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Polymer Technology Systems CardioChek PA lipid system

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Polymer Technology Systems CardioChek PA lipid system

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Summary

We have evaluated the CardioChek PA lipid system, which uses dry reagent test strips for the quantitative determination of total cholesterol (TC), high density lipoprotein cholesterol (HDL cholesterol), and triglyceride on 40µl of capillary or venous whole blood. From the three measured analytes, the instrument is capable of providing automatically calculated low density lipoprotein (LDL) and TC/HDL ratio. The results from a lipid panel test strip are available in approximately 2 minutes. Individual test strips are also available for the measurement of total cholesterol, HDL cholesterol and triglyceride. The meter is compact and portable, does not require any calibration by the operator other than inserting the correct memo chip into the meter and is simple to use.

The manufacturer's user's guide states that the system is intended for in-vitro diagnostic use by health-care professionals and is capable of lipid screening. This evaluation was designed to assess the accuracy and imprecision of the lipid panel test strip by trained medical laboratory personnel.

We assessed the performance of the CardioChek PA meter with fingerstick capillary blood samples, using the lipid profile test strips on 106 subjects recruited from the general public, laboratory staff, and patients attending a lipid out patient clinic. Comparison of the results obtained was made against results from serum samples (venous blood) with routine laboratory methods on a Vitros 950 for the total cholesterol and triglyceride assays and an IL600 analyser for the HDL cholesterol assay. The correlations between the laboratory reference assay results and those from the CardioChek were 0.86, 0.74 and 0.98 for total cholesterol, HDL cholesterol and triglyceride respectively. A significant overall bias is evident in total cholesterol and triglyceride results from the CardioChek relative to the Vitros 950 of 0.23 and 0.11 mmol/L respectively. That bias varies with concentration, becoming more negative in total cholesterol and more positive in triglyceride with increasing concentration. The overall bias in HDL cholesterol results is not significant, nor is there a significant trend in bias with concentration.

In the clinical study, imprecision was approximately 12%, 22% and 14% for total cholesterol, HDL cholesterol and triglyceride respectively, although imprecision was slightly better in the laboratory study for some analytes. Total error ranged from 6 to 11%, 17 to 31% and 17 to 31% in the laboratory study. The US National Cholesterol Education Program guidelines for acceptable total error are ±8.9 % for total cholesterol, ±13 % for HDL cholesterol and ±15 % for triglyceride. The CardioChek failed to meet these standards with HDL cholesterol and triglyceride and at the higher concentration of total cholesterol. In the population studied all three analytes appear to have a bias which was affected by whether the subject had fasted prior to testing. There is also a strong association between bias and haematocrit in total cholesterol and HDL cholesterol results.

Sensitivity and specificity for detecting individuals at high risk of coronary heart disease as defined by the US National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guidelines were 85 % and 80 % respectively using total cholesterol results alone (with a cut-off of 6.2 mmol/L) and 75% and 79% respectively using HDL cholesterol alone (with a cut-off of 1.04 mmol/L).

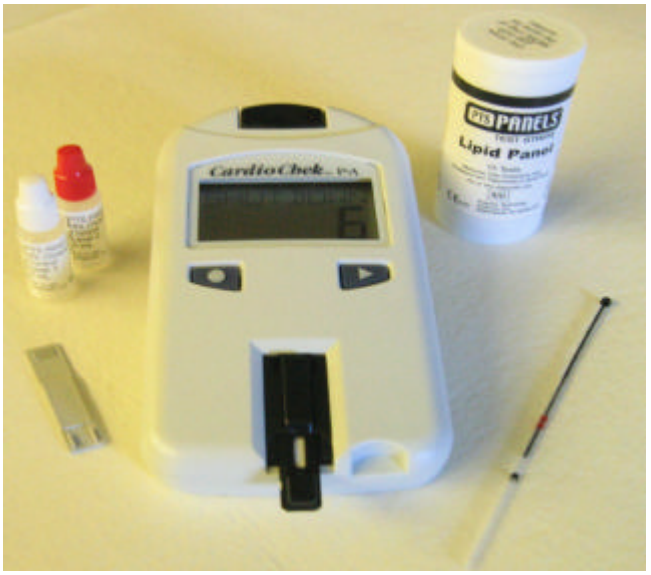
Introduction

An increase in demand for cholesterol measurement has occurred in recent years, due to the publicity linking elevated cholesterol levels and coronary heart disease and the availability of Statin - used to lower LDL cholesterol, as an over-the counter medicine. Members of the general public interested in better health-care and interested in purchasing Statin, are offered free cholesterol measurements by some pharmacists. The availability of small, portable and relatively inexpensive instruments and kits, capable of use by non-laboratory personnel has led to total cholesterol screening becoming widely available in primary care, and for home monitoring by the general public. Issues related to the safety and management of point-of-care devices are covered in guidelines issued by the Medicines and Healthcare products Regulatory Agency [1, 2].

The CardioChek has been evaluated as part of an ongoing programme to assess the suitability of analytical systems for use in primary care and health screening locations. To see other evaluation reports carried out by WASP please visit the MHRA website at www.pasa.nhs.uk/cep.

Instrument description

The CardioChek PA lipid system is a small hand held battery-operated, reflectance meter capable of performing either lipid panel testing (total cholesterol, HDL cholesterol, triglyceride, calculated LDL and cholesterol/HDL ratio) or a single test for cholesterol, HDL, triglyceride, glucose, ketones, or creatinine from a single drop of blood. The front of the instrument has a liquid crystal display panel for messages and results, and two control buttons labelled with a circle (enter), and triangle (next) to operate the system. The test strip insert opening is located two thirds down the meter and the memo chip port is located at the top. The instrument is powered via two AAA batteries.



