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ABSTRACT

Objectives: To evaluate the optimal lipid to measure in monitoring patients, we assessed three factors that influence the choice of monitoring tests: (1) clinical validity; (2) responsiveness to therapy changes and (3) the size of the long-term 'signal-to-noise' ratio.

Design: Longitudinal analyses of repeated lipid measurement over 5 years.

Setting: Subsidiary analysis of a Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) study—a clinical trial in Australia, New Zealand and Finland.

Participants: 9014 patients aged 31–75 years with previous acute coronary syndromes.

Interventions: Patients were randomly assigned to 40 mg daily pravastatin or placebo.

Primary and secondary outcome measures: We used data on serial lipid measurements—at randomisation, 6 months and 12 months, and then annually to 5 years—of total cholesterol; low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol and their ratios; triglycerides; and apolipoproteins A and B and their ratio and their ability to predict coronary events.

Results: All the lipid measures were statistically significantly associated with future coronary events, but the associations between each of the three ratio measures (total or LDL cholesterol to HDL cholesterol, and apolipoprotein B to apolipoprotein A1) and the time to a coronary event were better than those for any of the single lipid measures. The two cholesterol ratios also ranked highly for the long-term signal-to-noise ratios. However, LDL cholesterol and non-HDL cholesterol showed the most responsiveness to treatment change.

Conclusions: Lipid monitoring is increasingly common, but current guidelines vary. No single measure was best on all three criteria. Total cholesterol did not rank highly on any single criterion. However, measurements based on cholesterol subfractions—non-HDL cholesterol (total cholesterol minus HDL cholesterol) and the two ratios—appeared superior to total cholesterol or any of the apolipoprotein options. Guidelines should consider using non-HDL cholesterol or a ratio measure for initial treatment decisions and subsequent monitoring.

Strengths and limitations of this study

- This study had a large randomised cohort of patients with good adherence and long follow-up. There was some crossover of patients during the trial, but if the crossover effects have equal impact on all lipid measures, the relative rankings should remain the same.
- Assessment of response to changes in treatment used the initial and fixed treatment dose, rather than dose titration. This assumes that detectability of any titration of treatment is similar to the detection of the initial treatment threshold, which may not be true if the dose–response curves are different for the different lipid measures.
- The relationships between lipid changes and outcomes appear consistent across statins, but the rankings may not hold exactly for other statins or other lipid treatments such as fibrates.
- The conclusions need to be replicated in other data sets.

Since the marketing of 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitors, lipid measurement workloads have increased markedly.[1] Much of this testing appears to be for monitoring rather than screening. However, it may be unnecessary: an analysis of the Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) trial[2] suggested that 3–5 yearly monitoring may be sufficient for patients in good control. Subsequent work in a primary prevention population in Japan found that similar intervals were adequate for untreated patients, but also suggested that ratio measures (cholesterol/high-density lipoprotein (HDL) or low-density lipoprotein (LDL)/HDL cholesterol) were superior as monitoring tests.[3] Apolipoproteins are a further option for monitoring, either as a single measure or as a ratio of apolipoprotein B/A1. With widening indications and use of cholesterol-modifying treatment, it is timely to re-examine the most appropriate lipid measurements for monitoring purposes.

The methods and targets for monitoring have incrementally changed over the past two decades. Early guidelines focused on total cholesterol for screening, as a target,

