Assessing the Accuracy of a Point of Care Analyzer for Hyperlipidemia in Western Kenya

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Thesis submitted in partial fulfillment of
the requirements for the degree of
Master of Science in the Department of
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ABSTRACT

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Abstract

The prevalence of hyperlipidemia, along with other non-communicable diseases, is on the rise in low- and middle-income countries. Given the resource-limited setting, a myriad of diagnostic challenges exist with traditional laboratory-based lipid tests, including mobility, timeliness, and laboratory infrastructure. Novel technology in the form of "point of care" devices seeks to overcome such barriers by providing immediate results without dependency on significant laboratory infrastructure. CardioChek PA (Polymer Technology Systems, Inc., Indianapolis, United States) is a point of care lipid measuring device and is readily available in Kenya. However, it has not been validated in this setting. In this study, I assess the accuracy of CardioChek PA with respect to standard laboratory-based testing, which is currently the gold standard.

In Webuye, Kenya, two blood samples were collected from 246 subjects to simultaneously measure the lipid levels via both CardioChek PA and the gold standard. All subjects were adults, and geographic stratified sampling methods were applied. Statistical analysis of the novel device's accuracy was based on percent bias, which is the standardized approach established by the National Cholesterol Education Program (NCEP) of the National Institute of Health (NIH). The NCEP suggests that percent bias be ≤±3% for low-density lipoprotein (LDL) cholesterol, ≤±5% for high-density lipoprotein

(HDL) cholesterol, ≤±5% for total cholesterol (TC), and ≤±4% for triglycerides (TG). Misclassification rates and absolute percent bias were also analyzed.

This study found the CardioChek PA analyzer to be substantially inaccurate for LDL cholesterol (-25.9% bias), HDL cholesterol (-8.2% bias), and TC (-15.9% bias). For TG, the CardioChek PA performed well with a percent bias of 0.03%. However, the TG absolute percent bias (27.7%) and proportion of patients outside of the NCEP range (85%) reflected substantial inaccuracy of measurements. Moreover, those patients at higher risk of complications from hyperlipidemia were most likely to be misclassified into a lower risk category. Thus, we conclude that CardioChek PA is inaccurate and not suitable for our clinical setting. Furthermore, the findings highlight the need to validate new diagnostic tools in the appropriate setting prior to scale up regardless of its potential for novel utility.

Dedication

To community health workers across the globe and their tireless efforts to narrow the access to care gap in rural areas.

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1. Introduction

Novel methods of healthcare delivery are being sought to tackle the rising burden of non-communicable diseases (NCDs) in low- and middle-income countries (LMICs) [1]. More specifically, cardiovascular disease deserves heightened attention given its position as the leading NCD contributing to mortality. In addition, its myriad of modifiable risk factors require discrete interventions [2]. Hyperlipidemia, diabetes mellitus, hypertension, smoking, and obesity are just a few of these risk factors that demand primary and secondary prevention measures. In LMICs, point of care (POC) diagnostics have long been proposed as a potentially worthwhile avenue for overcoming many of the barriers to diagnostic care, including mobility, timeliness, and laboratory infrastructure. For diabetes, POC diagnostics for measuring real-time blood sugar levels, as well as average blood sugar levels over the past three months, have facilitated the process of screening for undiagnosed patients and monitoring those who are already diagnosed [3, 4]. Unfortunately, hyperlipidemia does not possess an established, formidable equivalent in terms of real-time diagnostic technology.

1.1 The rise of non-communicable diseases and hyperlipidemia

Non-communicable diseases are usually thought of as chronic illnesses that are not due to transmission of an infectious pathogen and often share similarities in terms of common risk factors. Examples of NCDs include high cholesterol, cancer, heart disease, and diabetes mellitus. Historically, infectious diseases were thought to be

predominantly diseases of resource-limited countries, and NCDs were seen as diseases of the affluent. However, the WHO reported in 2010 that NCDs already superseded communicable, or infectious, diseases to become the top cause of mortality in LMICs [2]. Among NCDs, cardiovascular disease alone was reported to cause 48% (17 million) of all NCD deaths in 2008.