The CardioChek system consists of the analyser, test strips, memo chip, optical check strip, capillary blood collection tubes and aqueous quality control materials. A printer is also available as an optional extra. Specifications of the CardioChek analyser are given in table 1.

The CardioChek uses reflectance photometry to determine the concentration of the analyte being measured. The colour changes are measured simultaneously, and the readings converted to concentration by the instrument's microprocessor.

The reagent test strips are supplied in a flip top container with a desiccant to minimise exposure to moisture. The strips are available in a pack of 25 or 6 test strips for the individual chemistries and in a pack of 15 for the Lipid Panel. The test strips can be stored unopened at room temperature (20 - 30 °C). After opening, the test strips are stable until the expiration date if the vial is properly stored and always capped according to the manufacturer's instructions.

Table 1: Details of the CardioChek PA lipid system

Manufacturer	Polymer Technology Systems Inc 7736 Zionsville Road Indianapolis IN 46268 USA
Suppliers	BHR Pharmaceuticals Ltd 41 Centenary Business Centre Hammond Close Attleborough Fields Nuneaton Warwickshire CV11 6RY
Analytical technology	Reflectance photometry.
Sample volume	40 µl for lipid panel, 15 µl for individual test.
Calibration code	Colour coded memo chip to the equivalent test strip supplied with the reagent pack.
Analytical range	Total cholesterol 1.3 to 10.36 mmol/L HDL cholesterol 0.39 to 2.59 mmol/L Triglyceride 0.28 to 5.65 mmol/L
Haematocrit range	30 to 45 %
Power	Two AAA 1.5 volt alkaline batteries (approximately 300 tests).
Operating temperature	Temperature 10 to 40 ºC.
Humidity	Relative humidity 20 to 80 %.
Dimensions and weight	H 2.54 x W 7.62 x L 13.97 cm; 122 grams (excl batteries)
Essential accessories	Lancing unit, lancet, absorbent tissue, alcohol swab, 40 µl capillary tubes and plungers, quality control materials.
Reagents (Excl. VAT)	Pack of 25 test strips: cholesterol £57.50, HDL cholesterol £67.00, triglyceride £67.25; Lipid Panel (TC/HDL/TG) a pack of 15 test strips £149.85, Multichemistry control materials at 2 levels (2 mL) £30.00 HDL control materials at 2 levels (2 mL) £22.99 Safetec Test Pipette (40 µl) £4.00/15.
Accessories	CardioChek printer.
Warranty	One year for meter and printer. Printer heads 6 months only.

Test principle

The three lipid analytes total cholesterol, HDL cholesterol and triglyceride are measured using a single test strip. A 40µl sample of either capillary or venous heparinised whole blood is dispensed on to the application window of the test strip . The plasma is automatically separated from the red blood cells through a separation system and a portion of the plasma flows to the three reaction pads. Prior to the HDL cholesterol measurement the LDL and VLDL are filtered from the plasma by dextran sulphate and magnesium acetate precipitating reagent. The filtrate is then transferred to the HDL cholesterol reaction pad. For HDL cholesterol measurement the LDL and VLDL are filtered from the plasma by phosphotungstic acid precipitating reagent. The measurement of total cholesterol and HDL cholesterol uses the same enzymatic method. The enzyme cholesterol esterase hydrolyses the cholesterol esters in the filtrate or the plasma to the corresponding fatty acids plus free cholesterol. Cholesterol oxidase, in the presence of oxygen, oxidises free cholesterol to form cholest-4-ene-3-one and hydrogen peroxide. The peroxide in the presence of the enzyme peroxidase, reacts with 4-aminoantipyrine and N-ethyl-sulfohydroxypropyl-m-toluidine to form a coloured quinoneimine dye. The intensity of the colour produced is proportional to the total cholesterol or HDL cholesterol in the sample.

The triglyceride method is based on the hydrolysis of triglyceride by cholesterol esterase to glycerol and free fatty acids. Glycerol, is converted to glycerol-3-phosphate by the enzyme glycerol kinase. This is then oxidized by glycerol phosphate oxidase to dihydroxyacetone phosphate and hydrogen peroxide. The colour reaction is the same as that in the HDL and total cholesterol method, based on horseradish peroxidase and a chromogen.

Calibration

The meter is pre-calibrated by the manufacturer, and carries the calibration curves within the memo chip supplied with each individual box of test strips. The memo chip is colour coded to match the test strips and contains information on: calibration curve and lot number code for the specific test strip, control test sequence and timing and measuring range for the test. The manufacturer states that the “operator must make sure that the meter is coded correctly by ensuring that the lot number printed on the test strip box matches that on the memo chip.” With the meter switched off, the memo chip is inserted into the notch at the top of the meter with the finger notch facing up ensuring that it is locked in place. The code number programmed in the meter is displayed each time a test strip is inserted into the meter’s test port.

