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Comparison of equations for the calculation of LDL-cholesterol in hospitalized patients

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ABSTRACT

Background: The Friedewald equation is widely used to calculate LDL-C for cardiovascular risk prediction but is less accurate with comorbidities and extreme lipid values. Several novel formulae have been reported to outperform the Friedewald formula.
Methods: We examined 14,219 lipid profiles and evaluated four formulae (Friedewald, Chen, de Cordova, Hattori) and compared these to direct measurement of LDL-C across various triglyceride (TG), total cholesterol (TC) and HDL-cholesterol (HDL-C) ranges using Beckman reagents and instruments. Linear regression and ROC analysis were performed.
Results: The de Cordova formula showed a high correlation with directly measured LDL-C ($r = 0.90$, $P < 0.001$), comparable to the Friedewald calculated values for directly measured LDL-C ($r = 0.95$, $P < 0.001$). The de Cordova formula was favorable in some ranges of HDL, TC and the lowest TG range ($r = 0.97$, $P < 0.001$) but performed least well in comparison with the three other LDL-C calculations (AUC = 0.8331), demonstrating inconsistent bias. The Chen formula performed better than Friedewald (AUC = 0.9049). The Hattori formula outperformed all formulae including Friedewald over various ranges of lipid values (AUC = 0.9097).
Conclusions: We observe favorable correlations of the de Cordova formula with Friedewald at low TG values. However, the Hattori formula appears to be best for application in hospitalized patients, even at extreme lipid values.

1. Introduction

LDL-cholesterol (LDL-C) is used for cardiovascular disease (CVD) risk assessment [1,2]. The gold standard for measurement of LDL-C is by ultracentrifugation and beta-quantification [3]. This is expensive and inconvenient for the routine laboratory. Other methods include direct measurement of LDL using a homogeneous assay, but this is too expensive for use in most laboratories. Furthermore, direct methods show poor performance with high triglyceride (TG) levels [4–6]. An earlier review comparing direct measurement of LDL-C vs calculation of LDL recommended the use of direct LDL measurements in hypertriglyceridemic patients [6]. However, a recent study comparing eight direct measurements of LDL-C and HDL-C failed to show improved CVD risk classification of most direct methods over calculated LDL-C [4].

The first formula to calculate LDL-C was developed over 40 years ago by Friedewald [7]. The formula requires fasting plasma high density lipoprotein-cholesterol (HDL-C), total cholesterol (TC), and TG, and is calculated as LDL-C = TC − HDL − (TG / 5) for mg/dl (2.2 in mmol/l). This formula is less accurate in extremes of TG or TC values [7–10] or in patients with co-morbidities (eg. renal failure or diabetes) [2,11], but is widely used. Several other formulae have been developed, but these did not perform better than Friedewald's calculation [12–14] or had varying results in different population groups [10,15–19] and including those considering TG ratios [20,21]. In the latest study validating a novel formula in comparison with Friedewald's calculation and the LDL-C reference method in 23,055 patients, the benefits over Friedewald were not considered substantial enough to replace its use in clinical practice [22], demonstrating positive bias at low levels of LDL (<1.81 mmol/l). The previously published formula by de Cordova et al. [23] has been reported to outperform several of the earlier LDL-C formulae, including Friedewald's formula, over a wide-range of lipid levels using the equation LDL-C = 0.7516 (TC − HDL-C) in 10,664 Brazilian patients, including those with co-morbidities. However, this formula also showed bias at low levels of LDL-C in a subsequent study of 576 healthy subjects in South Africa [24].

As difficulties with LDL measurements prevail, a search for new formulae and emerging cardiovascular risk markers to improve accurate CVD prediction is ongoing. We validated the application of four

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formulae (Friedewald, de Cordova, Chen, Hattori) to calculate LDL-C in our population of hospitalized patients. We compared the formulae to the direct measurement of LDL-C, using the largest sample size to date, where multiple formulae are compared.