The rising trend in NCD prevalence and incidence is compounded by the alarming economic ramifications. In a 2008 study assessing the economic burden of NCDs, a projected $84 million in healthcare resources would be lost due to heart disease, diabetes, and stroke alone between 2006 and 2015 [5]. These findings have resulted in a need for reassessing the global health community's approach to healthcare delivery [1, 6].

Specifically, hyperlipidemia is an NCD which merits attention given its direct relationship with morbid cardiovascular diseases, such as heart attack and stroke. Hyperlipidemia is an abnormal elevation of the naturally occurring lipid molecules in the body and includes both cholesterol and triglycerides. These molecules are necessary for cellular wall structure, digestion of food, production of hormones, as well as energy storage. An appropriate concentration of lipids is naturally synthesized by the liver, however genetic mutations and/or lifestyle choices (diet and physical activity) can lead to elevated lipid concentrations.

Clinically, there are four lipid parameters which are routinely measured: low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, total

cholesterol (TC) and triglycerides (TG). LDL cholesterol is known in the general population as "bad" cholesterol as it is responsible for transporting cholesterol throughout the body. When present in excess, it will deposit cholesterol on the walls of arteries, thus leading to atherosclerosis. The formation of atherosclerosis is a critical risk factor for the development of cardiovascular disease [7-10]. HDL cholesterol is routinely referred to as "good" cholesterol by the general population as it is responsible for transporting excess lipids within the blood vessels back to the liver for recycling. TC represents the cumulative total of all types of cholesterol, including LDL and HDL. Finally, TG are fat molecules which, when in excess, can be deposited with LDL cholesterol along the walls of arteries leading to atherosclerosis. TG are also responsible for energy storage.

In LMICs, the prevalence of hyperlipidemia is typically lower than that of high income countries (HICs), however new evidence projects a substantial rise in the near future. In 2008, the WHO reported the global prevalence of elevated cholesterol to be 39% and an estimated 2.6 million deaths annually to be due to high cholesterol [2]. The WHO Africa and Southeast Asia regions had the lowest prevalence rates at 23% and 29%, respectively. Kenya, specifically had a prevalence of 26% [11]. However, multiple studies are projecting an inevitable rise in the burden of hyperlipidemia for LMICs due to its strong correlations with urbanization, western diet, obesity, and rising national income, which are increasingly prevalent in LMICs [7, 12, 13].

1.2 Current diagnostic barriers for hyperlipidemia

Hyperlipidemia inherently poses multiple challenges in diagnosing and monitoring given its potential for "silent" progression and turnaround time. Despite its status as a significant risk factor for cardiovascular events, most patients are unlikely to present with any symptoms [14]. Thus, in LMICs where patients commonly do not present to a health facility until their quality of life is significantly affected by a condition [15] , the challenge to diagnose hyperlipidemia at an early stage and prevent progression of cardiovascular disease becomes even greater. The current gold standard of diagnosing hyperlipidemia is a laboratory-based serum study. Due to its lack of immediate results, patients may also find it challenging to return to the health facility to obtain results and medical recommendations given barriers of transportation and related costs. Furthermore, the current gold standard requires significant laboratory infrastructure and therefore lacks mobility.