and for monitoring. However, the shift to assessment of absolute cardiovascular disease risk and the better predictive ability of lipid ratios (total /HDL cholesterol or LDL /HDL cholesterol) has led to a move to measure and use a combination of HDL cholesterol and total cholesterol or LDL cholesterol for screening and monitoring.[4 5] The National Institute of Health and Care Excellence (NICE) 2008 guideline[6] pointed out: "Both HDL cholesterol and total cholesterol form integral aspects of the Framingham, QRISK (QRESEACH Cardiovascular Risk Assessment Calculator) and ASSIGN (ASSessing cardiovascular risk using SIGN—Scottish Intercollegiate Guidelines Network) equations," but suggested that LDL cholesterol measurement is not required for risk assessment. LDL cholesterol measurement is also complicated by the need for specialist assays to measure it directly or the analysis of a fasting sample to allow indirect calculation (using the Friedwald equation).[7] The National Cholesterol Education Program guidelines for the USA recommend a 6-monthly monitoring of LDL cholesterol, as do the Australian guidelines of the National Heart Foundation and Cardiac Society.[8] In addition, apolipoprotein B and non-HDL cholesterol can be obtained from fasting or non-fasting samples, but apolipoprotein B also allows a measure of the total number of atherogenic lipoprotein particles, which is particularly important in people with diabetes and the metabolic syndrome.[9]

Selection of an optimal monitoring measure should be based on a consideration of three technical factors: (1) clinical validity, that is, how well the measure is associated with cardiovascular outcomes; (2) responsiveness to therapy changes, that is, how clearly and rapidly the measurement responds to new or changed treatment; (3) a large "signal-to-noise" ratio to identify real changes from background within-patient variability ('noise') and a non-technical factor, (4) practicality, including costs, clinicians' familiarity and interpretability, access to the test and the speed of results (including whether it is available as a near-patient test).[10]

We therefore aimed to examine the three technical factors for the potential lipid measurements for long-term monitoring: total, LDL, HDL and non-HDL cholesterol, the cholesterol ratios, and apolipoproteins (A1 and B), and ratios.

METHODS

Data from the LIPID trial were analysed. In LIPID, 9014 patients from Australia, New Zealand and Finland, aged 31–75 years, who had had acute myocardial infarction or hospitalisation for unstable angina 3–36 months previously and total cholesterol 4–7 mmol/L, were randomised to 40 mg of pravastatin (4512 patients) or matching placebo (4502) and followed up for an average of 6 years.[2] The trial included 6 monthly cholesterol measurement, as well as information on compliance to assigned therapy and 'drop-in' to other cholesterol-modifying therapy. LDL cholesterol was estimated by using the Friedwald equation, and patients with fasting serum triglycerides >4.5 mmol/L (445 mg/dL) were excluded from the study. The prespecified primary outcome for subgroup analysis was death from coronary heart disease (CHD) or non-fatal myocardial infarction and that outcome has been used here. Deaths from CHD were further classified as death due to fatal myocardial infarction, sudden death, death in the hospital after possible myocardial infarction, or death due to heart failure or another coronary cause.

Clinical validity was assessed by examining the association of each measure with occurrence of coronary events (CHD death and non-fatal infarction, as was prespecified as the primary outcome for subsidiary analyses in the protocol) in all patients over 5 years of follow-up. This built on a previous analysis of the LIPID study,[11] which estimated the HR for such events per unit change. However, the HRs are expressed in the arbitrary units of their measurement, and do not account for population prevalence or spread. Hence, to account for the range in the population, and to make the measures comparable, we calculated the HR from measures in the interquartile range (IQR).

Responsiveness to change in therapy was assessed by two methods. First, we estimated the proportional change in response to initiation of pravastatin treatment; if the lipid measure had clinical validity, then the proportional change would be a good surrogate measure of treatment response. Second, we divided this proportional change by the short-term variability ('noise') in the particular measure.[12] This was equivalent to estimating the ratio of the percentage change to the coefficient of variation, and was a standardised measure of the maximum potential variability in response. However, it was not a direct measure of the between-person variability in response and might appear substantial even when all patients had the same response to treatment.

Short-term variability, which involves multiple factors including assay variability, diurnal variation, short-term variation in diet or physical activity, etc, was estimated by two methods. The first used assays during the run-in period (excluding the first measurement), which were taken only a few weeks apart. Second, because of the possible short-term correlation, this result was checked with linear extrapolation backwards from the longer-term measures, to establish what the apparent variance at time 0 would be (this method is known as a 'variogram').

