

Cordova Formula for Low-Density Lipoprotein-Cholesterol Estimation: Not Only the Simplest of All But Also Superior to Other Formulae at a Higher Range of Triglyceride

SCIENTIFIC LETTER

INTRODUCTION

Low-density lipoprotein cholesterol (LDL-C) is an important risk factor for atherosclerotic cardiovascular disease.¹ The reduction in LDL-C levels is associated with a decreased risk for the incidence of vascular events and all-cause mortality.² Various guidelines have emphasized the significance of reducing LDL-C levels for mitigating the risk of atherosclerotic cardiovascular disease.³ Various formulae had been developed to calculate the LDL-C from other lipid profile parameters to supplant the need for direct estimation. The pioneering formula in this field is the one derived by Friedewald, where they use a fixed factor of 5 to estimate very-low-density lipoprotein cholesterol (VLDL). But Friedewald and all other similar formulae failed to take into consideration the inter-individual variation in the triglyceride (TG): VLDL ratio. However, Martin et al⁴ derived an equation similar to Friedewald but with novel factors depending on the individual patient's TG and non-high-density lipoprotein cholesterol (HDL-C) levels. This method was shown to have greater accuracy in calculating LDL-C at low LDL-C levels and has been proposed to be useful in patients with low LDL-C levels, high TG levels, and in the non-fasting state.⁴⁻⁶

Recently, another new formula has been devised by Sampson et al. which has demonstrated better accuracy in the calculation of LDL-C with TG levels up to 800 mg/dL (9.03 mmol/L). This newer formula led to 35% fewer misclassifications in hypertriglyceridemia patients when classified into different LDL-C groups.⁷ The formula proposed by Cordova which did not use TG levels in the calculation of LDL-C gains traction in this context. Limited studies have attempted to compare the newly derived formulae of Martin's and Sampson's with Cordova's at higher levels of TG. Vargas-Vázquez et al⁸ and Song et al⁹ have explored Sampson's, Martin's, and Friedewald's equations in patients with higher TG, but Cordova's formula was not included in the analysis. Interestingly, Piani et al¹⁰ have compared Martin's and Sampson's with Cordova's formula at higher levels of TG in the Italian population. However, no study has specifically compared Martin's and Sampson's formula with respect to the Cordova formula in Asian patients with high TG levels. Therefore, we aimed to assess the newer Martin's and Sampson's formula, in comparison with the Cordova formula, in calculating LDL-C in Asian patients with TG levels of more than 2.82 mmol/L (250 mg/dL).

METHODS

After obtaining approval from the Institutional Ethics Committee on human subjects' research, we carried out this analytical cross-sectional study at the All India Institute of Medical Sciences, Jodhpur, India. The lipid profile data were collected from the clinical laboratory database of the All India Institute of Medical Sciences, Jodhpur, India, from January 2020 to May 2021. The study excluded those samples that have incomplete data regarding lipid profiles. The lipid profile,

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including TG, total cholesterol (TC), HDL-C, and LDL-C by direct assay, was estimated in Beckmann AU 680 clinical chemistry analyzer (Table 2). All the parameters were calibrated using a system multi-calibrator provided by Beckman Coulter, Inc. (Brea, California, USA). Quality Control was assessed using 2 levels of Liquichek Lipids Control from Bio-Rad Laboratories, Inc. (Hercules, California, USA) The calibrators used were traceable to the US Centers for Disease Control LDL Cholesterol reference method.¹¹ The Friedewald's, Anandaraja's, Cordova's, Ahmadi's, Martin's, and Sampson's formulae were used to assess the calculated LDL-C (Table 3). The results were described as means and standard deviations. Student's *t*-test was used to compare the results of LDL-C using different formulae and LDL-C by direct assay. Bland–Altman diagram was used to evaluate the results obtained using different formulae and direct assay.