1.3 Point of care technology and hyperlipidemia

In response to the limitations presented by traditional laboratory methods for diagnosing a variety of conditions in LMICs, POC technology has been proposed as a potentially effective method of delivering diagnostic care [16-18]. Points of care tools oftentimes involve mobile handheld devices which can be carried to rural areas that lack

laboratory infrastructure. Results are frequently produced in less than 10 minutes, and clinicians are subsequently able to make medical management decisions or seek expert consultation within the same patient encounter. In addition, screening campaigns are able to inform patients within their homes of the results and make referrals to the appropriate health facility if necessary. More recently, POC technology has become simplified for patients to use at home without assistance of health professionals, thus allowing them to circumvent barriers of access to diagnostic services or stigma that may prevent them from presenting to a public facility for testing. However, not all POC technology offers all these advantages. Potential disadvantages for some POC devices include: cost, requirement of refrigeration for test reagents, need for laboratory infrastructure to house a large bench-top machine or computer, requirement of reliable electricity source, need for extensive laboratory training, and lack of quality control leading to inaccurate results [16-18]. Thus far in LMICs, several studies have shown promising early results for a broad range of pathologies, including diabetes mellitus, HIV, hepatitis B, venous thrombosis, and syphilis [4, 19-21].

In regards to hyperlipidemia, several POC devices have been produced, but with varying performance characteristics. A review of six different POC lipid analyzers assessed in high-income countries (HICs) concluded that insufficient evidence exists to displace traditional laboratory lipid testing [22]. The model Cholestech LDX (Alere Inc., Waltham, United States) had the most promising results matching the accuracy of

laboratory lipid testing in several studies [23-25], though not all [26, 27]. However, this model requires that individual cartridges not used within 30 days be refrigerated, which is not possible in many LMIC settings. Furthermore, one study showed Cholestech LDX to have the highest cost among six different POC lipid diagnostic models [22].

CardioChek PA (Polymer Technology Systems, Inc., Indianapolis, United States) is another model which has a lower cost and does not require refrigeration. However, it has had limited and conflicting results. In a comparison study of CardioChek PA versus Cholestech LDX by Dale et al. [23] in the United States, only Cholestech was able to produce a full lipid panel with accuracy comparable to that of the gold standard. CardioChek PA was only able to produce triglyceride levels with sufficient accuracy. Moreover, CardioChek PA showed poor clinical relevance by consistently underestimating the Framingham Risk Score. A similar comparison study was performed by Shephard et al. in Australia which also showed CardioChek performing accurately only for triglyceride measurements [28]. However, Panz et al. performed the same comparison in South Africa and concluded that both analyzers performed with sufficient accuracy with respect to the gold standard [29]. The study did note that higher levels of LDL results were underestimated by CardioChek. While the results across studies for CardioCheck PA are conflicting, the only independent study supporting its use is from sub-Saharan Africa. This single study has yet to be reproduced anywhere else on the continent.

