**Influence of analytical error in lipid levels and LDL-c calculation on cardiovascular risk classification**

**ABSTRACT**

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| **Introduction** High levels of Low-Density Lipoprotein Cholesterol(LDL-c) are associated with a high risk of cardiovascular diseases. The LDL-c value is the basis for a classification of the subject into low risk, moderate risk and very high risk of developing cardiovascular diseases. Nevertheless, analytical error could be reflected in the various calculation parameters. The aim of this study was to determine the influence of analytical error and the method of LDL- c calculation on patient classification.**Materiel and methods**This was a retrospective study with data collection on lipids panel carried out in the laboratories of three hospitals of Gabon, between January 2023 and December 2023. Each data set included concentrations of total cholesterol (TC), HDL-c, LDL-c and triglycerides (TG) measured simultaneously for each patient. Not included were all patients with TG >4 mmol/L. The LDL-c concentration was determined using the direct and Friedewald method. The total analytical error (TAE) used are for TC ≤ 9%, TG ≤ 15%, LDL-c ≤ 12% and HDL-c ≤ 13%.**Results** A total of 2060 patients made up the study population. Before application of the TAE, proportion of LDL-c concentration with the direct method against Friedewald method were comparable (p=0.14). After application of the positive TAE, proportion of LDL-c concentration were statistically higher with the indirect method compared to direct method [596 (28.93%) versus 355 (17.23%); p<0.0001]. Thus applying the positive TAE to the calculation formula and to direct LDL-c, Friedewald method had more patient at very high risk and at high risk compare to direct method (p<0.0001). However, the negative TAE on indirect method classified less patients at very high risk and at high risk. We found that, the positive TAE reduced patients at low and intermediate risk and reclassified them at very high and at high risk of developing cardiovascular disease (CVD) (p<0.0001).**Conclusion**The present study, which aimed to assess the influence of analytical error and LDL-c calculation method on patient classification, highlighted a high frequency of patients whose risk classification for developing CVD was changed overall. This classification shifted a proportion of patients from a lower to a higher risk of developing cardiovascular disease. This suggests that TAE should be take into account for better treatment of the patient. |