To estimate the detectability of long-term changes (the signal-to-noise), we needed to estimate the long-term variability (the 'signal') and compare this with the short-term variability (the 'noise': see previous paragraph). The long-term variability was derived from the average squared difference of the measure compared with the baseline, that is $(\text{measure at time}_i - \text{measure at time}_0)^2$, where time_i is the 6-month, 12-month or 18-month time point. The within-person variability for

Table 1 Clinical validity for prediction of coronary heart disease death or non-fatal myocardial infarction, in 4502 patients randomised to the placebo group*

Lipid	HR per unit (95% CI)	p Value	HR (95% CI) over IQR*	Rank†
Total cholesterol (mmol/L)	1.12 (1.02 to 1.23)	0.02	1.13 (1.02 to 1.26)	9
LDL cholesterol (mmol/L)	1.15 (1.04 to 1.27)	0.01	1.15 (1.04 to 1.28)	8
HDL cholesterol (mmol/L)	0.53 (0.37 to 0.74)	0.001	1/1.20 (0.74 to 0.92)	5
Total to HDL cholesterol ratio	1.14 (1.08 to 1.19)	0.001	1.29 (1.17 to 1.42)	2
LDL to HDL cholesterol ratio	1.19 (1.12 to 1.27)	0.001	1.30 (1.18 to 1.43)	1
Non-HDL cholesterol (mmol/L)‡	1.18 (1.08 to 1.30)	0.001	1.20 (1.09 to 1.34)	5
Triglycerides (mmol/L)	1.07 (0.99 to 1.16)	0.09	1.07 (0.99 to 1.15)	10
Apolipoprotein A1 (g/L)	0.48 (0.34 to 0.70)	0.001	1/1.22 (0.74 to 0.90)	4
Apolipoprotein B (g/L)	1.64 (1.21 to 2.21)	0.001	1.18 (1.06 to .130)	7
Apolipoprotein B/A1	2.05 (1.54 to 2.73)	0.001	1.28 (1.16 to 1.41)	3

*Data derived from Simes and coauthors.[12]
†Rank is based on the predictive power irrespective of direction: higher HDL and apolipoprotein A are protective.
‡Total minus HDL cholesterol.
HDL, high-density lipoprotein; LDL, low-density lipoprotein.

each of the different periods is half the variance of this difference. By subtracting the short-term variability from the long-term variability, the 'random drift' with time could then be estimated, and hence the likelihood of a patient's 'true' measure having drifted beyond the upper or lower boundaries around the target.

As the aim was to estimate change in those on stable treatment, a key issue was coping with the patients who dropped into or dropped out of treatment. Hence, when patients dropped in to cholesterol-modifying medication, they remained in the analysis but the data were 'truncated', and values were thereafter replaced with an imputed value (eg, the last value carried forward).

CIs based on the 2.5th centile to the 97.5th centile from 2000 bootstrap estimates of each of the measures are provided.[13]

RESULTS

Clinical validity

Among all patients, 12.3% (557) of those assigned pravastatin and 15.9% (715) assigned placebo had a major CHD event during follow-up. Among the 4231 patients assigned placebo who had all baseline lipid measures, there were 664 events; all the lipid measures showed a statistically significant association with future coronary events (table 1).

All had positive HRs except HDL cholesterol and apolipoproteins B and A1, which were negative (protective). The HR per unit (column 1) depends on the units used. To compare the different measures, the HR from the upper to the lower quartile was calculated (final column; also see table 2). On this scale, the association with CHD events of the three ratio measures (total or LDL cholesterol to HDL cholesterol, and apolipoprotein A1 to B) was better than any of the single measures. For example, for LDL cholesterol the hazard increases by 15% between the lower and upper quartile, whereas for the LDL/HDL cholesterol the hazard increases 30% from the lower to upper quartile. Similarly, the apolipoprotein B/A1 ratio was better than either of the apolipoproteins alone. Thus, the ratios appeared more strongly associated with coronary events during the study than single measures.

