseline variance to be about 0.325. This is between the 2 values found previously by using the prerandomization measurements, which were taken 4 weeks apart.

Figure 1. **Modeled and direct estimates of the variance of difference among individual cholesterol levels in the pravastatin group over 5 years.**



The variance can be partitioned into the constant variance of the short-term differences (equal to twice the within-person variance of single measurements) plus the increasing long-term variation. The dashed line back from 1 to 0 years is used to estimate the short-term variability.

Figure 2. **Within-person variances of difference in total cholesterol concentration for pravastatin and placebo.**



The initial difference (*bracket*) between pravastatin and placebo is due to the variation in true response to pravastatin.

As shown in **Figure 2**, the variation in difference occurred in both the placebo and pravastatin groups. The variation in difference in the pravastatin group starts from a higher initial value because this includes not only the short-term biological variability but also a component of variation in true response to pravastatin treatment during the first 6 months. From the starting point of 6 months, the increase in variance was similar in the 2 groups.

The long-term variance increases over time from 0 at baseline to about 0.19 mmol/L (SD, 0.44) (7 mg/dL [SD, 17]) by year 4.

The LDL cholesterol levels in the placebo and pravastatin groups were 3.9 and 2.8 mmol/L (151 and 108 mg/dL), respectively. The variances of difference from baseline for years 1, 3, and 5 were 0.32, 0.42, and 0.45 mmol/L (12, 16, and 17 mg/dL), respectively, for the placebo group and 0.49, 0.53, and 0.56 mmol/L (19, 20, and 22 mg/dL), respectively, for the pravastatin group. These are about the same as the cholesterol level variances, but with a lower mean. Therefore, the coefficients of variation for LDL cholesterol levels will be slightly larger.

Bland–Altman plots (9) (not shown) demonstrated that between-person variability and within-person variabil-

Table 2. **Estimated Percentages of True-Positive and False-Positive Total Cholesterol Measurements**

Initial True Level in Adherent Patients	True Level >5 mmol/L (>195 mg/dL), %	True-Positive Results of All Measurements, %	False-Positive Results of All Measurements, %	False Positive–True Positive Ratio
4.5 mmol/L (176 mg/dL)				
Year 1	1.5	0.87	14	16
Year 3	13	8.9	14	1.6
Year 5	21	15	13	1
4.0 mmol/L (156 mg/dL)				
Year 1	0.0004	0.0006	1.7	>1000
Year 3	0.7	0.43	4.3	10
Year 5	2.7	1.7	6.0	3

ity were stable at different starting cholesterol levels within the range of the LIPID study patients.

Detectability of Long-Term Changes

To illustrate the effect of true and apparent change with time, we used 2 alternative assumed values for the true cholesterol level—4.5 or 4.0 mmol/L (174 or 154 mg/dL)—after the initial response to treatment (approximated by taking the average of many posttreatment cholesterol level measurements). Using these true values and the estimated short-term and long-term variations, we calculated the chance that true and observed values would exceed a threshold of 5.0 mmol/L (193 mg/dL) at different time points. **Table 2** shows the resulting rate of true-positive results and false-positive results. We may also interpret the values in **Table 2** as the likelihood of a 0.5- or 1.0-mmol/L (19- or 39-mg/dL) true drift at different time intervals.

Discussion

The data from the LIPID study suggest that, after treatment, true long-term changes in total and LDL cholesterol levels occur relatively slowly. The average increase in cholesterol levels of 0.5% per year is a little less than the 1% observed rate in cohort studies (10), but this may be because of either the dietary adherence to the monitoring or the addition of further cholesterol-lowering therapy in some patients in the LIPID study.

Our estimate of within-person coefficient of variation of 7% is similar to estimates in other studies. For example, cholesterol level measurements obtained 1 year apart in the 14 600 patients with mild hypertension in the United Kingdom Medical Research Council trial (11) showed a within-person coefficient of variation of 7%. However, the estimates vary with time between measurements. For example, a study of 41 healthy volunteers (12) showed a coefficient of variation of 2% to 3% for measurements done 24 hours apart that increased to 4% to 5% for measurements done 4 weeks apart. Similarly, a study of 458 patients showed a coefficient of variation of 3% for total cholesterol level at a median of 4 days between blood collections (13) and a geometric mean of the within-person SD of 0.13 mmol/L (5 mg/dL).

In the placebo and pravastatin groups, the modest relative increase in within-person variability (**Figures 1** and **2**) per year suggests that, in the first few years, most of the variation is due to short-term biological and analytic variability. The changes found in the LIPID study are consistent with the shorter-term changes seen in other studies, but we have not been able to identify published results for variation beyond 1 year.