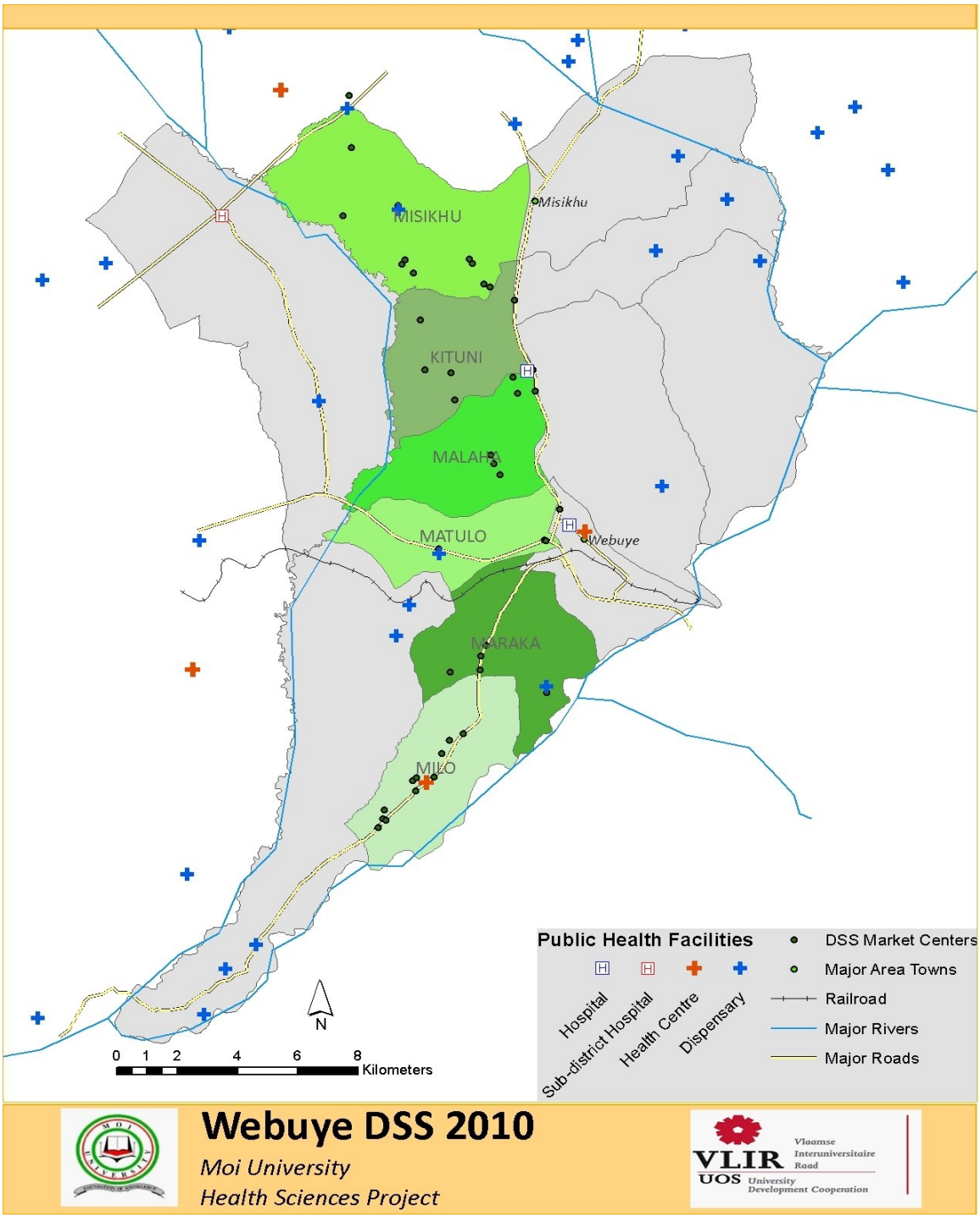
In Kenya, CardioChek PA is readily available and is the only POC lipid analyzer that is accessible in Kenya [30], however it has yet to be validated. In this study, we assessed the accuracy of CardioChek PA with respect to traditional laboratory lipid testing in western Kenya.

2. Methods

A cross-sectional, prospective study was performed in the catchment area of Webuye District Hospital (WDH) of western Kenya.

2.1 Setting

Webuye is a town in western Kenya located approximately 400 km northwest of the capital, Nairobi. The area is primarily agricultural and WDH serves a primarily rural population with some peri-urban clients. Farming is the main economic activity. Sugar cane is the main cash crop while maize, beans, millet and sorghum are grown for subsistence. Small-scale dairy and poultry farming is widely practiced. A paper factory and chemical processing plant are located in the adjacent area. Social amenities like clean water, sanitation and electricity are not available to the majority of the residents. Webuye is also home to the Health and Demographic Surveillance System (HDSS) which is a household-level database of approximately 80,000 people living in about 13,500 households within the Webuye division.



Credit: Webuye Health and Demographic Surveillance Site

Figure 1: Map of Webuye Division, home of the Health and Demographic Surveillance System (HDSS)

2.2 Ethical Considerations

All patients provided informed consent. Ethics approval was obtained by the Institutional Research Ethics Committee at Moi Teaching and Referral Hospital, which includes the research ethics oversight of Webuye District Hospital. An exemption was obtained by Duke University Institutional Review Board to perform the data analysis and final report based on a de-identified data set.