Check strip test
A grey check strip is provided to verify that the meter’s optics and electronics are functioning correctly. The manufacturer’s instructions stipulate that the check strip test is performed “when using the meter for the first time, if unexpected results are

obtained or if the meter was dropped or banged". The meter is switched on by pressing either one of the two buttons. When "INSTALL MEMO CHIP" or "RUN TEST" is displayed, the 'next' button is pressed until the message "UTILITY" is displayed. The 'enter' button is pressed and pressed again when the message "CK STRIP" is displayed. The check strip is inserted into the test strip port, ribbed side up. The analyser should display "PASSED" if the meter is working properly. If an error message "FAILED" is displayed, the operator must first check that both the check strip and meter optics are cleaned and the check strip test must be repeated. If the error persists the operator must call the customer help line number for assistance.

Operation of the meter

Quality control

The performance of the CardioChek system can be assessed by using aqueous, viscosity adjusted control solutions at two levels. The multichemistry control solution is used to test the cholesterol and triglyceride measurement, a separate control material is available for the HDL cholesterol. The solutions are stored at room temperature, and have a two month open vial stability.

The control solutions must be run in the control testing mode, which is selected from the "UTILITY" menu. The correct mode is selected by continuously pressing the 'next' button until the meter displays the message "RUN CONTROL". The display briefly shows the programme number in use then the message "INSERT STRIP" When the test strip is inserted into the test port the message "APPLY SAMPLE" is displayed. A drop of control material is applied on to the white reaction area of the test strip ensuring that the tip of the bottle does not come into contact with the test strip. The meter beeps to indicate sufficient sample has been applied and the measurement initiated automatically. A message "TESTING" is flagged up. The result is displayed at the end of the measurement period lasting approximately two minutes. The control ranges are lot specific for the test strip in use, and the appropriate ranges are provided on the 'Quality Control Range card' included with control solutions. The test strip is removed from the meter, discarded and the meter switched off.

Fingerstick capillary blood glucose measurement

Having analysed the quality control materials, the system is ready to perform a patient lipid measurement using fresh capillary blood samples collected into either a 40 µl lithium heparin anticoagulated plastic coated glass capillary tube ('Drummond Pipette') or a plastic 'Safetec Lipid Test Pipette' (BHR Pharmaceutical Ltd, UK).

During this evaluation of the CardioChek system the plastic coated glass capillary Drummond Pipettes were used. To ensure the correct volume of capillary blood is collected and dispensed the Drummond capillary tubes have a white plug located within

the capillary tube beyond which uptake of blood will not take place. The white plug also ensures that the entire sample of blood is dispensed, and residual blood is not left clinging inside the capillary wall. The sample is dispensed from the capillary tube, using a black plastic plunger.

The manufacturer states “not to store or operate the analyser in direct light, such as sunlight, spotlight, under a lamp or by a window. Direct light may adversely effect test results.” The manufacturer also states that “use of lotions and handcreams should be avoided before testing. Hands should be washed in warm water with antibacterial soap and rinsed and dried thoroughly.”

A capillary plunger is inserted into the capillary tube at the end with the red marking. The plunger cannot be inserted incorrectly. A fingerstick sample of whole blood is obtained by lancing a finger, and the first drop of blood is wiped off. A large drop of free flowing blood is obtained and collected by holding the glass capillary tube to the droplet of blood; the tube fills by capillary action. The capillary tube is wiped carefully, and the blood applied to the white application window of the test strip by pushing down with the plunger onto the white plug, until it reaches the end of the capillary tube. The measurement is automatically initiated when sufficient sample has been detected and a result displayed within approximately 2 minutes.

Results are automatically stored within the meter's memory. The test strip is removed from the meter and discarded. The CardioChek has a memory capacity of up to 30 results of each chemistry and 10 results of each control test. Each result is displayed with date and time.

The analytical ranges quoted by the manufacturer are:

total cholesterol 1.3 to 10.36 mmol/L
HDL cholesterol 0.39 to 2.59 mmol/L
triglyceride 0.28 to 5.65 mmol/L

Error messages are shown on the visual display panel to indicate procedural or system errors such as: change battery, failed check strip test, expired lot, temperature of instrument is outside operating temperature range, results outside the limit of measurement.

Minimal maintenance is required to ensure the meter and test strip holder are kept clean. The manufacturer suggests that the “exterior of the meter be wiped with a clean lint-free cloth dampened with mild detergent or soap. If necessary, the test strip holder can be cleaned with with a clean, damp lint free tissue or cloth ensuring that the glass is very clean with no dust or fingerprints. The glass must be completely dry before running a test.”

Methods and materials

The CardioChek evaluation was carried out on two meters and lipid panel reagent test strips obtained directly from the manufacturer and operated throughout according to the manufacturer's instructions.

Method comparison

The performance of the CardioChek lipid analyser was evaluated by laboratory personnel, on 106 patient specimens using routine laboratory methods performed on a Vitros 950 analyser (Ortho Clinical Diagnostics, Johnson & Johnson, USA) for the total cholesterol and triglyceride assay and the IL 600 (Instrument Laboratory, USA) for the HDL cholesterol assay.

The Vitros 950 utilises dry reagent slides, and the calibrators used for the total cholesterol and triglyceride assay are traceable to the Centers for Disease Control referenced materials. The enzymatic cholesterol measurement is based on cholesterol ester hydrolase, cholesterol oxidase, peroxidase and colorimetry. The Vitros 950 triglyceride measurement is based on an enzymatic method utilising lipase, glycerol kinase, L-α-glycerophosphate peroxidase and colorimetry at 540 nm.