As can be deduced from **Figure 1**, it is not until 3 years that this long-term variation is greater than the short-term variation. As **Table 2** suggests, this means that monitoring adherent patients will probably lead to detection of many more false-positive than true-positive results (those truly over target).

Our data have limitations. First, we studied only 1 cholesterol-lowering treatment, 40 mg of pravastatin; other agents may have different degrees of variation in response. Although the average change may be different with other doses and other statins, we would expect that the between-person variation in response would be similar; however, this needs to be confirmed in other data sets. Second, there may be some attenuation of variation because of the need to impute future values in patients who began or stopped taking treatment. However, a range of different methods of imputation did not make a substantial difference to our conclusions. This is likely to be a limitation in all such studies of long-term variation, and indeed, adherence was generally better in the LIPID study than in other trials or in usual care. The lower adherence in practice would probably increase the

Table 3. **Key Clinical Messages**

- For cholesterol measurements, the coefficient of variation for short-term variation is about 7%; therefore, a 95% CI is typically −0.80 to 0.80 mmol/L (−31 to 31 mg/dL).
- The initial decrease in response to statin therapy varies: For 40 mg of pravastatin, the average reduction is 1.16 mmol/L (45 mg/dL), but the range of true decrease is 0.42 to 1.90 mmol/L (16 to 73 mg/dL).
- Long-term increases in fixed-dose therapy are small compared with short-term variation.
- It takes approximately 3 years before plausible changes in true cholesterol values could be comparable with the short-term variation—that is, before "signal" equals "noise."

variation seen. Finally, in calculating the false-positive rates shown in **Table 2**, we assumed a known true cholesterol level, which can only be approximated by multiple measurements.

These results have clinical implications (**Table 3**). A key implication of our findings is that after the initial decrease in cholesterol level in response to treatment (perhaps with dose titration to reach a target value), subsequent cholesterol level monitoring might be much less frequent than is currently recommended. Much of current testing will detect only false-positive results—that is, changes that are related to either short-term biological variation or analytic error. On the basis of the results in **Table 2**, retesting adherent patients every 3 to 5 years may be sufficient once adequate response has been attained. At such intervals, a single high or borderline-high value might warrant retesting within a few weeks to obtain a better estimate of the true cholesterol concentration. However, clinicians may be unwilling to tolerate such long delays because of concerns about adherence, and patients may wish to have more rapid feedback about their status. Although the combination of regular visits, education, adherence assessment, and point-of-care testing has improved initial adherence to treatment (14), it is not clear what contribution testing makes to this effect. Furthermore, other ways to assess adherence may be preferable, such as prescription refill records or nonthreatening inquiries about adherence (15). However, the incremental role of testing in follow-up visits warrants further research.

There is generally a weak signal–noise ratio in cholesterol level monitoring. The signal of a small increase in cholesterol level will be difficult to detect against the background of a short-term variability of 7%. Current guidelines that recommend annual or more frequent monitoring should be reconsidered.

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Appendix

This Appendix sets out the possible models of cholesterol level change over time, taking into account both measurement error and long-term true changes.

As explained in the Methods section, the apparent changes in cholesterol level measurements over time have 3 components:

1. A short-term variation, which is a combination of analytic variability and day-to-day biological fluctuation around a stable average.

2. The average true, long-term change in cholesterol level of the whole group.

3. A variation in long-term true change between individuals (as would be seen with the theoretical average of a large number of measurements per individual).

We set out 3 models. The first is a simple model that assumes no change in true cholesterol level (as described by Rosner and Willett [16]). The next 2 include a change over time: a linear model and a simple direct model.

Measurement Error, with No Trend

Suppose that T_i is the true long-term cholesterol for patient i but that measurements of true cholesterol will be imperfect. The measurement of cholesterol $CHOL_{it}$ for patient i at time t will have a measurement error ω_{it}, so that for times t_1 and t_2:

$$CHOL_{i1} = T_i + \omega_{i1}, \qquad CHOL_{i2} = T_i + \omega_{i2},$$

or, more generally:

$$CHOL_{it} = T_i + \omega_{it}$$

We generally assume (but need to check) that the true values T_i are distributed normally, $N(\mu_T, \sigma_T^2)$ and that the error ω_{it} is also distributed normally, $N(\mu, \sigma_W^2)$. In addition, T_I and ω_{it} are independent and the error terms ω_{it} for $t = 1, 2, \ldots n_i$ are independent from each other even for the same patient.

In this model, σ_T^2 is the between-person variability and σ_W^2 is the within-person variability.

