Using Big Data: The Very Large Database of Lipids

NLA Spring Clinical Lipid Update, March 19th, 2016

Disclosures

- Support of VLDL project from the David and June Trone Family Foundation and PJ Schafer Cardiovascular Research Fund
- Grants from American Heart Association, Aetna Foundation, and Google, outside scope of topic today
- Honoraria from the American College of Cardiology for dyslipidemia-related educational activities
- Co-inventor on pending patent filed by Johns Hopkins University for novel method of LDL-C estimation
Outline

• Big data and the VLDL project
• Insights into LDL-C discordance
• Taking insights back to the bedside
“What is Big Data? A meme and a marketing term, for sure, but also shorthand for advancing trends in technology that open the door to a new approach to understanding the world and making decisions. There is a lot more data, all the time, growing at 50 percent a year, or more than doubling every two years...”
“…none of these students would have imagined that they could produce new, meaningful knowledge, and new hypotheses, from existing data, not their own,” she [Marcie McClure] says. Big data in biology add to the possibilities for scientists, she says, because data sit “under-analysed in databases all over the world…”


The National Institutes of Health’s Big Data to Knowledge (BD2K) initiative: capitalizing on biomedical big data

Ronald Margolis,¹ Leslie Derr,² Michelle Dunn,³ Michael Huerta,⁴ Jennie Larkin,⁵ Jerry Sheehan,⁴ Mark Guyer,⁶ Eric D Green⁶


“Big data are not only a new reality for the biomedical scientist, but an imperative that must be understood and used effectively in the quest for new knowledge.”
**AIM:** create new knowledge through careful examination of granular lipid data on a large scale

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**Very Large Database of Lipids**

- Ongoing database protocol harnessing de-identified data from daily operations of commercial lipid lab (Atherotech)
- VAP tests ordered by thousands of clinicians across a wide variety of clinical facilities in the US
- Majority of samples (~85%) from primary care clinics
- ~30% enrolled in Medicare and ~60% private health insurance
- In 1st harvest (VLDL 1.0), from 2009-2011, there were 1,340,614 adult and 10,294 pediatric patients
- Adult sample w/ median age of 59 years (IQR, 49–70) and even representation by sex
Limitations of Friedewald:

VLDL Study

March 29, 2016

VLDL Database Structure

<table>
<thead>
<tr>
<th>Naming</th>
<th>Included</th>
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<tbody>
<tr>
<td>Summation dataset</td>
<td>VLDL</td>
<td>First VAP test for each patient</td>
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<td>Large-scale contemporary data analysis; secular trend assessment</td>
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<td>Serial lab dataset</td>
<td>VLDL-5</td>
<td>All VAP tests for patients with repeated testing</td>
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<td>Reproducibility of measurements; associations of changes in parameters</td>
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<td>Ancillary datasets</td>
<td>VLDL-XXXX where XXXX is the other non-VAP analyte (eg, VLDL-ApoB, VLDL-VLDL, VLDL-ChyCRP)</td>
<td>Samples with VAP plus another relevant analyte, nested within summation dataset</td>
</tr>
<tr>
<td></td>
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<td>Assessment of association of VAP test parameters with other analytes</td>
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</table>

Abbreviations: ApoB, apolipoprotein B; hCRP, high-sensitivity C-reactive protein; VAP, Vertical Auto Profile; VLDL, Very Large Database of Lipids.
Research Synergy

Outline

• Big data and the VLDL project
• Insights into LDL-C discordance
• Taking insights back to the bedside
Friedewald, Levy and Fredrickson

Total subjects: n=448
Number with LDL-C <100mg/dL: approximately 35
Accuracy of VLDL-C estimate

• “Simple division of the plasma TG by five does not give a very accurate estimate of VLDL-C.”
  – Friedewald et al

• Inaccuracy tolerated because absolute error in VLDL-C estimation small relative to concentration of LDL-C

Need for reappraisal 4 decades later with big data in modern era

Objectives

– Examine accuracy of Friedewald-estimated LDL-C relative to direct measurement by ultracentrifugation

– Quantify the impact of any inaccuracy on guideline treatment group classification
Friedewald-Estimated Versus Directly Measured Low-Density Lipoprotein Cholesterol and Treatment Implications