HDL cholesterol measurement was made on the IL 600 using the IL Test™ HDL Cholesterol reagent. The assay does not require pre-treatment to remove the chylomicrons, very low density lipoproteins (VLDL), and low density lipoproteins (LDL). Anti human B-lipoprotein antibody binds to lipoproteins (LDL, VLDL and chylomicrons) other than HDL. The formed antigen-antibody complexes block enzyme reactions allowing enzymatic measurement of HDL cholesterol using cholesterol oxidase, peroxidase and colorimetry. The calibrators used for the HDL cholesterol assay are traceable to the Centers for Disease Control referenced materials.

To ensure that the evaluation tested the Cardiochek meter over the whole of its analytical range, volunteers were recruited from patients attending the lipid clinic at Sandwell District General Hospital, volunteers from local hospital and Wolfson Research Laboratory staff. Ethical approval was obtained for the study from the Sandwell and West Birmingham Health Authority Research Ethics Committee, before recruiting subjects into the trial. Although lipid measurements ideally should be performed on subjects after a 12 hour fast, for this study the primary interest was in comparing the results against a reference method and covering the entire analytical range. However, a note was made of whether the subject was fasting or non-fasting.

The subject was allowed to sit quietly for 5 minutes, and the entire procedure explained. Capillary blood was obtained from a fingerstick using a Safe-T-Pro lancet (Roche, UK). Lipid measurements on the CardioChek meters 1 and 2 were carried out first. It is well documented [3 - 5] that results obtained from systems using dry reagent chemistry can be influenced by the haematocrit of the blood sample, low haematocrit giving a high result and a high haematocrit giving a low result. To assess the extent to which results would be affected on the CardioChek and to gauge the haematocrit levels in the population studied,

haematocrit measurements were carried out on each capillary blood sample in duplicate, using a Microspin haematocrit centrifuge (Bayer Diagnostics, Basingstoke, UK).

Whilst the measurement was proceeding on the CardioChek, a venous blood sample for a full lipid profile by the reference methods on the Vitros 950 and IL 600 was collected. The patient continued to sit quietly, and ensuring the tourniquet was applied for no more than one minute, 7 mL of venous blood was collected into a vacutainer serum separator tube (Sarstedt, UK). This was the first sample when a series was obtained for other measurements in the lipid clinic. The venous blood was allowed to clot at room temperature for approximately 30 to 40 minutes, and centrifuged for 10 minutes at 4000 rpm. The serum was separated into two 2 mL plastic cryotubes and kept on ice for transportation. The samples were then stored at -20 °C for analysis on the laboratory analysers at a later date.

Results comparison for total cholesterol assay

Correlation obtained on the 106 results from patient specimens using the CardioChek and the Vitros 950 are shown in figure 1 (correlation coefficient = 0.86). Results were on average 6 % higher than those obtained by the Vitros 950. Table 2 gives the mean cholesterol level obtained for 106 patient specimens using the CardioChek and the Vitros 950. There is a statistically significant overall mean bias of 0.23 mmol/L, with standard error of 0.07 mmol/L (t_{105} = 3.39, p = < 0.001).

Figure 1: Correlation obtained for total cholesterol results from 106 patients' fingerstick capillary blood using the CardioChek (meter 1)

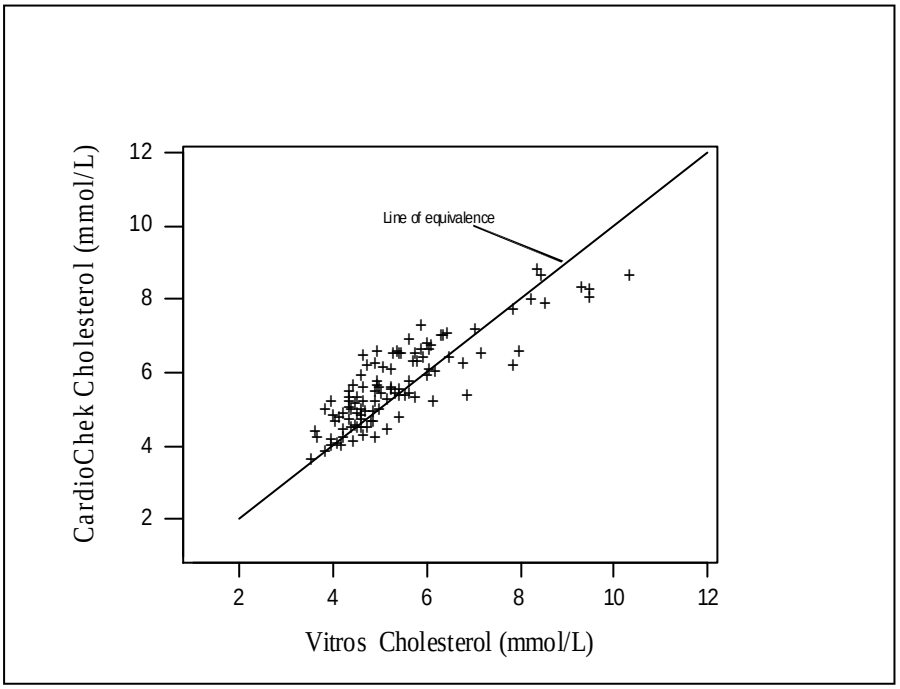
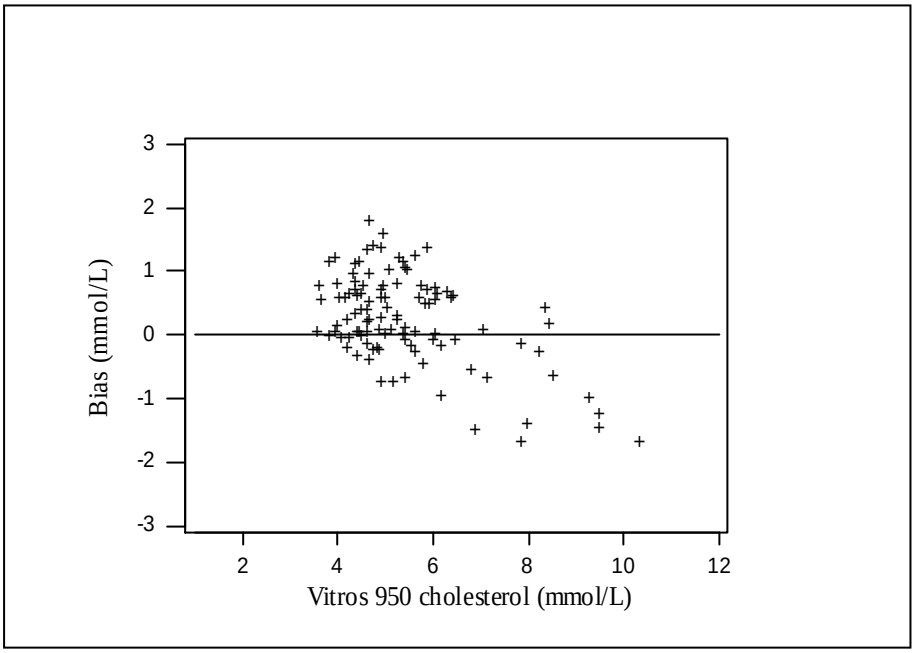