We can use differences in cholesterol level between time points to estimate the within-person variability. For example, using baseline and subsequent times we can compute σ_W^2 as

$$\text{var}(\triangle CHOL_i) = \text{var}(CHOL_{it}) + \text{var}(CHOL_{i0}) = 2\sigma_W^2$$

Therefore, we can calculate σ_W^2 by dividing $\text{var}(\triangle CHOL_i)$ by 2, or by dividing the SD of any difference by the square root of 2 to get an estimate of SD_W.

Linear Model with an Increasing Variance

As the true cholesterol level may change with time, the simple model needs to be extended. One approach is to assume that each patient has a linear increase over time but that the increase varies between patients—that is, each patient i has a rate of increase β_i with time and these follow a normal distribution $N(\beta, \sigma_1^2)$. In that case, the model becomes:

$$CHOL_{it} = T_i + \beta_i t + \omega_{it}$$

with T_i again being the true cholesterol level at baseline. Two special cases of this model are (i) $N(0, \sigma_1^2)$, which has no average increase of the population but allows individual changes, and (ii) $N(\beta, 0)$, in which everyone has the same change over time.

There are now 3 terms and 3 components for the variance: the population baseline variation (between-person variability), the individual variation in trend, and the measurement error (within-person variability). That is:

$$\text{var}(CHOL_{it}) = \sigma_T^2 + \sigma_1^2 t^2 + \sigma_W^2$$

With this model, the formula for the variance of the change from baseline is derived as:

$$\text{var}(\triangle CHOL_{it}) = \sigma_1^2 t^2 + 2\sigma_W^2$$

In our calculations on the LIPID trial, baseline is actually 6 months, because we started timing from when the cholesterol level stabilized after commencement of pravastatin treatment. We therefore use 0, 0.5, 1.5, 2.5, 3.5, and 4.5 for time values at 6 months and 1 through 5 years, respectively.

From the LIPID pravastatin group, our parameter estimates were:

$$\sigma_T^2 = 0.487 + \sigma_1^2 t^2 = 0.0080, \sigma_W^2 = 0.176.$$

Nonlinear Increase in Variance (Direct Method)

The linear model assumes that the cholesterol level and SD will increase approximately linearly with time, but this is likely to be true only for short ranges of time. An alternative, therefore, is to use a separate parameter for each time point.

That is, for each time point, there is an average increase and a distribution to that increase, so we have β_{it} for each time t, and these follow a normal distribution $N(\beta_t, \sigma_1^2)$. In that case, the model becomes:

$$CHOL_{it} = T_i + \beta_{it} + \omega_{it}$$

Appendix Table. **Comparison of the Results from the Model and Direct Methods***

Time, *y*	Model (Equation 2)				Direct Method (Equation 4)		
	σ_T^2	$2\sigma^2_W$	σ_{1t}^{2}*	var($\Delta CHOL_{it}$)	$2\sigma^2_W$	σ_{1t}^{2}*	var($\Delta CHOL_{it}$)
0	0.487	0.352	0.000	0.352	0.325	–	–
1	0.487	0.352	0.008	0.360	0.325	0.047	0.372
2	0.487	0.352	0.032	0.384	0.325	0.098	0.423
3	0.487	0.352	0.072	0.424	0.325	0.137	0.462
4	0.487	0.352	0.128	0.480	0.325	0.179	0.504
5	0.487	0.352	0.200	0.553	0.325	0.194	0.519

* Data are the estimates of long-term variance, which are the key element of interest.

with T_i again being the true cholesterol level measurement at the commencement of monitoring.

Again, there are 3 terms and 3 components for the variance: the population baseline variation (between-person variability), the individual variation in trend, and the measurement error (within-person variability). That is:

$$\text{var}(CHOL_{it}) = \sigma_T^2 + \sigma_{1t}^2 + \sigma_W^2$$

With this model, the formula for the variance of the change from baseline is derived as:

$$\text{var}(\triangle CHOL_{it}) = \sigma_{1t}^2 + 2\sigma_W^2$$

Thus, we can estimate the variance in long-term, true change by subtracting twice the within-person variability:

$$\sigma_{1t}^2 = \text{var}(\triangle CHOL_{it}) - 2\sigma_W^2$$

In which σ_W^2 is estimated from short-term variability studies or the variogram method (see Methods section).

Comparison of Model Results for LIPID Data

We fitted both the direct method and the linear model to compare the results for the LIPID cholesterol level data. As can be seen in the **Appendix Table**, the methods gave similar results in the later years, but the direct method has higher estimates of long-term variability in the earlier years. We therefore chose to use the direct method for calculations because it makes fewer assumptions and is more conservative about the likelihood of early change and is thus more likely to suggest shorter monitoring intervals.