2. Methods

2.1. Study population

This was a retrospective evaluation of lipid profiles in 14, 219 patients in South Africa, from 1 January 2013 to 30 June 2013, using a database from the National Health Laboratory Services, the largest provider of laboratory services in South Africa. The laboratory is accredited by the South African National Accreditation System (SANAS), and serves a large tertiary academic hospital and surrounding clinics. The laboratory participates in the EQA program, the Thistle Lipid Programme. Procedures followed were approved by the Faculty of Health Sciences Research Ethics Committee of the University of Pretoria in accordance with the Helsinki Declaration.

Blood samples were collected into serum separator tubes to determine LDL-C, HDL-C, TG and TC. Samples were centrifuged after collection and analyzed immediately. Patient details were anonymized, with only patient age and gender reported.

Measurements of LDL-C, HDL-C, TC and TG were performed using reagents by Beckman Coulter, according to the specification of the manufacturers using the Beckman DXC automated analyser (Brea, CA, USA).

The direct LDL-C method is a homogeneous assay without the need for any pretreatment or centrifugation steps and based on the Daiichi two-phase method [25]. The coefficient of variation (CV) of LDL-C using the homogenous method was 4.5% for level 1 and 4.0% for level 3.

The HDL-C measurement was performed using a homogenous, colorimetric, enzymatic method. The CVs of the HDL at levels 1 and 3 respectively were 6.3% and 4.3%. Total cholesterol measurement involved a colorimetric, enzymatic, timed-endpoint method; the CVs of the TC at levels 1 and 3 was 3.4% and 4.6% respectively. Triglyceride measurement used a sequence of three coupled enzymatic steps to form a red quinoneimine dye. The CVs of the TG measurements at levels 1 and 3 was 4.3% and 3.9% respectively. The performance standards in terms of the CVs for the lipid analysis were all within the acceptable CV for Beckman DxC800.

2.2. Data analysis

Microsoft Excel was used to capture the data, according to the different lipid levels and for the calculation of LDL-C. STATA was used to perform the statistical analysis, which included a descriptive statistics summary. Pearson's correlation was performed for directly measured LDL-C and non-HDL-C, as well as between the four formulae and directly measured LDL-C values obtained from the laboratory measurements. The root mean square error (rMSE) was calculated as a measure of accuracy in the differences between values predicted by an estimator and values observed from those being estimated to compare the formulae across various lipid ranges. Bland–Altman plots were used to evaluate the agreement between the four formulae and the directly measured LDL-C. ROC curve analysis was used to compare the performance of the different formulae considering the area under the curve (AUC). The coefficient of concordance was used to assess the relative performance of the different methods relative to the direct LDL-C measurement.

3. Results

A total of 14,219 lipid profiles were identified, of which 39% were male and 61% were female. Patient-specific data about the presence/absence of disease, treatments and ethnicity was not available. The average age was 52 years with a range of directly measured LDL-C from 10.81–712.74 mg/dl, mean 111.97 mg/dl [0.28–18.46 mmol/l (mean 2.9 mmol/l ± 1.15 Standard deviation (SD)]; for HDL-C from 4.63–400.39 mg/dl, mean 44.02 mg/dl [0.12–10.37 mmol/l (mean 1.14 mmol/l ± 0.39 SD)]; for TC from 9.28–1184.84 mg/dl, mean 184.45 mg/dl [0.24–30.64 mmol/l (mean 4.77 mmol/l ± 1.47 SD)], and 9.74–5837.91 mg/dl, mean 162.10 mg/dl [0.11–65.91 mmol/l (mean 1.83 mmol/l ± 1.90 SD)] for TG. The mean (SD) calculated LDL-C values are shown in Table 1.