Table 2: Summary statistics of total cholesterol concentrations (mmol/L) obtained by the CardioChek (meter 1) and Vitros 950 (n = 106)

	CardioChek (capillary blood)	Vitros 950 (venous serum)	CardioChek - Vitros 950
Mean	5.66	5.43	0.23
SD	1.17	1.39	0.72

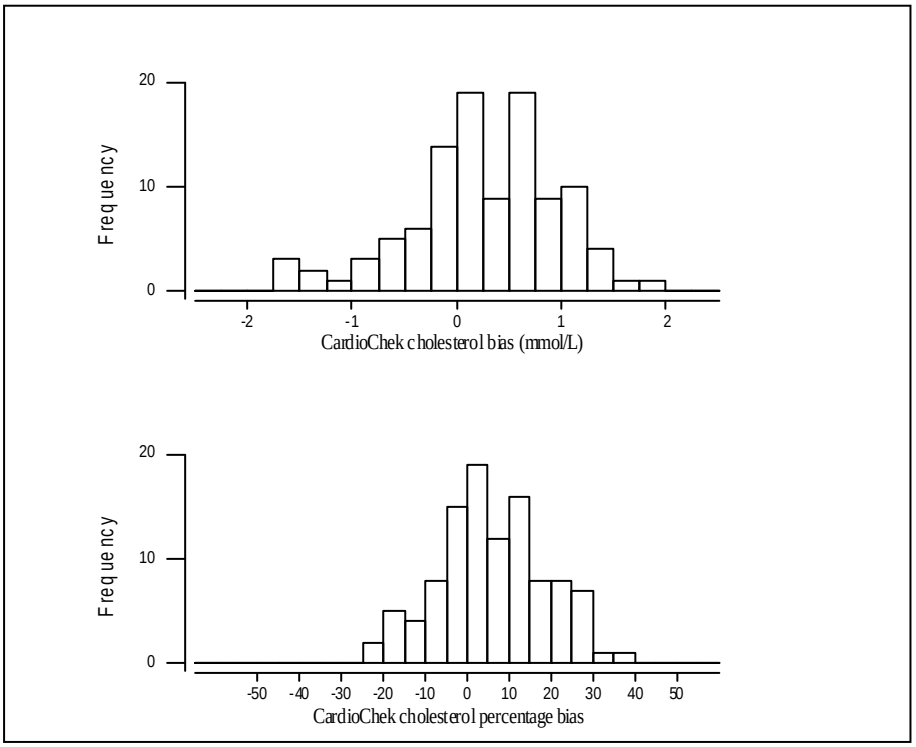
Figure 2 shows the differences between the CardioChek and the Vitros 950 total cholesterol results plotted against the Vitros 950 results. Perfect agreement between the two sets of results would give a horizontal line of points passing through zero on the y axis and a persistent trend away from that general pattern would indicate some pattern of bias. The pattern evident in figure 2 suggests a downward trend in bias with increasing concentrations.

Figure 2: Differences between the CardioChek (meter 1) and the Vitros 950 results plotted against the Vitros 950 total cholesterol result



Visual evidence of the overall bias is provided in figure 3 which displays in histogram form the bias and percentage bias of each of the 106 results. There is an overall positive bias which conceals the trend evident in figure 2. The corresponding plot of percentage bias shows 34% of results from the CardioChek having a negative bias relative to the Vitros 950 method.