2.3 Sampling and Data Collection

Adult subjects (n=246) were selected by stratified sampling from the HDSS database. The stratification parameter applied was sub-location within the Webuye division, and we then applied simple random sampling to each stratum of adults. The sample size calculation was based on applying the estimated diabetes mellitus prevalence of 3% and a confidence interval of +/- 3%, and produced a minimum sample size value of 129 subjects. This value represents the number of subjects required to detect a significant difference between the results of the two lipid measuring tools. The determination of significant difference is based on percent bias ranges described below. Of note, the prevalence of diabetes mellitus was applied because this study is part of a larger study looking at multiple cardiovascular risk factors across the Webuye division. Given that diabetes mellitus is expected to have the lowest prevalence among the diseases under study, the sample size calculation was based on diabetes.

Venous and capillary blood specimens were collected for the laboratory lipid testing as well as CardioChek PA analyzer, respectively, by trained laboratory technicians. Patient encounter settings included local health centers as well as local schools and churches as to accommodate any transportation challenges for the subjects. Two CardioChek PA analyzers were used during the study and each was calibrated. CardioCheck PA results were produced at the time of patient encounter, and venous samples were transported to the Academic Model Providing Access to Healthcare (AMPATH) reference laboratory (ARL) in Eldoret, Kenya. Delay due to transportation of venous samples ranged from 4 to 9 hours. During this time period, specimens were stored in an ice box. The ARL uses COBAS analyzers (Roche Diagnostics, Basel, Switzerland) for lipid testing, and all LDL values are calculated, as opposed to measured. The ARL uses established Standard Operating Procedures which have been reviewed by a site assessment team from Pharmaceutical Product Development Ltd. Furthermore, the ARL is certified by the Kenyan Medical Licensing Board, and is accredited by the NIH Division of AIDS international laboratory standardization program.

2.4 Statistical analysis

Statistical analysis was based on the methods established by the Working Group on Lipoprotein Measurements of the National Cholesterol Education Program (NCEP), which sought to establish a standard approach for assessing the accuracy and precision

in measuring LDL, HDL, TC, and TG [31, 32]. These regulations were subsequently submitted to and published by the National Heart, Lung, and Blood Institute of the National Institute of Health (NIH) [31]. As per NCEP guidelines, the diagnostic accuracy of a novel method for measuring blood lipids should be judged by calculating the percent bias. Percent bias is defined as the mean of the difference between the values reported (experimental and reference) when calculated as a percent of the reference value:

$$\text{Percent bias} = [\Sigma[(X_e - X_r)/X_r]/n] \times 100\%$$

where X_r is the reported "reference" value of the gold standard method, X_e is the reported "experimental" value of the method under study, and *n* is the sample size for a given parameter. The acceptable bias ranges are different for each of the four lipid parameters and have been described by the NCEP (see Table 1). A bias value within this range would indicate that the method being studied has accuracy not significantly different from that of routine use of the gold standard laboratory method. Additionally, we calculated the proportion of subjects whose individual percent bias values were outside the acceptable range.

Table 1: Standards for Accuracy of Lipid Measurements by NCEP Guidelines

Parameter	Bias (%)
LDL* Cholesterol	≤±3
HDL+ Cholesterol	≤±5
Total Cholesterol	≤±5
Triglycerides	≤±4

*LDL=Low density lipoprotein
+HDL=High density lipoprotein

The absolute percent bias was determined in a nearly identical fashion as the methods of determining percent bias with the exception of taking the absolute value of the difference between the values reported (experimental and reference):

$$\text{Absolute percent bias} = [\Sigma[|X_e - X_r|/X_r]/n] \times 100\%$$

No standard values or guidelines for absolute percent bias are provided by NCEP.