RESULTS

A total of 4096 patients' data were included in the study after removing the duplicates. Samples with TG level more than 2.82 mmol/L (250 mg/dL) were identified from the total samples for further evaluation. A total of 422 patients' data, with TG more than 2.82 mmol/L (250 mg/dL), were selected and stratified based on the TG levels. The stratification was done into 4 groups as follows: group 1 with TG \geq 11.29 mmol/L (1000 mg/dL), group 2 with TG \geq 5.64 mmol/L (500 mg/dL) and $<$ 11.29 mmol/L (1000 mg/dL), group 3 with TG \geq 3.95 mmol/L (350 mg/dL) and $<$ 5.64 mmol/L (500 mg/dL), and group 4 with TG \geq 2.82 mmol/L (250 mg/dL) and $<$ 3.95 mmol/L (350 mg/dL).

We compared the LDL-C calculated with direct estimation and LDL-C calculated using various formulae in each TG group individually. The different formulae such as Friedewald's, Ahmadi's, Anandaraja's, Martin Hopkins's, and Sampson's were observed to calculate LDL-C that was significantly different from directly estimated LDL-C in all the groups. The formulae by Friedewald, Ahmadi, and Anandaraja calculated highly discordant LDL-C levels when compared with direct estimation in the TG ranges between 3.95 mmol/L (350 mg/dL) and 11.29 mmol/L (1000 mg/dL). For both Friedewald's and Anandaraja's formulae, the underestimation of LDL-C increased with an increase in TG and finally

yielded negative values in the TG range above 11.29 mmol/L (1000 mg/dL). However, Ahmadi's formula increasingly overestimated LDL-C with the increase in TG levels.

On comparison of newer formulae of Cordova's, Martin Hopkins's, and Sampson's, all formulae calculated LDL-C that were significantly different from that of direct estimation in various TG groups, except Cordova formula in TG levels between 3.95 mmol/L (350 mg/dL) and 5.64 mmol/L (500 mg/dL). However, among the newer formulae, it was Cordova's formula that calculated LDL-C in approximation with direct estimation in groups with TG levels between 3.95 mmol/L (350 mg/dL) and 11.29 mmol/L (1000 mg/dL) (Table 1).

The Bland–Altman plots confirmed the greater approximation of the Cordova formula with direct estimation compared with the commonly used Friedewald's formula and the newly derived formulae such as Martin Hopkins' and Sampson's (Figure 1). The localization of individual dots around the baseline of zero in the Bland–Altman plot of the Cordova formula highlights the close approximation of the Cordova formula with direct estimation. The quadratic modeling for difference in percentage of various formulas with varying TG levels demonstrated Cordova to have a better approximation within a larger range of TG levels when compared with the newer Martin Hopkins' and Sampson's formulae as evidenced by the approximation toward the baseline of zero (Figure 2).

DISCUSSION

Our results confirm the well-known limitation of Friedewald's formula for calculating LDL-C in patients with TG levels above 3.95 mmol/L (350 mg/dL). The non-performance of Ahmadi's formula is also not surprising, taking into consideration the fact that the formula has been derived for lower ranges of TG. The Anandaraja's formula with only TG and TC in its calculation also did not yield comparable results at high TG ranges.

In our study, the newer formulae of Cordova's, Martin Hopkins's, and Sampson's fared better than the older formulae in higher ranges of TG. Cordova's formula yielded comparable LDL-C with respect to direct estimation in TG levels between 3.95 mmol/L (350 mg/dL) and 5.64 mmol/L (500 mg/dL) as evidenced by a *P* value of .9646. On overall comparison, Cordova's formula calculated LDL-C in close approximation with direct estimation when compared with other newly derived formulae such as Martin Hopkins's and Sampson's.

The newer formula of Martin Hopkins, which has introduced the novel TG factor instead of fixed factor like that of Friedewald's, performed better than Friedewald's and Anandaraja's. However, using a single novel factor for any TG value above 400 mg/dL (4.516 mmol/L) acts as a limitation. The same is reflected in our study, as evidenced by the persistent negative bias observed in the Bland–Altman plot. The recently derived Sampson's formula also had a persistent negative bias in the Bland–Altman plot.

