Reference standardization and analytical performance of a liquid homogeneous high-density lipoprotein cholesterol method compared with chemical precipitation method

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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
High-density lipoprotein cholesterol (HDL-C) determinations on the Hitachi 911 using LN-gen (Liquid N-geneous, a technique which employs a highly selective detergent, ensuring specificity for HDL and allowing for the direct and fully automated measurement of HDL-C) or phosphotungstic acid (PTA)/magnesium chloride precipitation for analysing specimens stored at 4 centigrade within 48 hours after collection; and using HDL-C RM (high-density lipoprotein cholesterol reference method, a 3-step technique employing ultracentrifugation, precipitation, and cholesterol analysis) or HDL-C DCM (high-density lipoprotein designated comparison method, involving the elimination of ultracentrifugation, and direct precipitation of apo B-containing lipoprotein) for analysing specimens stored at -70 centigrade within 1 month after collection.

Type of intervention
Diagnosis.

Economic study type
Cost-effectiveness analysis.

Study population
Serum and plasma specimens collected from seemingly healthy donors.

Setting
Hospital. The economic study was carried out in Rotterdam, The Netherlands.

Dates to which data relate
No dates were specified.

Source of effectiveness data
Effectiveness data were derived from a single study.

Link between effectiveness and cost data
Costing was retrospectively performed on a sub-sample of the patients used in the effectiveness analysis.

Study sample
Power calculations were not used to determine the sample size. The study sample consisted of 115 normotriglyceridemic serum specimens (triglyceride values of 0.36 - 1.99 g/L). 71 of the specimens were collected at Genzyme (Cambridge, Mass) and 44 were from the University Hospital Rotterdam. The LN-gen and PTA precipitation
methods were performed on the Genzyme sample; a subset of 46 specimens was used to perform HDL-C DCM. The LN-gen, PTA precipitation, and HDL-C DCM were performed on the Rotterdam sample. The study sample further consisted of 69 serum specimens with triglyceride of more than 2.0 g/L (27 from Genzyme and 42 from Rotterdam). The LN-gen, PTA precipitation, and HDL-C RM analyses were performed on all of the samples described above.

**Study design**

This was a prospective diagnostic study, carried out in three centres on samples from two settings. A before and after study was carried out on 10 subjects experiencing 10 to 12 hours' overnight fasting, who then had a meal consisting of egg, meat, cream, and butter. The duration of storage time for specimens was until 1 month after collection. No loss to follow-up was reported.

**Analysis of effectiveness**

The principle used in the analysis of effectiveness (intention to treat or treatment completers only) was not explicitly specified. The outcome measures were linearity, and analytical performance in terms of total error, bias, and imprecision. The outcome results were reported for the individual sites and for the combined data set. Linear regressions of the HDL-C values attained by the PTA and LN-gen HDL-C were performed relative to DCM to estimate the mean percent bias. Total cholesterol, triglycerides, and LN-gen HDL-C were measured for specimens taken from subjects experiencing periods of fasting and non-fasting.

**Effectiveness results**

It was reported that the analytic precision of the LN-gen HDL-C assay (with within-run and between-run coefficients of variation (CV) of less than 1% and 2.06%, respectively) fulfilled the 1998 National Cholesterol Education Program (NCEP) targets of CV equal to or less than 4% at the HDL-C level greater than or equal to 0.42 g/L and an SD of less than or equal to 0.017 at the HDL-C level of less than 0.42 g/L.

In the comparison between liquid N-geneous HDL-C and DCM, the mean percent bias for the normotriglyceridemic specimens was 4.4 for the Genzyme sample and 2.1 for the Rotterdam sample, and 3.3 for the combined data set. The values in the comparison between PTA precipitation and DCM were 0.6 (Genzyme), -6.3 (Rotterdam), and -2.8 (combined), respectively. The respective values in the comparison between liquid N-geneous HDL-C and PTA precipitation were 3.6, 9.1, and 5.7.