The clinical relevance of inaccurate results was assessed by identifying the misclassification rate of each lipid panel parameter. Misclassification rate is determined by calculating the proportion of subjects that are categorized by the POC analyzer into a risk group that is different from the risk group categorized by the gold standard. The risk groups were defined by value ranges from the Adult Treatment Panel III (ATP III) report [33] (see Table 2). The ATP III guidelines seek to establish correlations between rising lipid parameter values and risk of coronary heart disease. These guidelines are routinely used in the clinical setting in order to determine the appropriate step in treating or preventing hyperlipidemia. Thus, the misclassification rate is a reflection of

the frequency in which a physician may be misguided by the POC results when making medical management decisions.

Table 2: Adult Treatment Panel III (ATP III) Risk categories by lipid parameter

Risk group*	LDL (mg/dL)	HDL (mg/dL)	TC (mg/dL)	TG (mg/dL)
Optimal	<100	>40	<200	<150
Above optimal	≥100 and <130	--	--	--
Borderline high	≥130 and <160	≥50 and <60	≥200 and <240	≥150 and <200
High	≥160	≥60	≥240	≥200

*The risk groups and their respective values are applicable towards adults who otherwise do not have other risk factors for coronary heart disease.

3. Results

3.1 Accuracy per NCEP guidelines

The accuracy of CardioChek PA in relation to venous laboratory testing was markedly low. As seen in Table 4, the percent bias values of all lipid parameters were outside of the acceptable ranges with the exception of that of triglycerides (0.03%). However, the absolute percent bias for triglycerides was 27.7%, and 85% (*n*=206) of subjects had triglyceride results outside of the accepted NCEP ranges (Table 5). All other parameters resulted in higher proportions of subjects with results outside of the acceptable range. LDL cholesterol had the highest proportion at 98% (*n*=235). Furthermore, 38% (*n*=98) of total cholesterol values and 33% (*n*=80) of triglyceride values from CardioChek PA were "undetectable." None of the results produced by the laboratory method were "undetectable."

Table 3: Percent bias for lipid measurements via CardioChek PA

Parameter	Bias, % [95% CI]	Absolute bias, % [95% CI]
LDL Cholesterol	-25.9 [-29.7,-22.1]	33.5 [30.9, 36.2]
HDL Cholesterol	-8.2 [-12.9,-3.6]	24.7 [21.1, 28.3]
Total Cholesterol	-15.9 [-19.8,-12.1]	24.3 [21.1, 27.4]
Triglycerides	0.03 [-8.6,8.6]	27.7 [19.8, 35.5]

Table 4: Proportion of subjects outside of NCEP percent bias standards

Parameter	Proportion outside of acceptable range
LDL Cholesterol	98%
HDL Cholesterol	86%
Total Cholesterol	90%
Triglycerides	85%

3.2 Clinical accuracy

The misclassification rate of CardioChek PA varied by parameter and largely supported previous findings in the literature which noted a tendency for underestimation of the true value (Table 6). The total misclassification rates ranged from 0.8% (triglycerides) to 36.7% (LDL cholesterol). Within each parameter, the misclassification rate was generally higher for the higher value categories within each parameter.

Table 5: Misclassification rate by CardioChek PA within specific ranges of lipid results

	No. Subjects (lab method)	No. Subjects misclassified (POC method)	Misclassification rate (%)
LDL (mg/dL)			
<100	141	2	1.4
≥100 and <130	74	63	85.1
≥130 and <160	16	14	87.5
≥160	9	9	100.0
Total	240	88	36.7
HDL (mg/dL)			
<40	49	13	26.5
≥40 and <60	128	72	56.3
≥60	66	28	42.4
Total	243	113	46.5
TC (mg/dL)			
<200	208	1	0.5
≥200 and <240	29	25	86.2
≥240	6	6	100.0
Total	243	32	13.2
TG (mg/dL)			
<150	233	2	0.9
≥150 and <200	6	5	83.3
≥200	3	1	33.3
Total	242	8	3.3

Figure 2 displays a line graph of paired values. Each pair includes a group mean laboratory LDL cholesterol result as well as the respective group mean POC result. The groups were formed by establishing 18 evenly distributed cutoff points to encompass the entire range of laboratory LDL cholesterol values. The figure illustrates the under-estimation of the true LDL values by CardioChek PA among higher LDL values.