Responsiveness to therapy changes

The responsiveness to change in therapy is ideally measured by examining the size and variation in responses

Table 2 25th and 75th centiles and IQR for baseline lipid measurement in the placebo group, corresponding to table 1

Lipid	25th centile	75th centile	Difference (IQR)
Total cholesterol (mmol/L)	5.08	6.20	1.12
LDL cholesterol (mmol/L)	3.40	4.41	1.01
HDL cholesterol (mmol/L)	0.79	1.09	0.30
Total to HDL cholesterol ratio	1.18	2.12	0.94
LDL to HDL cholesterol ratio	1.17	1.45	0.28
Non-HDL cholesterol (mmol/L)*	1.16	1.49	0.33
Triglycerides (mmol/L)	5.12	7.14	2.02
Apolipoprotein A1 (g/L)	3.45	4.98	1.53
Apolipoprotein B (g/L)	0.86	1.20	0.34
Apolipoprotein B/A1	4.14	5.24	1.10

*Total minus HDL cholesterol.
HDL, high-density lipoprotein; LDL, low-density lipoprotein.

to up-titration or down-titration of long-term therapy through changes in dose or additions of medications. However, in the LIPID trial, patients were all maintained on a fixed dose of therapy for the duration of the study. Hence, the size and variation in response to initial therapy were examined as a surrogate for responsiveness to ongoing titration. The changes in 4512 patients randomised to pravastatin are consistent with known responses to statins, demonstrating a substantial decrease in total cholesterol and LDL cholesterol, and a small increase in HDL cholesterol (table 3). LDL cholesterol ranks highly on the percentage change and the ratio of percentage change to the coefficient of variation. Ideally, these results would be supplemented by a similar analysis of the effects of a further titration step, for example, increasing the dose or adding additional cholesterol-modifying medication.

Large signal-to-noise ratio

The ratios of signal-to-noise (table 4) were best for the ratio measures, with only total/HDL cholesterol and LDL /HDL cholesterol exceeding 1 after 3 years. The values in table 4 are for the 4502 patients in the placebo group, as this allows the signal to be estimated from the baseline rather than in later follow-up when the effect of statin treatment has become stable. However, the signal-to-noise results were similar when the shorter follow-up available for the (not presented) statin-treated group was examined.

Summary rankings

Judged by rankings (table 5), no single measurement was best for all three criteria. However, total cholesterol did not rank highly on any of the criteria, although the measures based on cholesterol subfractions did rank highly. None of the measures based on apolipoproteins ranked particularly well, though the ratio of apolipoprotein A1–B performed best.

DISCUSSION

On the three criteria of clinical validity, responsiveness to treatment changes and detectability of long-term changes, differences between the potential lipid measures were substantial. No single measure was best on all three criteria. Total cholesterol did not rank highly on any single criterion. However, measurements based on cholesterol subfractions—the two ratios and non-HDL cholesterol (total minus HDL cholesterol)—appeared superior to either total cholesterol or any of the apolipoprotein options.

The findings for the separate criteria are generally consistent with previous studies. For initial risk measurement, there is evidence from cohort studies[14–16] and a meta-analysis[17] to suggest that lipid ratios (total/HDL cholesterol and LDL/HDL cholesterol) have higher associations with CHD than individual serum total or LDL cholesterol levels. The results for the third criteria were similar to those of a study of a primary-prevention population in Japan, which showed that lipid ratios have larger signal-to-noise ratios than single standard lipids (1.6 for total/HDL cholesterol and 1.5 for LDL/HDL cholesterol compared with 0.8 for total cholesterol and 0.99 for LDL cholesterol).[3]