HIGHLIGHTS

- A significant difference in calculated low-density lipoprotein cholesterol (LDL-C) was observed in different triglyceride (TG) groups for Friedewald's, Ahmadi's, Anandaraja's, Martin Hopkins's, and Sampson's formulae.
- Cordova formula calculated LDL-C in approximation with direct estimation in Asian patients with TG levels between 3.95 mmol/L and 11.29 mmol/L.
- Cordova had a better approximation within a larger range of TG levels when compared with the newer Martin Hopkins' and Sampson's formulae.

Table 1. Comparison of Means Between Calculated LDL Cholesterol and Direct Estimation

TG	Mean ± SD	Direct LDL	Friedewald	Ahmadi	Cordova	Anandaraja	Martin Hopkins	Sampson
>11.29 mmol/L (>1000 mg/dL) n=9	mmol/L	3.08 ± 1.09	-1.10 ± 0.92	21.6 ± 4.10	4.27 ± 1.16	-0.81 ± 1.02	0.96 ± 0.69	1.04 ± 0.44
	mg/dL	119.10 ± 42.15	-42.53 ± 35.57	835.27 ± 158.54	165.12 ± 44.85	-31.32 ± 39.44	37.12 ± 26.68	40.21 ± 17.01
	P	NA	<.0001	<.0001	.0391	<.0001	.0002	.0001
5.64-11.29 mmol/L (500-1000 mg/dL) n=46	mmol/L	3.39 ± 1.22	1.22 ± 1.68	11.49 ± 2.49	3.40 ± 1.22	1.13 ± 1.70	2.50 ± 1.42	1.93 ± 1.28
	mg/dL	131.09 ± 47.17	47.17 ± 64.96	443.15 ± 96.28	131.47 ± 47.17	43.69 ± 65.73	96.67 ± 54.91	74.63 ± 49.49
	P	NA	<.0001	<.0001	.9646	<.0001	.0019	<.0001
3.95-5.63 mmol/L (350-499 mg/dL) n=112	mmol/L	3.52 ± 1.43	2.14 ± 1.79	7.96 ± 1.61	3.16 ± 1.34	2.02 ± 1.93	2.90 ± 1.65	2.48 ± 1.56
	mg/dL	136.11 ± 55.29	82.75 ± 64.96	307.81 ± 62.25	122.19 ± 51.81	78.11 ± 74.63	112.14 ± 63.80	95.90 ± 60.32
	P	NA	<.0001	<.0001	.0527	<.0001	.0029	<.0001
2.82-3.94 mmol/L (250-349 mg/dL) n=255	mmol/L	3.13 ± 1.10	2.13 ± 1.24	5.90 ± 1.14	2.71 ± 0.94	1.97 ± 1.35	2.60 ± 1.14	2.37 ± 1.15
	mg/dL	121.03 ± 42.53	82.36 ± 47.95	228.15 ± 44.08	104.79 ± 36.34	76.17 ± 52.20	100.54 ± 44.08	91.64 ± 44.47
	P	NA	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001

P value < .05 indicates statistical significance; Statistical test used: Student's t-test. Comparisons have been performed between respective calculated LDL cholesterol with direct estimation in different TG groups. LDL, low-density lipoprotein; TG, triglyceride.

However, the quadratic modeling depicts a superior performance of Sampson's over Martin Hopkins's at higher TG levels. Piani et al¹² have also demonstrated the superiority of Sampson's over Martin Hopkins's at TG levels above 250 mg/dL (2.82 mmol/L). Piani et al.¹⁰ in their recently published study, have demonstrated the superiority of

Cordova's formula over Martin's at TG above levels above 250 mg/dL (2.82 mmol/L) in the Italian population. However, contrary to our results from the Asian population, the aforementioned study observed Sampson's to be outperforming Cordova's formula at TG above levels above 250 mg/dL (2.82 mmol/L).