Keywords: Total analytical error; lipids; cholesterol; cardiovascular risk

1. **INTRODUCTION**

Cardiovascular disease refers to all pathologies affecting the cardio-circulatory system, such as the heart and blood vessels. They mainly comprise ischemic or coronary heart disease, cerebrovascular disease and peripheral arterial disease. Other groups include congenital and rheumatic heart disease, deep vein thrombosis and pulmonary embolism [1]. According to Global Burden Diseases (GBD) study in 2019, cardiovascular disease is the leading cause of morbidity and mortality worldwide [2]. Indeed, cases is rising sharply worldwide. Between 1990 to 2019 people living with cardiovascular disease has risen from 271 million to 523 million respectively [2-3]. Furthermore, mortality rates from cardiovascular disease are dominated by atheromatous diseases, in particular ischemic heart disease and stroke. Ischemic heart disease is responsible for around half of all cardiovascular disease deaths (49.2%), while stroke accounts for a quarter (25.1%), around half of which is of ischemic etiology [2]. In Gabon, 13.3% of these diseases were estimated in 2012 [4]. Atheromatous cardiovascular diseases are chronic pathologies, secondary to cholesterol sticks on artery walls. Long-term exposure to high concentrations of cholesterol leads to its retention and accumulation on the inner walls of the blood vessels. Risk factors contributing to the development of cardiovascular disease are classify into non-modifiable risks factors such as age, gender, ethnicity, family history, and modifiable risks factors including physical inactivity, diabetes, obesity, smoking, hypertension and hypercholesterolemia [5-6]. However, reduction in the morbidity and mortality of these diseases could be predicted by modifying sedentary lifestyle, smoking, diet, a reduction in hypercholesterolemia as well as adequate drug management [5-9]. In addition, several studies have reported that high levels of Low-Density Lipoprotein Cholesterol(LDL-c) are associated with a high risk of cardiovascular diseases [5; 9-10]. According to the GBD study, elevated LDL-c is one of the main modifiable metabolic risk factors and one of the markers most closely associated with atheromatous cardiovascular disease. In 2021, 3.81 million cardiovascular disease-related deaths were attributed to elevated LDL-c levels [11]. LDL-c measurement is therefore essential in the prevention and treatment of these diseases. Since cholesterol plays considerable role in the pathogenesis of cardiovascular disease, an accurate estimate of LDL-c is crucial for better patient management. Moreover, LDL levels can be obtained in two ways, either by the more costly direct assay, or by the indirect method, which is a less costly computational method. The indirect method most widely used by laboratories is the Friedewald method [12]. This calculated value, which is comparable to the direct method and enables an assessment of cardiovascular risk, is the basis for a classification of the subject into low risk, moderate risk and very high risk of developing cardiovascular diseases. This classification is a guideline for appropriate management by the physician [13]*.* According to the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) of 2021, statins are the most recommended drug treatment for hypercholesterolemia, due to their lipid-lowering efficacy and safety [13-14]. They are introduced into patient management relayed on LDL-c classification and cardiovascular risk assessment. Nevertheless, analytical error could be reflected in the various calculation parameters. Current analytical performance, as determined in 1990 and 1995 by NCEP, allows total errors of 9%, 13% and 15% for total cholesterol, HDL-c and triglycerides respectively [15]. Applying these errors to values obtained in the laboratory would lead to a change in the LDL-c value, reclassification of patients and, consequently, a change in the treatment procedure. Consequently, the analytical error and the LDL-c calculation method can have direct impact on the treating physician's decision. It is therefore essential to avoid classification errors that could lead to poor care management. In regard of this, the aim of this study was to determine the influence of analytical error and the method of LDL- c calculation on patient classification.

1. **MATERIALS AND METHODS**
	1. **Study site and population**

This was a retrospective study with data collection on lipids panel carried out in the laboratories of three hospitals of Gabon, two in Libreville, the *Centre Hospitalier Universitaire Mère- Enfant Fondation Jeanne Ebori (*CHUME-FJE*)* and the *Hôpital d'Instruction des Armées OMAR BONGO ONDIMBA (*HIAOBO*)*, and one in Akanda, the *Hôpital d'Instruction des Armées d'Akanda (*HIAA*)*. Test results from patients who underwent lipid testing between January 2023 and December 2023 at the 3 sites CHUME-FJE, HIAOBO and HIAA were collected. Each data set included concentrations of total cholesterol (TC), HDL-c, LDL-c and triglycerides (TG) measured simultaneously for each patient. Data were collected with the agreement of all hospitals chiefs’ heads officers. Anonymity and confidentiality of patient data were respected.

**2.2 Inclusion and non-inclusion criteria**

Where included all patients with records biochemistry registries running from January 1 to December 31, 2023, patients with an age range between 01 and 90 years, and patients of both sexes who performed triglycerides (TG), total cholesterol (TC), HDL-c and LDL-c determinations. Not included were all patients with TG >4 mmol/L.

**2.3 Calculation of LDL-c concentration before and after application of the total analytical error**

The LDL-c concentration was determined using the direct and indirect method (Table 1). The total analytical error (TAE) of the different lipid parameters that were used in this study are for TC ≤ 9%, TG ≤ 15%, LDL-c ≤ 12% and HDL-c ≤ 13%. Then a widening factor is then applied to the result, which was k=2 (Table 1).