Using Pearson's analysis, we show high correlations between the four formulae and directly measured LDL-C using the Daiichi two-phase method (Table 1 and Supplementary Fig. 1). The de Cordova formula, although highly correlated with directly measured LDL-C ($r = 0.90$, $P < 0.001$), was lower than the correlation observed with the other three formulae. The Friedewald formula had a higher correlation ($r = 0.9518$, $P < 0.001$) than the Chen formula ($r = 0.9498$, $P < 0.001$) but was lower than the correlation observed with the Hattori formula ($r = 0.9626$, $P < 0.001$) (Fig. 1).

We also examined correlations between directly measured LDL-C and non-HDL-C (TC–HDL-C), LDL-C and TG, LDL-C and HDL-C/TG ratio, LDL-C and TC/HDL-C ratio, LDL-C and HDL-C/LDL-C ratio, and LDL-C and LDL-C/non-HDL-C ratio. Strong correlations were observed between LDL-C and non-HDL-C ($r = 0.93$) and TC and non-HDL-C ($r = 0.964$).

Using a ROC curve (Fig. 2), the Hattori formula was shown to perform the best with an AUC of 0.9097, followed by the Chen (AUC = 0.9049), the Friedewald (AUC = 0.9018) and the de Cordova (AUC = 0.8331) formulae. Sensitivities and specificities are shown in Table 2, and are based on an LDL cut-off of 2.5 mmol/l.

Table 3 demonstrates the rMSE of the four different formulae across different levels of HDL-C, TG and TC. The de Cordova formula was the least accurate at low HDL levels with a rMSE of 559 but at high HDL-C performed better (a rMSE of 102.7) than the Friedewald and Chen formulae with a rMSE of 130.2 and 106, respectively. The Hattori formula outperformed the other equations across all HDL-C and TG ranges, and TC ranges 73.10–218.87 mg/dl (1.89–5.66 mmol/l). At TG < 187 mg/dl (<2.11 mmol/l), the Hattori formula had a rMSE from 55.6 up to 85.9 with a rMSE of 280 for TG >187 mg/dl (>2.11 mmol/l), compared to a rMSE of >400 for the other three formulae. At the high end of TG ranges [>187 mg/dl (>2.11 mmol/l)], the de Cordova showed the lowest accuracy (rMSE 479.6), followed by the Chen formula (a rMSE of 433.9) then the Friedewald formula (a rMSE of 418.5). At the lowest end of TG levels [17.71–90.35 mg/dl (0.20–1.02 mmol/l)], the de Cordova formula had the highest accuracy with a rMSE of 54.2; the Friedewald formula had the lowest accuracy with a rMSE of 74.8. The Friedewald formula had the highest accuracy at the high end of TC ranges [250.20–522.82 mg/dl (6.47–13.52 mmol/l)], with a rMSE of 120. At the different TC ranges, the rMSE for the Friedewald formula was from 92.5 up to 316.9, compared with 130.1–272 for the Chen formula, 163.1–323.7 with de Cordova and 82–185.6 with the Hattori formula.

Fig. 3 shows Bland–Altman difference plots of the directly measured LDL-C and the LDL-C derived from the four formulae. The mean bias for the Friedewald formula was 4.10 ± 27.84 mg/dl (0.106 ± 0.72 mmol/l), 6.73 ± 37.51 mg/dl (0.174 ± 0.97 mmol/l) using the de Cordova formula, −6.57 ± 27.84 mg/dl (−0.17 ± 0.72 mmol/l) for the Chen formula, and 1.39 ± 23.98 mg/dl (0.036 ± 0.62 mmol/l) for the Hattori formula.

4. Discussion

LDL-C concentrations are a primary target of diagnosis and treatment of patients with hyperlipidemia defined by The National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III [1,2]. LDL-C monitoring remains significant in the management of CVD risk despite the revised AHA practice guidelines which no longer support the use of a LDL target [26]. One of the most common problems in the laboratory is to accurately estimate LDL-C. This has important implications on CVD classification, and if done incorrectly can adversely

Table 1
Mean (SD) values of LDL-C and correlation with directly measured LDL-C per formula analyzed.