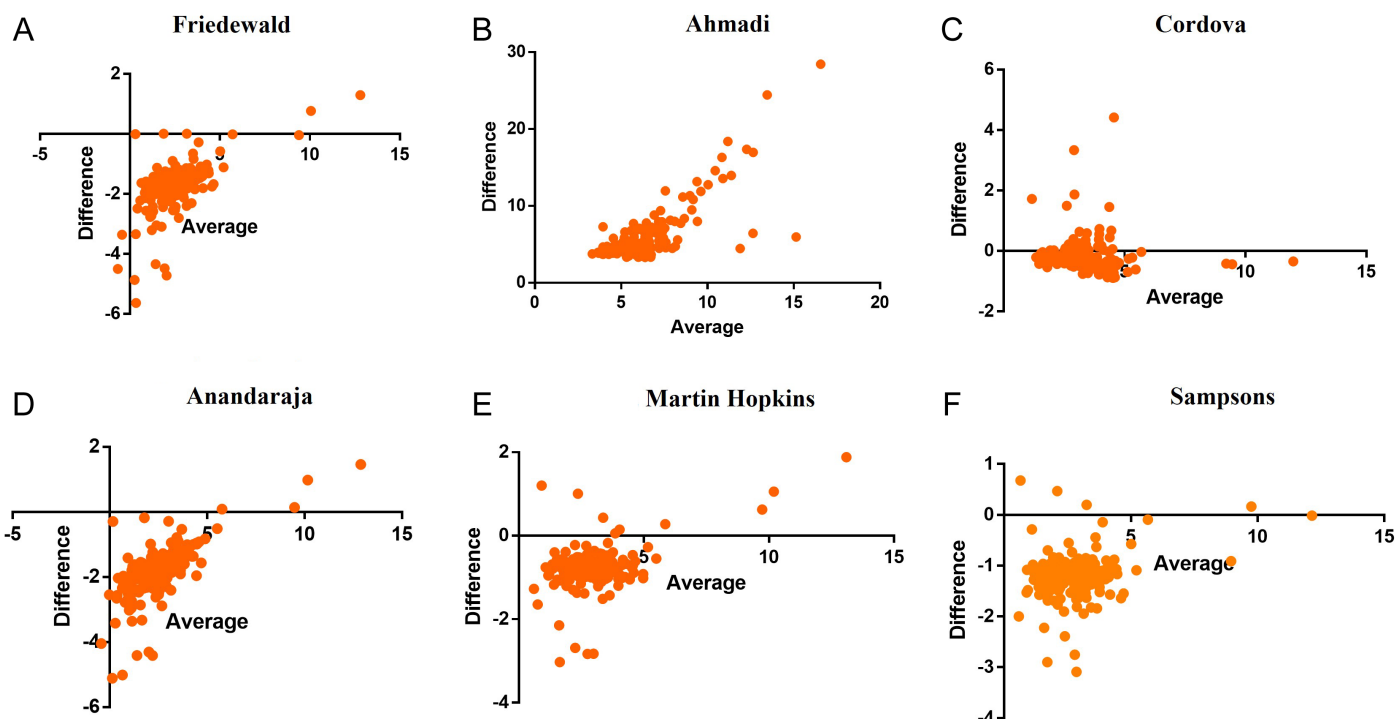


Figure 1. Bland–Altman plots for calculated low-density lipoprotein cholesterol and direct estimation. (A) Friedewald, (B) Ahmadi, (C) Cordova, (D) Anandaraja, (E) Martin Hopkins, and (F) Sampson.