**Table 1: LDL-c concentration methods after total analytical error (TAE) application**

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| --- | --- | --- | --- |
| **Methods** | **Equations** | **Equation of total analytical error (TAE)**  | **TAE** |
| Direct measurement | $$LDLc= Direct data values$$ | $$TAE of LDL₋c$$ | ±0.12 |
| Friedewald [16] | $$LDL₋c=TC-HDL₋c-\frac{TG}{5}$$ | $$LDLc=\sqrt{\left[TAE.TC-TAE.HDL^{-}c-\frac{TAE.TG}{5}\right]}.K$$ | ±0.53 |

**2.5 Statistical analysis**

Data were entered into Microsoft Excel 2010 and analyzed using Excel 2010, Kutools TM for Excel, Epi-info 7.2.6.0, and MedCalc statistique software version 22.023. Positive and negative TAE were determined as well as means of quantitative and qualitative variables. Bland-Altman was used to compare the different methods of calculating LDL-c against the direct method, and provided areas of agreement. A p-value of less than 0.05 was statistically significant.

1. RESULTS

**Distribution of LDL-c concentration among patients according to LDL-c by method before and after application of the total analytical error (TAE)**

A total of 2060 patients made up the study population (Figure 1). More than 80% of patient had normal LDL-c (Table 2). Nevertheless, before application of the TAE, 14.76% of patients had high concentration of LDL-c with the direct method against 16.45% with Friedewald method (p=0.14). After application of the positive TAE, proportion of LDL-c concentration were statistically high with the indirect method [596 (28.93%) versus 355 (17.23%); p<0.0001] Table 2. With application of negative TAE, direct method was found to have more patients with high proportion of patient with elevated LDL-c concentration [268 (13.01%) versus 183 (8.89%); p<0.0001] Table 2.

Number of files consulted

(n=53429)

Lipid panel and number of each test measured

* Total cholesterol (TC): n=4015
* Triglycerides (TG): n=2690
* High density lipoprotein cholesterol (HDL-c): n=3385
* Low density lipoprotein cholesterol (LDL-c): n=3782

Number of patients who did simultaneous lipid panel (TC, TG, HDL-c and LDL-c)

(n=2094)

Excluded

(n=34)

Included

(n=2060)

All analysed

**Figure 1:** Flowchart of patient’s selection

**Table 2: Stratification of LDL-c according to methods used before and after total analytical error (TAE) application**

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| --- | --- | --- | --- |
| **Methods** | **Stratification of LDL-c before (TAE)** | **Stratification of LDL-c after positive (TAE)**  | **Stratification of LDL-c after negative (TAE)**  |
| **High n (%)** | **Normal n (%)**  | **High n (%)** | **Normal n (%)** | **High n (%)** | **Normal n (%)** |
| **LDL-c direct**  | 304 (14.76) | 1756 (85.24) | 355 (17.23) | 1705 (82.77) | 268 (13.01) | 1792 (86.99) |
| **Friedewald**  | 339 (16.45) | 1721 (83.55) | 596 (28.93) | 1464 (71.07) | 183 (8.89) | 1877 (91.11) |
| **p value** | 0.14 | <0.0001 | <0.0001 |

**Risk assessment according to methods used before and after application of the TAE**

In the total population, before application of the TAE, the direct LDL-c assay yielded direct LDL-c d 5.05% of patients at very high risk and 9.71% at high risk of developing atheromatous cardiovascular disease. However, using indirect LDL-c calculation methods, the Friedewald method yielded 6.11% and 10.34% of patients respectively at very high and high risk of developing cardiovascular disease (**Table 3**).

After applying the positive TAE to the calculation formula and to direct LDL-c, Friedewald method had more patient at very high risk and at high risk compare to direct method (p<0.0001) Table 3.

However, the negative TAE on indirect method classified less patients at very high risk and at high risk of developing cardiovascular disease compared to direct LDL-c (Table 3). More patients (n=+223 (10.82%) at low risk were found after application of negative TAE on Friedewald method compared to direct LDL-c (p<0.0001) Table 3.