LDL-C	Formula	Direct LDL method	Mean LDL-C (SD) mg/dl (mmol/l)	r (P value)
Direct LDL-C	Directly measured	Daiichi	112 ± 45 (2.9 ± 1.15)	1 (<0.000)
Friedewald	LDL = TC − HDL − (TG / 2.2)	Ultracentrifuge	108 ± 48 (2.8 ± 1.24)	0.9518 (<0.000)
De Cordova	LDL = 0.7516 (TC − HDL)	Wako	106 ± 41 (2.73 ± 1.06)	0.90 (<0.000)
Chen	LDL = (TC − HDL) × 0.9 − (TG × 0.1)	Roche	119 ± 46 (3.08 ± 1.19)	0.9498 (<0.000)
Hattori	LDL = 0.94TC − 0.94HDL − 0.19 × TG	Ultracentrifuge	111 ± 45 (2.87 ± 1.15)	0.9626 (<0.000)

influence therapy and outcomes in patients. We show that the recently published formula by de Cordova et al. to calculate LDL-C correlates highly with direct measurements of LDL-C and is comparable to the Friedewald calculation. However, based on the degree of variation, the Friedewald shows a better agreement with directly measured LDL-C [27.84 mg/dl (0.72 mmol/l)]. The de Cordova formula will underestimate an LDL-C by 6.57 mg/dl (0.17 mmol/l), varying from −30.94 to 44.47 mg/dl (−0.80 to 1.15 mmol/l), with a discrepancy of up to 37.5 mg/dl (0.97 mmol/l) for any value of LDL-C, which is higher than previously reported [24]. The Chen formula was the only one to overestimate LDL-C, with a level of discrepancy of 27.84 mg/dl (0.72 mmol/l). The Hattori formula will underestimate LDL-C by only 1.55 mg/dl (0.04 mmol/l), demonstrating the best agreement with LDL-C with a level of discrepancy of 23.98 mg/dl (0.62 mmol/l). We found a similar pattern of negative bias the higher the LDL-C values and a positive bias the lower the LDL-C level using the de Cordova formula, as shown in their study [24]. The other three formulae showed a more uniform distribution of points with the Bland–Altman plots, making the bias observed with these formulae more predictable than the de Cordova formula. We compared the accuracy between four formulae in calculating LDL-C, and found that the Hattori formula performed best across a range of lipid values in a large database of hospitalized patients.

The Friedewald formula is the most widely used to calculate LDL-C. However, there are several other formulae that have been developed in an attempt to address the limitations of the Friedewald formula [10,15–19]. The limitations of the Friedewald formula include inaccuracy in patients with hypertriglyceridemia [7], in those with very low levels of TG [<100.10 mg/dl (<1.13 mmol/l)] [10] and LDL [<92.81 mg/dl (<2.4 mmol/l)] [8], in patients with type III hyperlipidemia [7], in patients with renal [27] and liver [28] diseases, and those with diabetes mellitus [11] and other metabolic conditions [29]. The Friedewald formula cannot be used in non-fasting samples as it does not consider the cholesterol formed post-prandially in chylomicrons [30] or in the intermediate-density lipoproteins or in lipoprotein (a) (Lp(a)). The Friedewald formula does not distinguish between cholesterol derived from LDL and Lp(a), and thus the LDL-C fraction will be overestimated when Lp(a) levels are raised. Furthermore, the Friedewald formula was derived when an LDL-C lower than 70 mg/dl (1.8 mmol/l) was not yet established as an ideal secondary prevention target for treatment of high-risk patients [31,32]; thus these levels were not part of the original data set [7]. The de Cordova formula is the most recently published formula and reports better accuracy than the Friedewald in calculating LDL-C [23]. However, a subsequent analysis of 597 healthy subjects showed better agreement of the Friedewald formula with a directly measured LDL-C [24]. Another recent study compared four formulae in 164 subjects including those with dyslipidemias and comorbidities and found that the Friedewald equation had the best overall performance for calculating LDL-C [33]. These studies did not compare the Friedewald with the Hattori formula.