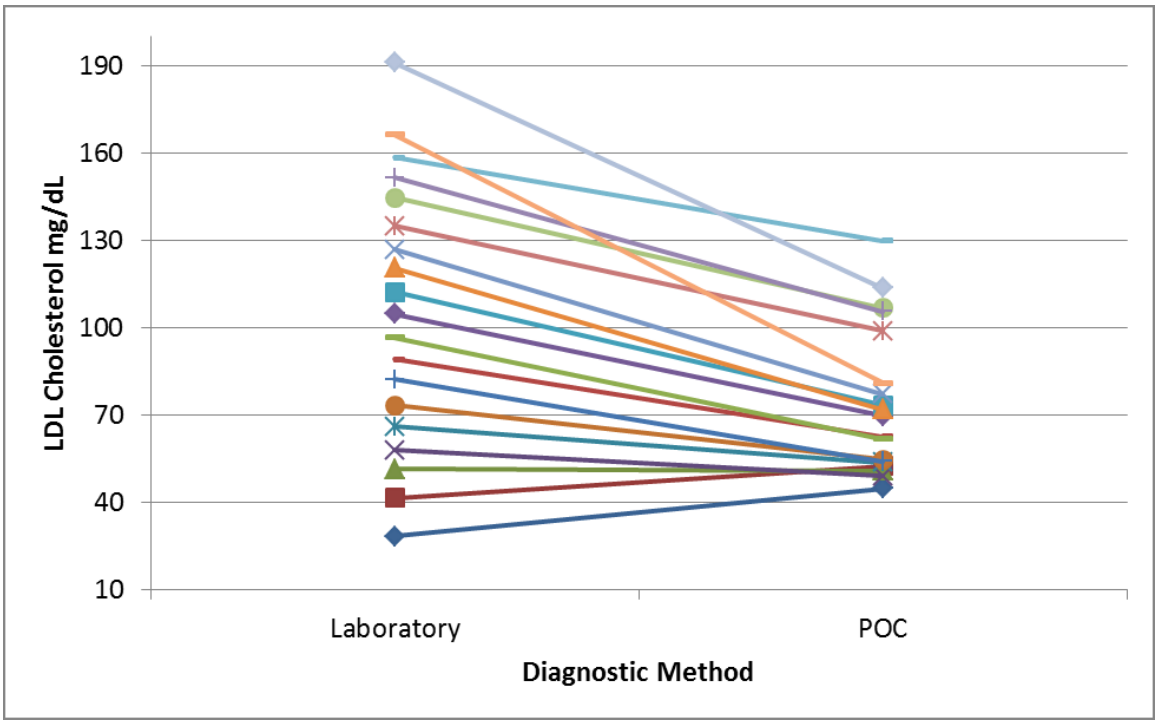


Figure 2: Comparison of LDL cholesterol values between laboratory results and respective POC results

4. Discussion

4.1 Accuracy of CardioChek PA

This was the first study of the accuracy of the CardioChek PA POC device for blood lipid measurement in western Kenya. Our analysis of the accuracy of this device using methods and guidelines recommended by the NCEP showed that CardioChek PA produced unacceptable results in regards to its accuracy of real-time lipid measurements.