Figure 3: Histogram of the bias and percentage bias in CardioChek total cholesterol results (meter 1)



The regression statistics presented in table 3 show that the slope of the regression line differs significantly from 1 (t_{104} = 6.65, p < 0.001), suggesting that there is a concentration dependent bias in the CardioChek results. This is more evident in detail in table 4, which presents the mean bias of the Cardiochek total cholesterol results at 6 different concentration levels. Thus the CardioChek would appear to give positive bias at low concentrations, but a negative bias at high concentration. The bias is relatively large, reaching 13% at 3 - 4 mmol/L and -10% at 7 - 8 mmol/L. Also presented in table 4 is the standard deviation of bias, which should reflect the imprecision of the CardioChek . This would suggest imprecision of around 12%, and this is confirmed by the linear regression analysis reported in table 3, which gave an 'about line' standard deviation of 0.60 mmol/L (a CV of 11%).

Table 3: Regression statistics for total cholesterol results on the CardioChek (meter 1) versus Vitros 950 (n = 106)

	Intercept (mmol/L)	**Slope**
Estimate (standard error)	1.76 (0.24)	0.72 (0.04)
95% confidence interval	1.28 to 2.24	0.64 to 0.80

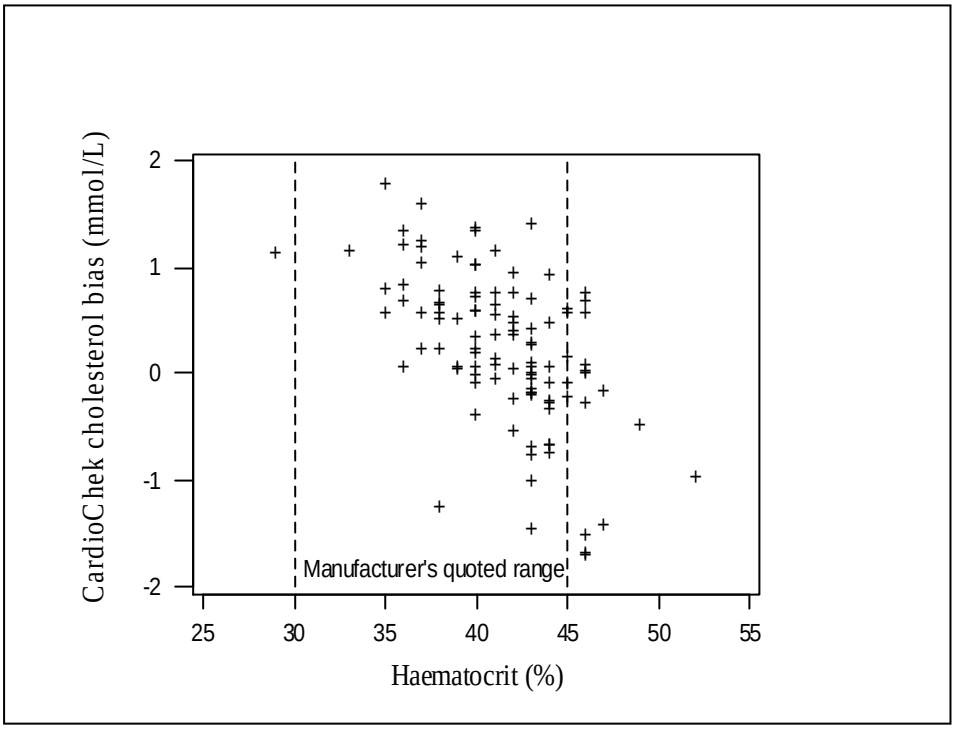
Table 4: The mean bias of the CardioChek total cholesterol results (meter 1) relative to the Vitros 950 results

Vitros 950 results (mmol/L)	**Number of results**	**Mean CardioChek bias** mmol/L (**% bias**)	**SD of bias** mmol/L (**% SD**)
3 - 4	8	0.48 (13 %)	0.49 (14 %)
4 - 5	45	0.43 (10 %)	0.57 (12 %)
5 - 6	27	0.41 (7 %)	0.60 (11 %)
6 - 7	13	0.02 (<1 %)	0.70 (11 %)
7 - 8	5	-0.78 (-10 %)	0.77 (10 %)
>8	8	-0.73 (-8 %)	0.77 (9 %)

The mean haematocrit level for the 106 specimens used in the evaluation was 41.4%, and the range was 29 to 52%. The manufacturer's quoted range is 30 to 45%.

Figure 4 illustrates the high level of correlation present between the bias of the CardioChek total cholesterol relative to the Vitros 950 and the haematocrit level. The correlation coefficient is r = -0.57 (p < 0.001) and a unit change in haematocrit is estimated to produce a change of 0.11 mmol/L in total cholesterol bias of the CardioChek relative to the Vitros 950. This correlation would appear to be evident at almost all total cholesterol levels examined in table 4 with r = -0.59, -0.46, -0.65, -0.63, -0.57 and 0.20 respectively at cholesterol levels of 3 - 4, 4 - 5, 5 - 6, 6 - 7, 7- 8 and >8.0 mmol/L.

Figure 4: Scatterplot of bias versus haematocrit for the CardioChek total cholesterol results (meter 1)



In the population studied, fasting produced a significant difference to non-fasting results of 0.4 mmol/L in bias relative to the Vitros 950 ($t_{99} = -2.65$, $p < 0.05$). However, there was an imbalance in the proportion fasting between results determined using the two batches of strips. In the second batch of test strips used (code 4P62) there was a more even balance of fasting and non-fasting results and for those strips the difference between fasting and non-fasting results is 0.6 mmol/L on average.

Comparison of two meters and two batches of test strips for total cholesterol

Two CardioChek meters designated 1 and 2 and two different batches of strips, lot 4P61 and 4P62 were used in parallel throughout the patient phase of this evaluation. Table 5 records the mean bias seen for each batch of strips. There was no significant variation in mean bias between batches or between meters in overall level of bias in total cholesterol relative to the Vitros 950.