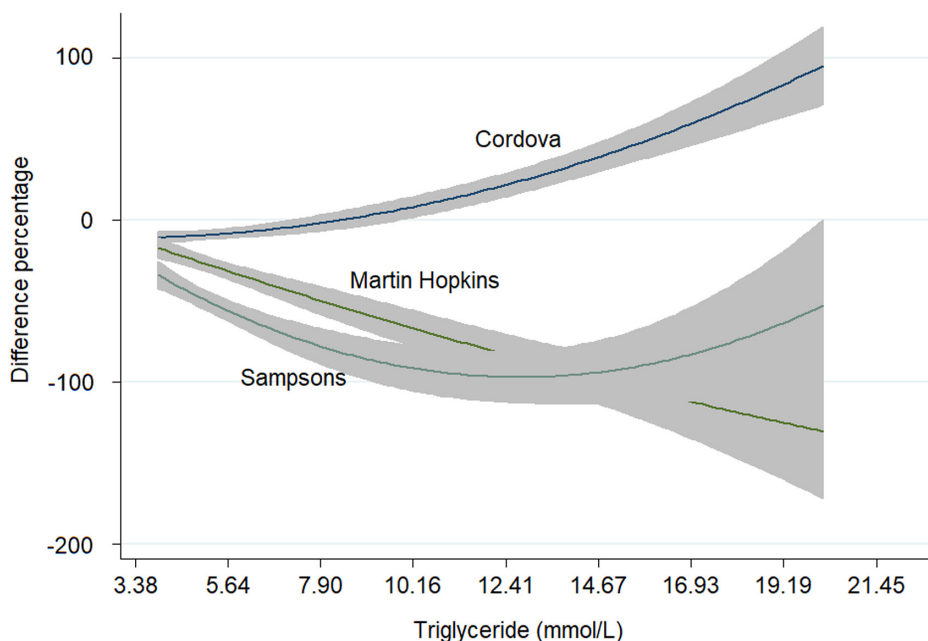


Figure 2. Quadratic modeling between the difference percentage of calculated low-density lipoprotein cholesterol and direct estimation with varying triglyceride levels.

Table 2. Performance Characteristics of the Lipid Profile Assays

S. No	Methodology	Analytical Range	Calibration Traceability
1	Triglyceride Glycerol phosphate oxidase-peroxidase Method	0.1-11.3 mmol/L (10-1000 mg/dL)	Isotope dilution mass spectrometry reference method
2	Cholesterol Cholesterol oxidase- peroxidase method	0.5-18.0 mmol/L (20-700 mg/dL)	CDC Reference Method (Abell-Kendall)
3	HDL-C Anti-human-β-lipoprotein antibody method	0.05-4.65 mmol/L (2-180 mg/dL)	US CDC HDL-cholesterol reference method
4	LDL-C Protecting agent method	0.26-10.3 mmol/L (10-400 mg/dL)	US CDC LDL-cholesterol reference method

CDC, Centre for Disease Control; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Sampson’s formula incorporates a correction factor to account for the presence of TG-enriched VLDLs in patients with extreme hypertriglyceridemia that affect the calculation of LDL-C. This incorporation of the correction factor helps it to fare better than Martin Hopkins at higher ranges of TG, as evidenced by the quadratic modeling. Interestingly, the Cordova formula (which is the simplest of all) appears to be superior to all other formulae at higher ranges of TG.¹³ The Cordova formula does not consider the TG levels of

the patient while calculating LDL-C, which acts in its favor at higher ranges of TG.

CONCLUSION

Our study depicts Cordova as superior to the recently derived Martin’s and Sampson’s formulae in Asian patients with TG levels above 3.95 mmol/L (350 mg/dL). The close approximation of calculated LDL cholesterol using the Cordova

Table 3. Mathematical Formulae for Various Calculated LDL Methodologies

S. No	Calculated LDL Methodologies	Formulae
1	Friedewald formula	$LDL-C = TC - HDL-C - 0.2 \times TG$
2	Ahmadi	$LDL-C = TC/1.19 + TG/1.9 - HDL-C/1.1 - 38$
3	Cordova	$0.75 \times (TC - HDL-C)$
4	Anandaraja	$LDL-C = (0.9 \times TC) - (0.9 \times TG/5) - 28$
5	Martin Hopkins	$LDL-C = TC - HDL-C - TG/\text{novel factor}$
6	Sampson	$LDL-C = TC/0.948 - HDL-C/0.971 - [TG/8.59 + (TG \times \text{non-HDL-C})/2140 - TG^2/16100] - 9.44$

formula with direct estimation between 3.95 mmol/L and 11.29 mmol/L (350-1000 mg/dL) makes it a plausible alternative to direct estimation at these ranges, where all other formulae yield highly discordant values.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of All India Institute of Medical Sciences (AIIMS), Jodhpur (approval no: AIIMS/IEC/2021/3517).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – S.S.; Design – S.S., P.S.; Supervision – S.S., P.S.; Materials – S.S.; Data Collection and/or Processing – S.T., S.S.; Analysis and/or Interpretation – S.T., S.S.; Literature Review – S.T.; Writing – S.T.; Critical Review – S.S., P.S.

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