Background – Evolocumab, a fully human monoclonal antibody to proprotein convertase subtilisin/kexin type 9 (PCSK9), reduced low-density lipoprotein cholesterol (LDL-C) and cardiovascular events in the FOURIER trial. The gold standard for LDL-C determination is beta-quantification (BQ), however it is mainly a research technique and LDL-C is usually estimated in clinical practice.

Objective – To investigate accuracy of two different methods for estimating LDL-C (Friedewald and Martin/Hopkins [M/H]) compared to gold standard BQ in patients with low LDL-C in FOURIER.

Methods – FOURIER was a randomized trial of evolocumab versus placebo added to statin therapy in 27,564 patients with atherosclerotic cardiovascular disease. To quantify LDL-C, FOURIER used the gold standard of BQ when the Friedewald estimate was <40 mg/dL. Friedewald LDL-C was estimated using a fixed conversion factor as TC – HDL-C – TG/5 whereas the Martin/Hopkins method used patient-specific TG:VLDL-C ratios to calculate LDL-C as TC – HDL-C – TG/personalized factor. This personalized factor, ranging from 3.1 to 9.5, was determined by the patient’s non-HDL-C and TG values available from the standard lipid profile. We created scatterplots of the two LDL-C estimates vs BQ, then examined regression lines, correlations, and mg/dL differences.

Results – A total of 56,624 observations (98.8% in Evolocumab pts) were recorded with Friedewald LDL-C <40 mg/dL. In scatterplots of estimated vs BQ LDL-C, M/H LDL-C appeared less prone to underestimation and more evenly distributed around the regression line (figure left) than Friedewald (figure right). Spearman’s correlation coefficient with BQ LDL-C was higher for M/H vs Friedewald LDL-C (0.918, [95% CI 0.916-0.919] vs 0.867, [95% CI 0.865-0.869]) and M/H LDL-C deviated less from observed values (Root MSE 4.32 [95% CI 4.25-4.39] vs 5.41 [95% CI 5.34-5.48] mg/dL). The median difference for M/H minus BQ LDL-C was -2 (25th to 75th: -4 to +1) mg/dL and for Friedewald minus BQ LDL-C was -4 (-8 to -1) mg/dL (p<0.001); differences were more pronounced in those with TGs ≥150 mg/dL: +2 [-1 to +6] vs -10 [-14 to -7] mg/dL (p<0.001). Overall, 77.1% of M/H LDL-C values were within 5 mg/dL and 97.4% within 10 mg/dL of BQ, which were significantly greater than respective proportions with Friedewald estimation (59.9% and 86.7%) (p<0.001).

Conclusion – In patients achieving low LDL-C with PCSK9 inhibition, the M/H method for LDL-C estimation correlates more closely than Friedewald LDL-C with gold standard BQ. These data suggest M/H estimation should be the preferred method to estimate LDL-C levels in such intensively treated patients.
Abstract

Evolocumab, a fully human monoclonal antibody to proprotein convertase subtilisin/kexin type 9 (PCSK9), reduced low-density lipoprotein cholesterol (LDL-C) and cardiovascular events in the FOURIER trial.

Introduction

The gold standard for LDL-C determination is beta-quantification (BQ), also known as preparative ultracentrifugation, however it is mainly a research technique and LDL-C is usually estimated in clinical practice.

Methods

Recent studies have shown that Friedewald underestimates LDL-C at lower levels, which could result in undertreatment of high-risk patients.

Results

A novel method (Martin/Hopkins [M/H]) appears to provide more accurate LDL-C, but has not been tested in PCSK9 inhibitor treated patients.

Conclusions

We aimed to investigate accuracy of M/H and Friedewald estimation compared to gold standard BQ in patients with low LDL-C in FOURIER.
FOURIER was a randomized trial of evolocumab versus placebo added to statin therapy in 27,564 patients with atherosclerotic cardiovascular disease

To quantify LDL-C, FOURIER used the gold standard of BQ when the Friedewald estimate was <40 mg/dL

Friedewald LDL-C = TC – HDL-C – TG/5

Martin/Hopkins LDL-C = TC – HDL-C – TG/patient-specific factor
  • This patient-specific factor, ranging from 3.1 to 9.5, was determined by the patient’s non-HDL-C and TG values available from the standard lipid profile

We created scatterplots of the two LDL-C estimates vs BQ, then examined regression lines, correlations, and mg/dL differences
Scatterplots of estimated LDL-C (X axis) vs BQ LDL-C (Y axis)
CONCLUSIONS

• In patients achieving low LDL-C with PCSK9 inhibition, compared with Friedewald, the Martin/Hopkins method more closely approximates gold standard measurement.

• These data suggest that Martin/Hopkins estimation should be the preferred method to estimate LDL-C levels and may prevent undertreatment due to underestimation.

References:

7. Seth S. Martin, M.D., M.H.S., 1 Robert P. Giugliano, M.D., S.M., 2 Sabina A. Murphy, M.P.H., 2 Scott M. Wasserman, M.D., 3 Peter S. Sever, Ph.D., F.R.C.P., 3 Anthony C. Keech, M.D., M.S., 4 Terje R. Pedersen, M.D., 5 and Marc S. Sabatine, M.D., M.P.H. 2 for the FOURIER Steering Committee & Investigators

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Beta-quantification LDL-C, mg/dL

BQ LDL-C = 5.22 + (0.83*M/H LDL-C)

Martin/Hopkins Estimate of LDL-C, mg/dL

Regression Line

BQ LDL-C = 7.22 + (0.88*Friedewald LDL-C)

Friedewald Estimate of LDL-C, mg/dL