One of the limitations of this study, as with similar previously published studies, is that the compared LDL-C formulae were derived using different methods to measure LDL-C. To avoid incorrect comparisons of formulae using LDL-C data obtained from different methods, we validated four previously published calculations using our own data set in which we measured LDL-C using the same direct method. In the calculation of LDL-C, three measurements are usually used, including TC, HDL-C, and TG. Therefore, the accuracy of calculated LDL-C can be affected by errors from any of these measurements. One study compared calculated LDL-C formulae with 8 directly measured HDL-C assays using homogenous methods and demonstrated that the optimum equation for calculating LDL-C depends on which direct HDL-C assay is used [33]. It was shown that the Daiichi 2-phase method used in our study to measure HDL-C had the third lowest percentage misclassifications using the Friedewald formula, and the second lowest with the Chen formula in a recent study comparing eight HDL-C assays. The use of different TC and TG methods is not as likely to significantly affect the calculation of LDL-C as much as direct HDL-C assays because of the better standardization of TC and TG. The TC and TG methods used in

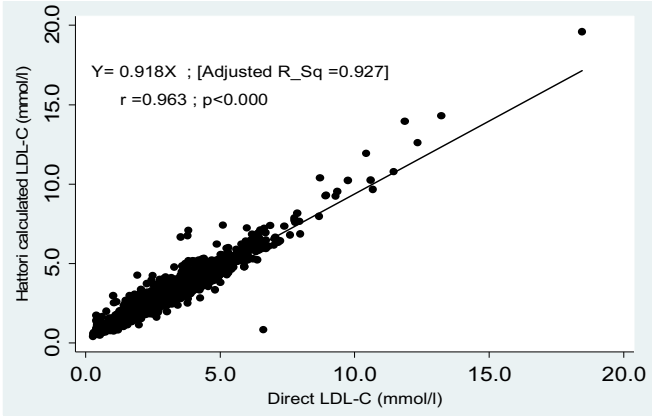

Fig. 1. Correlation between the calculated LDL-C by the Hattori formula and directly measured LDL-C.

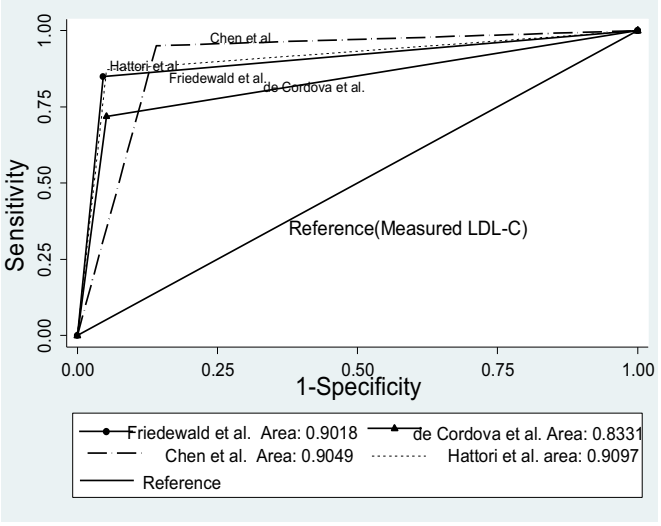

Fig. 2. ROC curve of LDL-C calculated vs measured LDL-C for the Friedewald, de Cordova, Chen and Hattori formulae.

Table 2
Sensitivity, specificity and AUC for the Friedewald, Chen, de Cordova and Hattori formulae using an LDL-C cut-off of 2.5 mmol/l.

