Performance of LDL-C by direct method compared to calculation by Friedewald and Sampson equations, to improve provision of lipid lowering therapy

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Introduction

Accurate low-density lipoprotein cholesterol (LDL-C) quantification is essential for cardiovascular disease risk stratification and therapeutic decision-making. Calculating LDL-C by Friedewald equation is simple and accessible, however demonstrates significant limitations when triglyceride ≥4.5mmol/L or LDL-C <1.5mmol/L. The Sampson equation[1] has recently been devised to calculate LDL-C based on beta quantification on 8,656 samples, compared to only 448 for Friedewald, and has improved accuracy for triglyceride concentrations up to 9mmol/L and at LDL-C <1.5mmol/L.

Aim

The aim of this study was to evaluate the clinical impact of Sampson equation implementation, in line with 2025 Heart UK and Association of Clinical Biochemistry and Laboratory Medicine guidelines[2].

Method

LDL-C was calculated using Friedewald and Sampson equations on all lipid requests analysed by Roche Cobas c702 units in four months. Direct Roche LDL-C method was also assayed on 48 samples spanning the triglyceride analytical range. Agreement between methods was assessed using linear regression and ANOVA. Clinical impact of methods was evaluated with regard to eligibility for lipid lowering therapy, according to guidelines.

Results 1: Correlation between Friedewald, Sampson and direct LDL-C

Friedewald and Sampson had excellent agreement at triglyceride ≤4.5 mmol/L (y= 0.99x + 0.09, R^2 0.99) (n= 39,576 samples) (figure 1). More variation was seen at LDL-C <1.5 mmol/L (R^2 = 0.76) than LDL-C >1.5mmol/L (R^2 = 0.98); a constant bias of 0.2 mmol/L (y=0.89x + 0.21) had a large effect at this concentration, causing lower Friedewald results (figure 2); Friedewald is known to be inaccurate at low LDL-C. The association was closest with triglyceride ≤3.0 mmol/L; Friedewald is known to overestimate LDL-C with high triglycerides. Sampson LDL-C concentrations were 9% lower than Friedewald (y=0.91x + 0.45) at triglyceride levels 3.0-4.5 mmol/L (figure 3).

Although there is a slight bias between Direct, Friedewald and Sampson methods (Table 4); one way ANOVA showed there was no significant difference between LDL-C by Friedewald, Sampson or direct measurement; F(2,23) = 0.24, p=0.79.

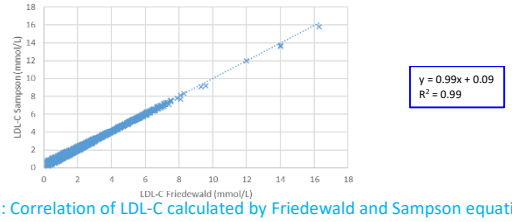

Figure 1: Correlation of LDL-C calculated by Friedewald and Sampson equations

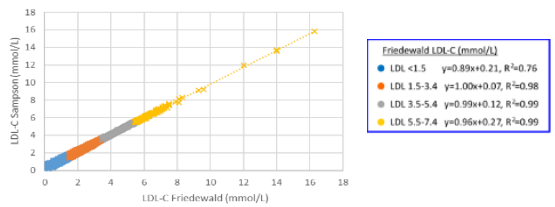

Figure 32: Friedewald and Sampson LDL-C at different triglyceride

Results 2: Clinical impact of Sampson LDL-C

Out of 45,915 samples assayed on Roche c702 analysers, LDL-C was unreportable by Friedewald in 1,042 (2.3%) as triglyceride >4.5 mmol/L. Sampson reduced the number of unreportable LDL-C to 175 (0.4%) which includes those with triglyceride >9.0 mmol/L.

More than half of patients in whom LDL-C is reportable by Sampson but not Friedewald (triglyceride 4.9-9.0 mmol/L), would meet the criteria for lipid lowering therapy for CVD prevention or therapy adjustment: 69% exceeded NICE (NG238)[3] target for secondary prevention of CVD, 33-87% exceeded ESC/EAS target[4] for CVD prevention depending on CVD risk level. Monoclonal antibodies (PCSK9 inhibitors)[5,6] and inclisiran[7] could be prescribed in 3-16% (depending on CVD risk) and 50%, respectively (table 1).

Guideline	Threshold treatment (LDL-C mmol/L)	LDL-C reportable by Sampson but not Friedewald above threshold (%)
Secondary prevention of CVD (NICE NG238[3])	>2.0	69
CVD prevention (ESC/EAS Guidelines 2019[4])	CVD risk V.high ≥1.4 High ≥1.8 Moderate ≥2.6 Low ≥3.0	 87 78 50 33
Alirocumab or evolocumab treatment for secondary prevention (NICE TA393[5], TA394[6])	V.high >3.5 High >4.0	16 8
Alirocumab or Evolocumab treatment for primary heterozygous-familial hypercholesterolaemia (NICE TA393[5], TA394[6])	High/v.high >3.5 None >5.0	16 3
Inclisiran treatment for primary hypercholesterolaemia or mixed dyslipidaemia (NICE TA733[7])	>2.5	50%

Table 1: Proportion of LDL-C results reportable by Sampson but not Friedewald above treatment thresholds

Conclusion

Adoption of Sampson LDL-C equation significantly increases the proportion of patients in whom LDL-C can be calculated, increasing the number of patients eligible to access appropriate treatment.

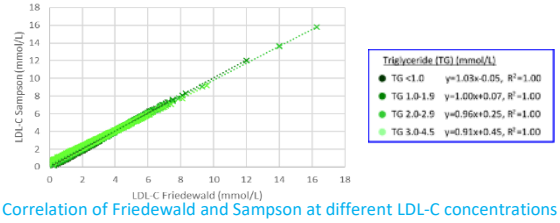

Figure 3: Correlation of Friedewald and Sampson at different LDL-C concentrations

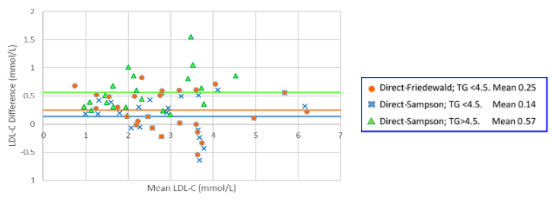

Figure 4: Bland-Altman plot of Direct, Friedewald and Sampson LDL-C

References

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