Friedewald Formula Significantly Underestimates LDL Cholesterol Compared to Preparative Ultracentrifugation below 70 mg/dL leading to Overestimation of the LDL Cholesterol Reduction for New drugs in Development.

Evan A Stein MD PhD, Traci Turner MD, Nan Plunkett BS, Rong Zhou PhD, Miriam Zangmeister MS, Christine Fritz MS
Medpace Reference Laboratories, Cincinnati, OH, USA. Medpace Biostatistics, Cincinnati, OH, USA.

Abstract

Background: Calculated LDL-C by Friedewald formula has been the basis for clinical and regulatory decision as a lipid endpoint for the past 40 years. The validity of this formula, however, has been under debate especially in the low LDL-C range. We compared LDL-C calculated by Friedewald formula with LDL-C measured in a central laboratory (Medpace Reference Laboratories, Cincinnati, OH, USA) and found significant discrepancy. Furthermore, according to a recent publication, the accuracy of LDL-C measurement may be even larger for low LDL-C levels.

Methods: Serum samples from patients in a specialized lipid clinic or clinical trial were collected over 6 years analyzed by Friedewald and PUC were compared, in a central laboratory CDC house developed serum calibrators directly traceable to CDC. All samples were processed in a central laboratory (Medpace Reference Laboratories, Cincinnati, OH, USA), which maintained CDC reference method, preparative ultracentrifugation (PUC), for the past 40 years. The validity at low LDL-C was assessed by comparing calculated LDL-C levels with LDL-C measured by PUC.

Results: Comparison of LDL-C measured by Friedewald and PUC was performed based on calculated LDL-C by Friedewald, VLDL-C, triglycerides (i.e. ≤100, 101≤200, 201≤300, 301≤400) is shown in Tables 3 and 4 which show mean percent and absolute differences between Friedewald and PUC respectively.

Conclusions: There are consequences for new drug trial design, as LDL-C reducing ability of the drug.

References


Methodology (Continued)

Results (Continued)

Summary

We demonstrate:

• The accuracy of the Friedewald formula compared to PUC is very reliable when LDL-C is >100 mg/dL.

• The accuracy of the Friedewald formula deteriorates as LDL-C decreases below 100 mg/dL, with significant overestimation of LDL-C, which may lead to inappropriate titration or discontinuation of LDL-C reducing therapies, while accurate LDL-C is usually <100 mg/dL, and always >70 mg/dL, will significantly underestimate LDL-C where treatment necessitating reevaluation of the LDL-C reducing ability of the drug is required.

• Second, clinical and regulatory concern regarding achieving, or maintaining, patients at their LDL-C goal, when defined as 25 or 30%, based on the Friedewald formula may lead to large number of “false” positives which will lead to inappropriate down-titration or discontinuation of LDL-C reducing therapies, which will be more pronounced in patients with moderately elevated TG (>100 mg/dL).

In conclusion, LDL-C levels ≤70 mg/dL, and possibly ≤50 mg/dL, treatment decisions should be based on more accurate determination of LDL-C, such as PUC.

Disclosure

None

Table 1. Percent Difference from Baseline (Mean ± Standard Error) Calculated LDL-C and LDL-C measured by PUC using LDL-C cut points of 100, 200, 300, and 400 mg/dL

<table>
<thead>
<tr>
<th>LDL-C cut point (mg/dL)</th>
<th>Overall</th>
<th>LDL-C ≤100</th>
<th>LDL-C &gt;100</th>
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<tr>
<td>Mean difference (mg/dL)</td>
<td>1.2% (2.4)</td>
<td>5.6% (13.4)</td>
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Table 2. Mean Absolute Differences (mg/dL) between Friedewald and PUC respectively

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<tr>
<td>Mean difference (mg/dL)</td>
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Table 3. Percent Difference from Baseline (Mean ± Standard Error) Calculated LDL-C and LDL-C measured by PUC using LDL-C cut points of 100, 200, 300, and 400 mg/dL

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Figure 1. Percent change from baseline for LDL-C by Friedewald and PUC

Figure 2. Mean absolute differences between Friedewald and PUC

Figure 3. Percent difference from baseline for LDL-C by Friedewald and PUC

Figure 4. Mean absolute differences between Friedewald and PUC

Figure 5. Percent difference from baseline for LDL-C by Friedewald and PUC

Figure 6. Mean absolute differences between Friedewald and PUC

Figure 7. Percent difference from baseline for LDL-C by Friedewald and PUC

Figure 8. Mean absolute differences between Friedewald and PUC

Figure 9. Percent difference from baseline for LDL-C by Friedewald and PUC

Figure 10. Mean absolute differences between Friedewald and PUC