Formula	Sensitivity (%)	Specificity (%)	AUC	(95% confidence interval)
Friedewald	84.9	95.4	0.902	(95% CI 0.893, 0.910)
Chen	95	85.9	0.905	(95% CI 0.897, 0.912)
De Cordova	71.9	94.4	0.833	(95% CI 0.821, 0.842)
Hattori	87.1	94.8	0.910	(95% CI 0.902, 0.918)

our study also differed from their respective reference methods by less than 2%.

We confirm previous findings that the Friedewald formula's performance decreases with increasing TG levels [23], and demonstrate that it performed most poorly at the lowest TG levels. The Friedewald formula was previously shown to incorrectly estimate LDL-C at the lowest TG levels [8,10], which might have implications for patients on lipid-lowering medications. At the lowest end of TG levels [17.71 mg/dl–90.35 mg/dl (0.20–1.02 mmol/l)], the de Cordova formula had the highest accuracy, contrary to a similar analysis in healthy subjects [24]. The differences between the two studies may be attributed to the different methods of measuring LDL-C and HDL-C (Wako vs Daiichi). However, our study findings are similar to those of de Cordova, despite our different methods of measuring LDL-C and HDL-C. The de Cordova study used a large Brazilian cohort including healthy persons and patients with hyperlipidemia and diabetes. For this reason, the de Cordova formula was suitable to be validated within a diverse hospital population such as ours. The similarities of our findings to those of de Cordova might be due to the populations studied, despite the different methods used. Although the de Cordova formula does not require fasting samples as it does not consider TG levels, it performed least well in the hypertriglyceridemic samples. At the highest level of TG [>187 mg/dl (>2.11 mmol/l)], the Hattori formula outperformed all other three formulae by a difference of more than 200 rMSEs, not seen in the large Brazilian database (22). This finding should take into consideration that the Hattori formula was not validated in subjects with TG [<30 mg/dl (<0.34 mmol/l)] and [>400.4 mg/dl (>4.52 mmol/l)] [17]. In contrast to the de Cordova study, the Chen formula outperformed the de Cordova formula at low TG levels in addition to high TG levels.

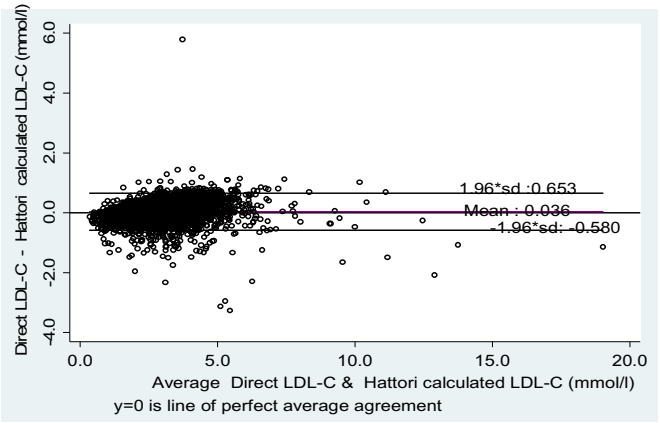

Fig. 3. Bland–Altman plot of direct LDL-C and Hattori calculated LDL-C. SI conversion from mmol/l to mg/dl for LDL-C: ÷0.0259.

Chen's formula includes TG values for the calculation of LDL-C [16], so the differences in comparison to other formulae at the extremities of TG are to be expected. Furthermore, methods to measure HDL-C used in the Chen formula (Roche) have fewer misclassifications than the method used by de Cordova (Wako) [33].

Other limitations of our study include the fact that racial origins were not specified and could not be considered in the analysis. However, the database is from a large hospitalized population representative of the various ethnic origins in South Africa. Secondly, although we used a non-reference method for the measurement of LDL-C, as with two similar previous analyses [23,24], our methods meet the NCEP standards of precision. Although we were unable to evaluate the formulae by disease categories, we had a large sample size with varying lipid ranges. We were thus able to consider the effect of the four formulae at high and low TG values, similarly to the de Cordova study. Another limitation is that we focused only on four LDL-C calculations, using the most recently published [23], most widely used [7] and two formulae previously confirmed in a large database to perform well in extreme lipid values [16,17,23], as seen in our hospitalized study sample. The samples we analyzed were from hospitalized patients and the findings cannot be

Table 3
Performance of four formulae across various HDL-C, TG and TC ranges.