Table 5: Mean bias for total cholesterol (mmol/L) using two CardioChek meters and two different batches of test strips

	Number of results	Meter 1 mean bias (SEM)		Meter 2 mean bias (SEM)	
Batch 1 (lot 4P61)	54	0.27	(0.10)	0.25	(0.10)
Batch 2 (lot 4P62)	52	0.20	(0.10)	0.05	(0.10)

Note:
SEM = standard error of the mean

Table 6 gives the slope and intercept for a linear regression of meter 1 results against the Vitros 950 total cholesterol readings. The same marked concentration dependence in bias is evident in each batch with slopes of 0.67 and 0.76 instead of the ideal value of 1.

Table 6: Regression statistics from two different batches of CardioChek test strips

	Intercept (SE)		Slope (SE)	
Batch 1 (lot 4P61)	2.06	(0.34)	0.67	(0.07)
Batch 2 (lot 4P62)	1.52	(0.34)	0.76	(0.06)

Results comparison for HDL cholesterol assay

Out of a total of 106 measurements, five patient samples gave values which were outside the analytical range of 0.39 to 2.56 mmol/L quoted by the manufacturer for the HDL cholesterol assay. The equivalent IL 600 results for the samples were 0.22, 2.73, 2.46, 2.52 and 1.12 mmol/L. In the latter result (1.12 mmol/L) the CardioCheck gave a result of <0.39 mmol/L. Correlation obtained on the remaining 101 results from patient specimens using the CardioChek and the IL 600 are shown in figure 5 (correlation coefficient = 0.77). Results were on average 3% lower than those obtained by the IL 600. Table 7 gives the mean HDL cholesterol level obtained for 101 patient specimens using the CardioChek and the IL 600. There is a non-significant overall mean bias of -0.04 mmol/L, with standard error of 0.03 mmol/L (t_{100} = -1.41, p = 0.16). The relatively low level of correlation between the IL 600 and the CardioChek, together with the absence of any pronounced bias, suggests a relatively high level of imprecision.

Figure 5: Correlation obtained for HDL cholesterol results from 101 patients' fingerstick capillary blood using the CardioChek (meter 1)

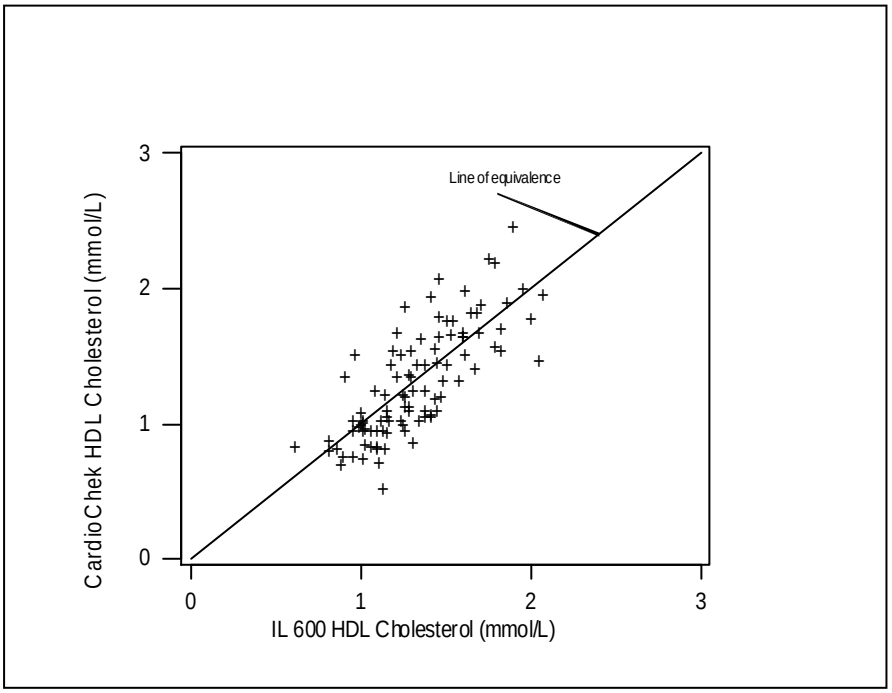
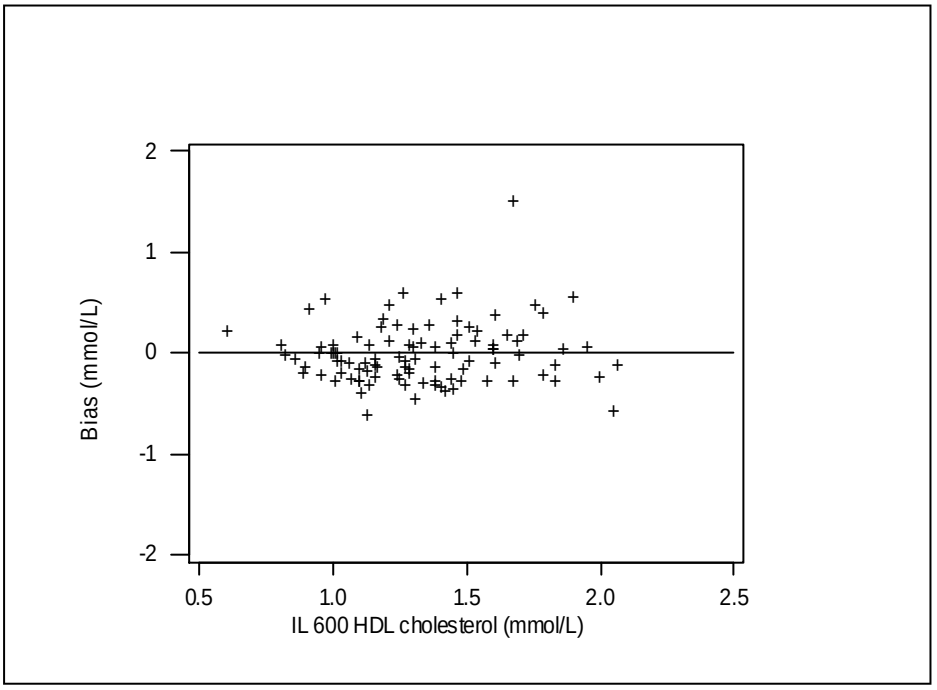