**Table 3:** Risk assessment according to LDL-c methods and TAE

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| --- | --- | --- | --- |
| **Parameters** |  | **Methods** | **p value** |
| **Risk** | LDL-c direct (1) | Friedewald (2) | **(2-1)** |  |
| **Before TAE application n (%)** | **Very high** | 104 (5.05) | 126 (6.11) | 22 (1.06) | 0.1540 |
| **High** | 200 (9.71) | 213 (10.34) | 13 (0.63) | 0.5336 |
| **Intermediate** | 1514 (73.50) | 1466 (71.17) | -48 (2.33) | 0.1016 |
| **Low** | 242 (11.75) | 255 (12.38) | 13 (0.63) | 0.5659 |
| **After positive TAE application n (%)** | **Very high** | 123 (5.97) | 257 (12.48) | 134 (6.51) | <0.0001 |
| **High** | 232 (11.26) | 339 (16.45) | 107 (5.19) | <0.0001 |
| **Intermediate** | 1507 (73.16) | 1378 (66.90) | -129 (6.26) | <0.0001 |
| **Low** | 198 (9.61) | 86 (4.17) | -112 (5.44) | <0.0001 |
| **After negative TAE application n (%)** | **Very high** | 86 (4.17) | 62 (3.01) | -24 (1.16) | 0.05 |
| **High** | 182 (8.83) | 121 (5.88) | -61 (2.95) | 0.0003 |
| **Intermediate** | 1482 (71.94) | 1344 (65.24) | -138 (6.70) | <0.0001 |
| **Low** | 310 (15.05) | 533 (25.87) | 223 (10.82) | <0.0001 |

*NB:* ***2-1****: [Friedewald – direct LDL-c]*

**Difference in patient distribution before and after application of the total analytical error (TAE)**

After application of the positive TAE, the direct method showed a difference of 0.92% patients (n= +19) for very high risk and 1.55% patients (n= +32) for high risk which mean that the positive TAE reduced patients at low and intermediate risk from n=-51 which was reclassified on very high and at high risk of developing cardiovascular disease (Table 4). The negative TAE, reclassified patients at very high and at high risk with the direct method to the intermediate and low risk of developing cardiovascular disease (Table 4). Accordingto Friedewald method reclassification of patients into very high and high risk after positive TAE was found (Table 4).

**Table 4: Difference between classification frequencies before and after TAE**

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| --- | --- | --- | --- | --- |
| **Parameters**  | **Risk** | **[B-A]** | **[D-C]** | **p value** |
| **After positive TAE n (%)** | **Very high** | 19 (0.92) | 112 (5.45) | <0.0001 |
| **High** | 32 (1.55) | 94 (4.56) |
| **Intermediate** | -7 (0.34) | -82 (3.97) |
| **Low** | -44 (2.14) | -99 (4.81) |
| **After negative TAE n (%)** | **Very high** | -18 (0.88) | -2 (0.10) |
| **High** | -18 (0.88) | -48 (2.32) |
| **Intermediate** | -32 (1.56) | -90 (4.37) |
| **Low** | 68 (3.30) | 210 (10.19) |

*NB:* ***A****= direct LDL-c without TAE;* ***B****= direct LDL-c with TAE;* ***C****=Friedewald without TAE;* ***D****= Friedewald with TAE*

1. **DISCUSSION**

Accurate estimation of LDL-c is essential in determining a treatment strategy for lipid disorders. Several studies show the limitations and challenges of standard direct and indirect lipid assays [17]. Lipid parameters remain the main biomarkers recommended in American guidelines for risk stratification of atheromatous CVD [18-20]. Any improvement in the measurement and reliability of LDL-c is therefore crucial. The aim of the present study was therefore to assess the influence of analytical error and the method of LDL-c calculation on patient classification. This involved calculating LDL-c concentrations by applying the total analytical error to the result and stratifying CV risk. To this end, we used Friedewald methods to determine LDL-c levels. Direct LDL-c levels were obtained retrospectively. Direct LDL-c was found to be elevated in 14.76% of the population, but with indirect calculation method, this increased to 16.45%. This could reflect biases in the determination of lipid parameters. When positive TAE is applied to direct method, the number of patients with elevated LDL-c rises from 14.8% to 17.23%. This shows that 2.43% of this study population should have been classified in an elevated range. But the total admissible negative error reduces the frequency of high LDL- c from 14.76% to 13.01%. With the indirect method same line was observed where after application of the positive TAE, a high LDL-c level is more frequent. This TAE should be communicated to physicians for better treatment of the patient.