Seth S. Martin, MD,* Michael J. Blaha, MD,* Mohamed B. Elshazly, MD,* Eliot A. Brinton, MD,† Peter P. Toth, MD, PhD,§ John W. McEvoy, MB BCH,* Parag H. Joshi, MD,* Krishnaji R. Kulkarni, PhD,¶ Patrick D. Mize, PhD,¶ Peter O. Kwiatkowski, MD,* Andrew P. DeFilippis, MD,*¶ Roger S. Blumenthal, MD,* Steven R. Jones, MD* Baltimore, Maryland; Salt Lake City, Utah; Sterling and Peruia, Illinois; Birmingham, Alabama; and Louisville, Kentucky

Living With Imprecision*

John C. Lefevre, MD
Brooklyn, New York
### Friedewald LDL Cholesterol <100 mg/dl

**N=567,656**

- Friedewald Overestimates
- Friedewald Underestimates

### Study Sample

**N=1,310,440**

- Friedewald Overestimates
- Friedewald Underestimates
Triglycerides 100 to 149 mg/dl
N=598,174
(30.4% of Sample)

Triglycerides 150 to 199 mg/dl
N=204,145
(15.6% of Sample)

Triglycerides 200 to 399 mg/dl
N=187,241
(14.3% of Sample)

Friedewald – Direct LDL Cholesterol, mg/dl

Friedewald LDL Cholesterol, mg/dl

Patients per Pixel

32768
16384
8192
4096
2048
1024
512
256
128
64
32
16
8
4
2
0
Guideline Reclassification

Proposed Solution

Original Investigation

Comparison of a Novel Method vs the Friedewald Equation for Estimating Low-Density Lipoprotein Cholesterol Levels From the Standard Lipid Profile

Serhi S, Mattil, MD; Michael J Blaha, MD; MPH; Mohamed B. Elsharky, MD; Peter P. Toth, MD, PPD; Peter D. Kottke-Vetter, MD, Roger S. Blumenthal, MD, Steven B. Jones, MD

**Importance.** In clinical and research settings worldwide, low-density lipoprotein cholesterol (LDL-C) is typically estimated using the Friedewald equation. This equation assumes a fixed factor of 5 for the ratio of triglycerides to very low-density lipoprotein cholesterol (TG/VLDL-C), however, the actual TG/VLDL-C ratio varies significantly across the range of triglyceride and cholesterol levels.
• The Friedewald equation:

$$LDL_f-C = \text{Total Cholesterol} - \text{HDL-C} - \frac{\text{TG}}{5}$$

• Novel method:

$$LDL_n-C = \text{Total Cholesterol} - \text{HDL-C} - \frac{\text{TG}}{\text{novel factor}}$$

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<td>5th to 95th percentile, range</td>
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<td>1st to 99th percentile, range</td>
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Median TG:VLDL-C by Non-HDL-C & Triglyceride Strata

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<th>Triglycerides (mg/dL)</th>
<th>Non-HDL-C (mg/dL)</th>
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Table 2. Concordance in Guideline Classification by Friedewald vs Novel Estimates of Low-Density Lipoprotein Cholesterol (LDL-C) in Relation to Direct LDL-C if Triglycerides are Lower Than 400 mg/dL.

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<th>LDL-C, mg/dL</th>
<th>No. Concordant/Total Group</th>
<th>% (95% CI)</th>
<th>No. Concordant/Total Group</th>
<th>% (95% CI)</th>
<th>No. Concordant/Total Group</th>
<th>% (95% CI)</th>
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<td>≥190</td>
<td>11 891/12 854</td>
<td>92.5 (92.0-93.0)</td>
<td>12 683/14 346</td>
<td>98.4 (87.9-88.9)</td>
<td>12 067/12 912</td>
<td>93.5 (93.0-93.9)</td>
<td>12 084/12 942</td>
<td>93.4 (92.9-93.8)</td>
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<td>160 to 189</td>
<td>27 322/31 323</td>
<td>87.5 (87.1-87.8)</td>
<td>29 076/33 072</td>
<td>97.9 (87.6-88.3)</td>
<td>29 448/33 371</td>
<td>98.3 (88.0-88.7)</td>
<td>29 407/33 284</td>
<td>98.3 (88.0-88.7)</td>
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<tr>
<td>130 to 159</td>
<td>69 670/78 974</td>
<td>88.2 (88.0-88.4)</td>
<td>73 471/80 368</td>
<td>91.4 (91.2-91.6)</td>
<td>75 838/83 885</td>
<td>90.4 (90.2-90.6)</td>
<td>76 882/84 306</td>
<td>90.3 (90.1-90.5)</td>
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<td>100 to 129</td>
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<td>87.1 (87.0-87.3)</td>
<td>119 277/132 417</td>
<td>90.1 (89.9-90.2)</td>
<td>120 514/131 804</td>
<td>91.4 (91.3-91.6)</td>
<td>120 526/131 704</td>
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<td>70 to 99</td>
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<td>84.7 (84.5-84.9)</td>
<td>114 826/125 533</td>
<td>91.5 (91.3-91.6)</td>
<td>117 320/126 670</td>
<td>92.6 (92.5-92.8)</td>
<td>117 256/126 491</td>
<td>92.7 (92.6-92.8)</td>
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<tr>
<td>&lt;70</td>
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<td>49 962/54 423</td>
<td>90.2 (89.9-90.4)</td>
<td>48 512/51 618</td>
<td>94.0 (93.8-94.2)</td>
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<td>12 084/12 942</td>
<td>93.4 (92.9-93.8)</td>
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<td>155 to 189</td>
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<td>38 297/42 564</td>
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<td>70 to 99</td>
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<td>48 435/51 452</td>
<td>94.1 (93.9-94.3)</td>
</tr>
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</table>