HDL-C range										
Method	12–130 mg/dl		12–40 mg/dl		40–47 mg/dl		47–56 mg/dl		>56–130 mg/dl	
	ρ	Err (N)	ρ	Err (N)	ρ	Err (N)	ρ	Err (N)	ρ	Err (N)
De Cordova	0.93	1103.0 (5396)	0.91	559.0 (2335)	0.88	294.5 (1244)	0.95	127.8 (1003)	0.96	102.7 (957)
Friedewald	0.95	699.6 (5318)	0.95	336.0 (2293)	0.95	141.1 (1237)	0.96	100.3 (960)	0.95	130.2 (975)
Chen	0.95	776.5 (5317)	0.94	382.3 (2293)	0.95	164.6 (1228)	0.96	89.9 (993)	0.96	106.0 (908)
Hattori	0.96	501.1 (5316)	0.96	242.4 (2295)	0.96	111.1 (1228)	0.97	76.0 (993)	0.97	72.3 (940)
Triglyceride range										
	17.7–2574 mg/dl		17.7–90 mg/dl		90–128 mg/dl		128–187 mg/dl		187–2574 mg/dl	
	ρ	Err (N)	ρ	Err (N)	ρ	Err (N)	ρ	Err (N)	ρ	Err (N)
De Cordova	0.93	849.1 (5337)	0.97	54.2 (1459)	0.98	66.3 (1256)	0.97	93.1 (1248)	0.92	479.6 (1463)
Friedewald	0.95	713.6 (5338)	0.97	74.8(1460)	0.98	63.0 (1223)	00.97	94.4 (1248)	0.95	418.5 (1452)
Chen	0.95	775.5 (5337)	0.98	67.5 (1459)	0.98	74.5 (1200)	0.97	103.8 (1226)	0.94	433.9 (1452)
Hattori	0.96	509.4 (5336)	0.98	55.6 (1459)	0.98	61.1 (1256)	0.97	85.9 (1248)	0.95	280.0 (1462)
Total cholesterol range										
	73–523 mg/dl		73–190 mg/dl		190–219 mg/dl		219–250 mg/dl		250–523 mg/dl	
	ρ	Err (N)	ρ	Err (N)	ρ	Err (N)	ρ	Err (N)	ρ	Err (N)
De Cordova	0.95	671.4 (5298)	0.85	323.7 (3181)	0.50	180.3 (1046)	0.44	163.1 (696)	0.65	374.4 (480)
Friedewald	0.95	671.4 (5298)	0.87	316.9 (3142)	0.78	138.1 (1032)	0.94	92.5 (687)	0.90	120.0 (463)
Chen	0.94	759.8 (5298)	0.90	272.0 (3141)	0.71	142.9 (1020)	0.66	130.1 (677)	0.83	195.4 (459)
Hattori	0.96	490.6 (5297)	0.92	185.6 (3141)	0.81	88.6 (1032)	0.78	82.0 (687)	0.87	135.6 (463)

generalized to the general population. However, we do report these analyses on the largest database to date — 14,219 patients. Although patient-specific data about the presence/absence of disease, treatments and ethnicity was not available, our database of hospitalized patients is representative of those with diabetes, dyslipidemia and other metabolic conditions and co-morbidities.