For specimens with triglyceride \( \geq 2.0 \) g/L, the mean percent bias was 1.5 between LN-gen HDL-C and RM, -5.8 between PTA and RM in the case of triglyceride concentrations \( \leq 19.48 \) g/L; the positive bias was reported to be rapidly increasing between LN-gen HDL-C and RM in the case of triglyceride concentrations \( > 19.48 \) g/L. The total error of the LN-gen HDL-C compared with RM was 5.1% at HDL-C decision points of 0.35 g/L and 5.3% at HDL-C decision point 0.60 g/L, fulfilling the NCEP target for total error of HDL-C methods of \( \leq 13\% \).

According to Genzyme data, the linearity of the LN-gen HDL assay was established up to 2.37 g/L HDL-C with an average percent recovery of the dilution series of 101% (range: 97% - 103%). For the range between 2.37 g/L and 3.39 g/L, the linearity of the assay decreased, with a mean percent recovery of 91%. The total cholesterol was 1.909 g/L for fasting versus 1.902 g/L for non-fasting. The total triglycerides were 1.727 g/L (fasting) versus 2.451 g/L (non-fasting), \( p=0.0002 \). The total LN-gen HDL-C was 0.509 g/L (fasting) versus 0.501 g/L (non-fasting).

**Clinical conclusions**

In conclusion, the LN-gen HDL-C assay easily fulfils the 1998 NCEP recommendations in terms of precision, bias, and total error in normotriglyceridemic specimens. In lipemic specimens, the LN-gen HDL-C assay remains unbiased up to approximately 20 g/L of serum triglycerides, suggesting a slightly better performance of the LN-gen HDL-C assay compared with the PTA/MgCl\(_2\) precipitation method, and again fulfils the NCEP total error recommendations.

**Modelling**
Linear regression modelling was used to analyse the different techniques.

**Measure of benefits used in the economic analysis**

No summary benefit measure was identified in the economic analysis, and only separate clinical outcomes were reported, as shown in the effectiveness results above.

**Direct costs**

Costs were not required to be discounted due to the short time frame of the study. Quantities of resource use were not reported separately from the costs. Cost items were reported separately. The cost analysis covered the costs of labour, instrument (price of the instrument, maintenance, and interest over its operational lifetime), reagent, and accessories for each of the 2 assays of LN-gen and PTA. The perspective adopted in the cost analysis was not explicitly specified. The source of costing information was the Lipid Reference Laboratory Rotterdam. The date of the price data was not explicitly specified.

**Indirect Costs**

Not considered.

**Currency**

US dollars ($).

**Sensitivity analysis**

No sensitivity analysis was performed.

**Estimated benefits used in the economic analysis**

Not applicable. The reader is referred to the effectiveness results reported above.

**Cost results**

The average total cost per test performed was $3.35 for the PTA assays versus $2.69 for the LN-gen assays.

**Synthesis of costs and benefits**

Costs and benefits were not combined.

**Authors' conclusions**

The LN-gen HDL-C assay offers a cost-effective convenient method for meeting the 1998 precision, bias, and total error recommendations of the (US) National Cholesterol Education Program.

**CRD COMMENTARY - Selection of comparators**

Justifications were provided for the choice of the comparators. You, as a database user, should consider whether these are widely used health technologies in your own setting.

**Validity of estimate of measure of benefit**

The internal validity of the effectiveness results is likely to be high in view of the prospective nature of the study. The study should be regarded as a cost-consequences analysis.
Validity of estimate of costs
Quantities were not reported separately from the costs although adequate details of the methods of cost estimation were given. The use of setting-specific rates means that the cost results may not be generalisable to other settings.

Other issues
The authors' conclusion may not be fully justified since the inherent uncertainties surrounding the variables included in the cost-effectiveness analysis were not tackled by performing sensitivity analysis. The issue of generalisability to other settings was addressed and appropriate comparisons were made with other studies.

Implications of the study
The authors envisage an important role for the LN-gen HDL-C assay in routine clinical chemistry and lipid laboratories in the near future.

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