Figure 3. Concordance of Direct Measurement With Friedewald and Novel Estimates in Classifying LDL-C Lower Than 70 mg/dL by Triglyceride Strata

[Graph showing concordance percentages for different triglyceride categories]
Validation by Multiple Groups

PLOS ONE

Research Article


Jongmoon Lee, Seokjeong Jung1,2, Heejong Son1,2

1. School of Business Administration, Hankyong University, Chungchun, Korea
2. Korea Association of Health Promotion

Cholesterol, Lipids, Lipoproteins, and Cardiovascular Risk Factors

Validation of a Proposed Novel Equation for Estimating LDL Cholesterol

Jeffrey W. Mares,3, Allen J. Lueke,4 Allan S. Jaffe,5,6,7 and Amy K. Sawin3

(Title page: LDL calculator.com and Validation by Multiple Groups)
Outline

• Big data and the VLDL project
• Insights into LDL-C discordance
• Taking insights back to the bedside

2013 ACC/AHA Guidelines

4 Statin Benefit Groups

• Clinical ASCVD*
• LDL-C ≥190 mg/dL, Age ≥21 years
• Primary prevention – Diabetes: Age 40-75 years, LDL-C 70-189 mg/dL
• Primary prevention - No Diabetes†: ≥7.5%‡ 10-year ASCVD risk, Age 40-75 years, LDL-C 70-189 mg/dL

Per VLDL, ~1 in 4 people w/ Friedewald LDL-C <70 truly have LDL-C 70 or greater
- If TG 200-399 mg/dL, then 2 in 3
Original Contribution


Terry A. Jacobson, MD†, Matthew K. Ito, PharmD, Kevin C. Maki, PhD, Carl E. Orringer, MD, Harold E. Bays, MD, Peter H. Jones, MD, James M. McKenney, PharmD, Scott M. Grundy, MD, PhD, Edward A. Gill, MD, Robert A. Wild, MD, PhD, Don P. Wilson, MD, W. Virgil Brown, MD

Table 3 Criteria for ASCVD risk assessment, treatment goals for atherogenic cholesterol, and levels at which to consider drug therapy

<table>
<thead>
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<th>Risk category</th>
<th>Criteria</th>
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<tr>
<td>Very high</td>
<td>• ASCVD</td>
</tr>
<tr>
<td></td>
<td>• Diabetes mellitus (type 1 or 2)</td>
</tr>
<tr>
<td></td>
<td>o &gt;2 other major ASCVD risk factors or</td>
</tr>
<tr>
<td></td>
<td>o Evidence of end-organ damage*</td>
</tr>
<tr>
<td>Treatment goal</td>
<td>LDL-C, mg/dL</td>
</tr>
<tr>
<td></td>
<td>Non-HDL-C, mg/dL</td>
</tr>
<tr>
<td>Treatment goal</td>
<td>LDL-C, mg/dL</td>
</tr>
<tr>
<td></td>
<td>Non-HDL-C, mg/dL</td>
</tr>
<tr>
<td>Consider drug therapy</td>
<td>&lt;100</td>
</tr>
<tr>
<td></td>
<td>≥100</td>
</tr>
<tr>
<td>Consider drug therapy</td>
<td>&lt;70</td>
</tr>
<tr>
<td></td>
<td>≥70</td>
</tr>
</tbody>
</table>

Food and Drug Administration
Center for Drug Evaluation and Research

The Endocrinologic and Metabolic Drugs Advisory Committee Meeting

June 9, 2015

Briefing Document

BLA 125559

Praluent (alirocumab) injection
Eligibility in PCSK9i Outcomes Trials

- FOURIER (Evolocumab)
  - Fasting LDL-C ≥70 mg/dL or non-HDL-C ≥100 mg/dL on statin