Formulae have reported poorer performance in low- and high-TG values, and it has been suggested to use direct measurements of LDL-C instead of calculations in hypertriglyceridemic samples [4,33]. Measurements of LDL-C are further complicated by LDL-C being a multiple molecular particle aggregate of protein, cholesterol and other lipids [34]. Normal LDL-C is often observed in myocardial infarction, but with increased LDL-apolipoprotein B (Apo B) [17,35]. It is these small dense LDL particles that are more highly correlated with CVD, rather than the concentration of particles present [36]. The contribution of these aggregates is not fully considered in the existing formulae to calculate LDL-C. In a prospective study of 2222 men free from ischaemic heart disease (IHD), correction of the Friedewald formula to account for Lp(a) levels (the Dahlen modification) did not improve the evaluation of IHD risk [37]. One recent study considered the variance in the TG:Very low density lipoprotein cholesterol (VLDL-C) ratio, and found that using a 180 panel specific to TG and HDL-C levels improves the accuracy of their formula (non-HDL-C − TG / adjustable factor mg/dl) as compared to Friedewald [21]. However, a subsequent validation study found uncertainties in both this novel formula and Friedewald at low LDL-C levels (<1.18 mmol/l) [22]. Accuracy of the formulae may be improved where TG/VLDL-C ratios are taken into consideration [21], particularly in hypertriglyceridaemic patients. The authors found that most of the variance in the ratios could be explained by TG and non-HDL-C levels. The latter observation could further explain the differences in performance of the formulae, as the Chen formula equates LDL-C to 90% of non-HDL-C plus 10% of triglycerides, whereas de Cordova takes 75% of non-HDL-C and Hattori 94% of non-HDL-C.

Debate thus exists on whether two alternative markers — non-HDL-C (the sum of masses of cholesterol in the Apo B lipoprotein particles) and Apo B (the main apoprotein of atherogenic lipoproteins) should supplant LDL-C in CVD risk calculations. At present, there exists insufficient evidence to warrant this substitution [38]. However, the markers may provide additive value to CVD risk assessment [39]. We have demonstrated that LDL-C and TC correlate highly with non-HDL-C, as shown previously [23]. Recent reviews have established the superiority of non-HDL-C and Apo B over LDL-C in predicting CVD risk in epidemiological studies [35] and in randomized trials of patients on statin treatment [40]. Non-HDL-C has been recommended by previous ATP III guidelines as a secondary target of therapy and to be used to assess risk in patients with elevated TG levels [>200 mg/dl (>2.26 mmol/l)] [1,2], with the latter confirmed by a subsequent study comparing non-HDL-C to direct and calculated LDL-C using 8 different assays [4]. In terms of clinical practice, revised guidelines by the AHA report no additional mortality benefit to further treat non-HDL-C levels once an LDL-C goal is reached [26]. Concerns also exist about the reliability of non-HDL-C measurements, as a result of problems with direct HDL-C measurements [29]. Alternatively, Apo B and its association with CVD risk have been recognized [39,40], reportedly performing better than LDL-C in hypertriglyceridemic patients [35,41] and as an index of LDL-lowering therapy [39]. The Hattori formula for LDL-C (0.94TC − 0.94HDL-C − 0.19 × TG) was developed to estimate LDL-Apo B and small dense LDL from blood cholesterol, TG and HDL-C and in this way be more accurate in patients with cardiovascular co-morbidities and dyslipidemias. Unlike the Friedewald formula, the Hattori formula excludes IDL to provide a more accurate estimate of LDL-C. The estimation of lipid particles in the Hattori formula may explain why that particular formula performs best across various TG, HDL and TC levels in our hospitalized population. Formulae that incorporate Apo B or non-HDL-C measurements may be of interest in pursuing LDL-C calculations to predict CVD risk.

5. Conclusions

In conclusion, we confirm recent findings that the Friedewald formula has a better agreement with directly measured LDL-C based on the Daiichi method compared with the agreement with the de Cordova [23], but not at low TG values in a large hospitalized population. Furthermore, we show that neither the Friedewald nor de Cordova formula performs as well as the Chen or Hattori formula in this population group.

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Competing interests

The authors have no conflicts of interest.

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