This showed that the application of this error changed the classification of patients at risk of being put on treatment from low to very high risk. On the basis of the risk classification before application of the total analytical error, it emerged that with the direct method 9.71% and 5.05% of patients were classified respectively as high and very high risk on developing cardiovascular disease and had to be systematically put on lipid-lowering medication, and with Friedewald 10.34% an 6.11% of patients were at high an very high risk. The difference between these two methods was 1.06% of patients (n=+22 for Friedewald). This difference represents the frequency of additional patients found using the indirect method. Given the involvement of LDL-c in the development of cardiovascular disease, these additional patients will benefit from appropriate management. After application of positive TAE, patient frequency increased with two methods used. Whereas with negative TAE, the direct method led to an increase in the frequency of high and very high risk patients. This difference in frequency also represents the additional patients who may be candidates for lipid-lowering therapy. This suggests that using the indirect method and applying the total analytical error would lead to an increase in the frequency of high and very high risk patients. This in turn would have an impact on patient risk classification.

On the other hand, for both direct and indirect methods of analysis, we obtained +1.55% versus +0.92% and 4.56% versus 4.45% respectively of high and very high risk patients after application of the positive TAE. Overestimation of values has already been demonstrated in several studies for indirect methods [16, 21]. Indeed, the TAE applied to the direct method was ±0.12, whereas with indirect method, it was ±0.53. This result was due to different lipid parameters of indirect calculation formula where analytical error was applied. Consequently, the TAE of each parameter was added together. This meant that patients could switch from a lower to a higher risk after classification. The frequency of patients requiring treatment should increase. However after application of the negative TAE difference in frequency of patients at risk decreases.

Consequently, in view of these results, which reveal a difference between the direct and indirect method, it follows that from the direct method to the indirect method before and after application of the total analytical error will underestimate risk classification. It would therefore be wise to use the indirect method, which appreciates the risk and leaves almost no patient untreated. For low-risk patients who are reclassified as being at intermediate risk of developing atheromatous cardiovascular disease, the application of hygienic-dietary measures will be suggested and beneficial to health. However, patients at intermediate risk who have been reclassified as high risk will benefit from lipid-lowering drugs. Nevertheless, antihyperlipidemics drugs have side effects [22-24]. For this reason, physicians should be aware of TAE for more appreciable interval in decision-making.

1. **CONCLUSION**

The present study, which aimed to assess the influence of analytical error and LDL-c calculation method on patient classification, highlighted a high frequency of patients whose risk classification for developing CVD was changed overall. In addition, the use of indirect methods to calculate LDL-c resulted in a higher frequency of high-risk and very high-risk patients. Similarly, after application of the total allowable error, whether using the direct or indirect method, the classification of patients according to risk was completely altered. This classification shifted a proportion of patients from a lower to a higher risk of developing cardiovascular disease. This suggests that TAE should be take into account for better treatment of the patient.

1. **LIMITATION OF THE STUDY**

This work had a number of limitations. The retrospective data obtained from the various sites did not include the patient's clinical data such as clinical information and anthropometric data such as height, weight and blood pressure. Those data would have provided more detailed interpretation of the results.

**ETHICAL APPROVAL**

This work was carried out with the approval of the chief’s executive’s officers of the three hospitals. Anonymity and confidentiality of patients’ data were respected according to Helsinki declaration.

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