- ODYSSEY OUTCOMES (Alirocumab)
  - LDL-C likely ≥70 mg/dL with evidence-based medical and dietary management

- SPIRE-2 (Bococizumab)
  - LDL-C ≥100 mg/dL or non-HDL-C ≥130 mg/dL on background lipid lowering rx

Very Low LDL-C On-Treatment with PCSK9 + Background Therapy

- eg, on alirocumab in ODYSSEY LONG TERM
  - LDL-C <25 mg/dL: 37%
  - LDL-C <15 mg/dL: 15%

- Per protocol, active safety monitoring if on-treatment LDL-C <25 and drug discontinued if LDL-C <15

- If Friedewald LDL-C is usually an underestimate at these levels, then this raises the question for unnecessary safety alarms
Hopkins Lipid Clinic: 1st PCSK9i Rx

- 52 y.o. man with heterozygous familial hypercholesterolemia, followed for several decades in lipid clinic
- Other cardiac risk factors: HTN, elevated BMI, OSA, elevated Lp(a)
- FHx of premature CAD; lost several brothers in 20's & father at 50
- Adherent to quadruple lipid-altering therapy with continued elevation of LDL-C between 130-160 mg/dl
  - Statin, ezetimibe, BAS, niacin
- Has been making recent progress with physical and dietary modifications
- Discussed evidence to date, including known benefits and side effects, and ongoing status of the long-term outcome trials
- After discussion, patient expressed a preference to start PCSK9i

Patient Follow-Up

- Follow-up lipids: TC 143, TG 298, HDL-C 59, Friedewald-estimated LDL-C 24, non-HDL-C 84
  - Friedewald LDL-C <25 and thus below safety limit triggering additional precautions in RCTs and per FDA guidance
  - We know with 100% certainty that his LDL-C is above that 25 mg/dL reference point based on our studies with ultracentrifugation
    - Quispe et al, AHA Scientific Sessions 2015
  - If we apply our novel LDL-C estimation then it is estimated at 53 mg/dL, or 29 mg/dL higher than the Friedewald equation
  - Also above the 40 mg/dL safety limit of the ACC/AHA guideline
Novel LDL-C = Total Cholesterol - HDL-C - TG/individualized novel factor

Summary

- Big data useful to:
  - Answer or (re-answer) fundamental, clinically relevant questions
  - Answer those questions quickly & inexpensively
  - Answer questions in finer detail & with more confidence
  - Then generate more questions
  - Mentor trainees & launch careers
  - Collaborate between academia and industry
  - Collaborate within and across institutions
Take Home Message: Related to Big Data

- Big data are big, and only getting bigger, and offer a tremendous opportunity to leverage previously untapped information to understand the world more completely and make better decisions.

Take Home Message: Related to LDL-C Discordance

- Friedewald-estimated LDL-C is commonly underestimated at low levels in the presence of hypertriglyceridemia, which has direct relevance to clinical decision making.
Completed & Ongoing Studies

- **VLDL-1A** Friedewald Bias (Martin, JACC)
- **VLDL-1B** LDL-C improved estimation algorithm (Martin, JAMA)
- **VLDL-1C** Friedewald Bias at Very Low LDL-C (Quispe, AHA ’15, NWYIA)
- **VLDL-2A** Non-HDL-C Discordance (Elshazly, JACC)
- **VLDL-2B** TC/HDL-C Discordance (Elshazly, Circ)
- **VLDL-3** Vitamin D vs. lipids (Lupton, JCL)
- **VLDL-4** TG/HDL-C correlates (Quispe, Atherosclerosis)
- **VLDL-5** LLDR density parameter, density vs. size (Ahmed, Lab Medicine)
- **VLDL-6** Lipid phenotype: types I, V c dyslipidemias (Hassan, ATVB 2013)
- **VLDL-7** Lipid phenotype: types IIb, III, IV dyslipidemias (Hassan, ATVB 2013)
- **VLDL-8** Lipid phenotype: non-FL phenotype lipid continuum (Hassan, ATVB 2013)
- **VLDL-9** Lipid phenotype: extremes of HDL-C <5th, >95th %ile (Quispe, JCL)
- **VLDL-10** Lipid trends by age and sex (Swiger, JAHA)

…

VLDL 2.0 Data Harvest

- >5 million unique subjects
- SSDI mortality data
- ICD-9/10 diagnosis codes
- Fasting status
- Relational tables of repeated measures
- Subsets with additional clinical data
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