Although this study had a large randomised cohort of patients with good adherence and long follow-up, there are some limitations. First, there was some crossover, both dropout from and drop-in to treatment, of patients during the trial, which will influence the assessment of clinical validity and the signal-to-noise ratios. However, if the crossover effects have equal impact on all lipid measures, then the relative rankings should remain the same. Another limitation is our assessment of response to changes in treatment, which used the initial and fixed

Table 3 The absolute and percentage change in lipids in response to initial statin treatment compared with the coefficient of variation, in 4512 patients randomised to pravastatin

Lipid	Change	Change (%)	Rank	Variation (coefficient of variation) (%)	Change/coefficient of variation (%)	Rank*
Total cholesterol (mmol/L)	1.16	21	7	0.30 (10)	2.13 (2.11, 2.19)	3
LDL cholesterol (mmol/L)	1.09	28	2	0.25 (28)	2.20 (2.16, 2.24	1
HDL cholesterol (mmol/L)	−0.04	−4	10	0.01 (11)	−0.35 (−0.38, −0.33)	10
Total to HDL cholesterol ratio	1.40	23	5	1.46 (20)	1.81 (1.78–1.84)	7
LDL to HDL cholesterol ratio	1.29	30	1	0.73 (20)	1.95 (1.92–1.99)	5
Non-HDL cholesterol (mmol/L)†	1.18	25	4	0.29 (11)	2.20 (2.14, 2.21)	1
Triglycerides (mmol/L)	0.19	11	8	0.27 (29)	0.37 (0.35, 0.40)	9
Apolipoprotein A1 (g/L)	−0.07	6	9	0.014 (9)	−0.62 (−0.66, −0.60)	8
Apolipoprotein B (g/L)	0.29	22	6	0.02 (12)	1.86 (1.83, 1.91)	6
Apolipoprotein B/A1	0.27	26	3	0.02 (13)	2.01 (1.98, 2.04)	4

*Rank is based on the absolute size of the change/coefficient of variation, irrespective of direction.
†Total minus HDL cholesterol.
HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Table 4 Signal-to-noise ratios at 1 and 3 years (change from placebo group; CV from all patients)

Lipid	Signal		Noise	Signal-to-noise ratio		
	Change from year 0			Change/CV		
	Year 1	Year 3	CV	Year 1	Year 3	Rank
Total cholesterol (mmol/L)	0.13	0.24	0.30 (10)	0.43 (0.38–0.51)	0.80 (0.73–0.89)	8
LDL cholesterol (mmol/L)	0.08	0.17	0.25 (13)	0.31 (0.26–0.39)	0.70 (0.61–0.78)	10
HDL cholesterol (mmol/L)	0.01	0.01	0.013 (12)	0.54 (0.44–0.63)	0.97 (0.85–1.09)	3
Total to HDL cholesterol ratio	0.37	0.86	0.63 (13)	0.59 (0.53–0.70)	1.37 (1.31–1.50)	1
LDL to HDL cholesterol ratio	0.22	0.54	0.42 (15)	0.53 (0.46–0.64)	1.29 (1.25–1.47)	2
Non-HDL cholesterol (mmol/L)	0.14	0.22	0.27 (11)	0.52 (0.45–0.70)	0.82 (0.73–0.89)	6
Triglycerides (mmol/L)	0.23	0.42	0.37 (34)	0.37 (0.29–0.53)	0.88 (0.73–0.89)	5
Apolipoprotein A1 (g/L)	0.01	0.02	0.02 (11)	0.33 (0.28–0.39)	0.77 (0.68–0.86)	9
Apolipoprotein B (g/L)	0.01	0.02	0.03 (12)	0.52 (0.38–0.62)	0.82 (0.69–0.93)	6
Apolipoprotein B/A1	0.01	0.01	0.02 (13)	0.45 (0.37–0.58)	0.89 (0.77–1.08)	4

CV, coefficient of variation; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

treatment dose, rather than dose titration. This assumes that detectability of any titration of treatment is similar to the detection of the initial treatment threshold. This may not be true if the dose–response curves are different for the different lipid measures. Related to this assumption is our use of a single large trial of pravastatin. While the relationship between lipid changes and outcomes appears consistent across statins,[18] the rankings here may not hold exactly for other statins, and less so for other lipid treatments such as fibrates.