Low density lipoprotein, HDL and TC were substantially outside of the acceptable percent bias range while TG percent bias was within the acceptable range. The seemingly positive outcome for TG measurements, however, must be considered in the context of the results of the absolute bias and highlights the potential for misleading results when using percent bias alone. For example, triglyceride measurements produced an absolute bias greater than that of HDL cholesterol and total cholesterol despite being the only parameter within the accepted range of percent bias. Furthermore, the percent bias confidence intervals of triglyceride show that CardioChek PA has the potential for equally over- and under-estimating the true triglyceride value while consistently underestimating the true values of LDL, HDL and TC. A similar trend across parameters was also identified by Dal, et al. when assessing the CardioChek PA analyzer [23]. By equally over- and under-estimating the true value, the cumulative difference from the true value trends towards zero regardless of the

magnitude of the individual over- and under-estimations. This potential for deception is relevant to the case of triglycerides in that despite having an acceptable percent bias, 85% of the individual percent bias values were outside of the NCEP acceptable ranges.

The misclassification rate was generally greater for those subject groups with higher lipid and lipoprotein values. This finding is consistent with prior studies showing that CardioChek PA is prone to underestimating the true value of cholesterol levels. Thus, those subjects in the highest risk categories for cardiovascular complications (based on LDL, TG, and TC levels) will be more likely to be misclassified into a lower risk category. For example, an LDL cholesterol level of 160 mg/dL is an important threshold which impacts clinical decision making for preventive and therapeutic measures [33]. Having an LDL level this high usually implies a markedly increased risk of developing coronary heart disease, and therefore warrants more aggressive treatment measures. In this study, 100% of subjects with true LDL cholesterol values ≥160 mg/dL were misclassified into a lower risk classification (Table 6). Therefore, screening high risk patients with CardioChek will oftentimes produce misleading results. This shortcoming precludes CardioChek PA from being a clinically reliable tool in our setting. The high rate of "undetectable" values by CardioChek PA also adds to the clinical challenges of the instrument. In comparison to discrete numerical values consistently produced by the gold standard, "undetectable" results are less clinically valuable when making management decisions.

Less than 5% (*n*=11) of all samples were non-fasting. Recent studies have noted the insignificance of fasting versus non-fasting lipid measurements [34, 35]. Thus, the minimal quantity of heterogeneity of specimens with respect to fasting status is unlikely to create a significant impact on the results.

4.2 Limitations

Limitations of the study included the lack of precision analysis, size limitations, and the comparison of capillary versus venous samples. Adequate data were not collected to be able to do precision analysis, thus a complete validation study could not be performed. As per NCEP guidelines, assessment of precision in lipid measurements requires multiple runs of each set of samples. The variation both between runs as well as within each run is then assessed [31, 32]. However, the clear shortcomings in accuracy alone deem the diagnostic tool inappropriate for our setting. In regards to size, the study was only based on a single center which questions reproducibility of results, and the sample size was limited such that lipid level categories of higher risk were substantially smaller than the other categories. Lastly, there is conflicting data regarding the comparability of capillary and venous blood samples with respect to lipids and lipoproteins [25, 36]. The difference in results from prior studies may be due to specimen collection technique.

4.3 Conclusion

This study highlights critical shortcomings of using the CardioChek PA POC instrument for assessing blood lipid levels in rural western Kenya. Its poor test characteristics were also shown in other geographic areas of greater resource availability. This diagnostic instrument's lack of accuracy in addition to its unacceptable clinical applicability nullifies any perceived advantage of this particular POC device.

This study shows that all novel technology with great potential utility should still be independently validated in the relevant setting. Despite relative success in its applicability in South Africa, CardioChek PA did poorly in Kenya. Findings from a LMIC setting cannot be generalized uniformly even within the sub-Saharan Africa region. Additionally, further studies assessing a broad spectrum of POC lipid devices would be of value to assess the broader applicability of POC lipid diagnostics in a resource-limited setting. The shortcomings of CardioChek PA may not be particularly true for other analyzers in this setting. The potential advantages of POC technology for critical diseases, such as hyperlipidemia, warrant a continued pursuit of instrument validation in this setting.

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