In addition to the need for replication in other populations and with other agents, there are some other limitations of our analyses. While the three technical criteria—clinical validity, responsiveness and good 'signal-to-noise'—are appropriate, many options to measure each are possible. For example, we assessed the predictive validity of the measures at baseline, but could also have assessed the predictive validity of the change values; similarly, while we used responsiveness to initial treatment as the measure, responsiveness in titration might be clinically more relevant, but would be more difficult to measure and less discriminating. In generalising these results to different populations and different agents, the assumption would be that while the exact values such as changes and CVs would be different, the rankings would remain the same. For example, the IQRs used for the clinical validity measure are likely to be larger in other populations (as LIPID had a restricted range), but if these increases in IQR were proportionately equal, then the rankings would be preserved. However, these assumptions, while not unreasonable, need to be tested in these other populations and agents.

The main implication of these results is that total cholesterol, based on the three technical criteria, is not the 'optimal' measurement for monitoring statin treatment. While LDL cholesterol is somewhat better, it was still low in the rankings. The most promising and practical measurement would appear to be either the non-HDL cholesterol or the LDL/HDL cholesterol ratio. The ratios (LDL /HDL cholesterol or total/HDL cholesterol) have the advantage of being widely used currently for the initial assessment of cardiovascular risk, with total/HDL cholesterol having the practical advantage of not needing LDL measurement.

Table 5 Summary of ranking of lipid measurements for three criteria: clinical validity; response to therapy changes and long-term signal-to-noise ratio

Lipid measurement	Validity	Change (%)	Change/coefficient of variation (%)	Long-term signal-to-noise
Total cholesterol	9	7	3	8
LDL cholesterol	8	2	1	10
HDL cholesterol	5	10	10	3
Total to HDL cholesterol ratio	2	5	7	1
LDL to HDL cholesterol ratio	1	1	5	2
Non-HDL cholesterol	5	4	1	6
Triglycerides	10	8	9	**5**
Apolipoprotein A1	4	9	8	9
Apolipoprotein B	7	6	6	6
Apolipoprotein B/A1	3	3	4	4

HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Using a ratio for monitoring would then mean that the same measure was being used for initial and subsequent measurement and would simplify guidelines and the numbers that clinicians and patients would need to know. One problem, however, is the instability of ratios in patients with very low HDL cholesterol. This latter problem does not occur with non-HDL cholesterol, which has several other advantages: it also appears to do well on most of the criteria; it does not require LDL measurement (direct or indirect); and it is readily available or can be easily calculated from current laboratory reports.

Our analysis suggests that, based on the three technical criteria, a cholesterol difference (non-HDL cholesterol) or ratio (LDL/HDL cholesterol) is preferable as lipid-monitoring measurements for patients taking statins (the issue of detecting non-compliance by monitoring was not considered, and has been analysed elsewhere).[19] However, the fourth criterion—practicality—will clearly also influence this choice: non-HDL is feasible and robust but less familiar to clinicians, whereas the ratios are more familiar but rely on an accurate LDL measurement and automated calculations carried out by laboratories. Furthermore, our conclusions are based on a single study in patients with established CHD and need to be replicated in other data sets. These should include assessment of the measures during treatment with cholesterol-modifying therapies other than HMG-CoA reductase inhibitors, which might have different effects on lipid parameters.

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Contributors PPG and LI conceived and designed the study. PPG drafted the manuscript. ACK analysed the data. All authors interpreted the data and contributed to the writing of the manuscript. All authors approved the final version of this paper for submission.

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Competing interests None.

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