Table 7: Summary statistics of HDL cholesterol concentrations (mmol/L) obtained by the Cardiochek (meter 1) and IL 600 (n = 101)

	CardioChek (capillary blood)	IL 600 (venous serum)	CardioChek - IL 600
Mean	1.29	1.33	-0.04
SD	0.41	0.30	0.26

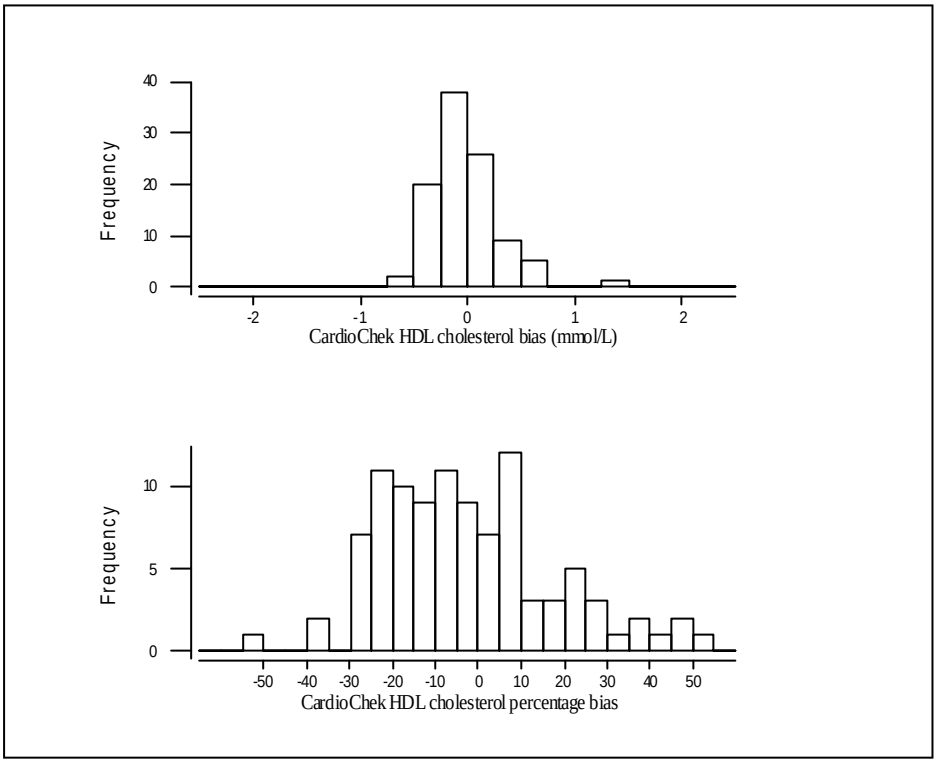
Figure 6 shows the differences between the HDL cholesterol results from the CardioChek and the IL 600 plotted against the IL 600 result. Perfect agreement between the two sets of results would give a horizontal line of points passing through zero on the y axis and a persistent trend away from that general pattern would indicate some pattern of bias. The pattern evident in figure 6 suggests a minimal bias at all concentrations but with relatively high imprecision.

Figure 6: Differences between the CardioChek HDL cholesterol (meter 1) and the IL 600 results plotted against the IL 600 result



Visual evidence of the lack of any overall bias is provided in figure 7, which displays in histogram form the bias and percentage bias of each of the 101 results. There is also no overall tendency for any concentration dependent bias. The corresponding plot of percentage bias shows 60 % of results from the CardioChek having a negative bias relative to the IL 600 results.

Figure 7: Histogram of the bias and percentage bias in HDL cholesterol results (meter 1)



The regression statistics presented in table 8 show that the slope of the regression line does not differ significantly from 1 (t_{99} = 0.22 p = 0.84), suggesting that there is no linear concentration dependent bias in the CardioChek HDL cholesterol results. This is more evident in detail in table 9, which presents the mean bias of the Cardiochek results at four different concentration levels. Thus the CardioChek would appear to give minimal bias on average at low concentrations and a non-significant bias with other concentrations. Also presented in table 9 is the standard deviation of bias, which should reflect the imprecision of the CardioChek . This would suggest relatively poor imprecision of between 15 and 24 %, and this is confirmed by the linear regression analysis reported in table 8, which gave an 'about line' standard deviation of 0.26 mmol/L (a CV of 19 %).

Table 8: Regression statistics for HDL cholesterol results on the CardioChek (meter 1) versus IL 600 (n = 101)

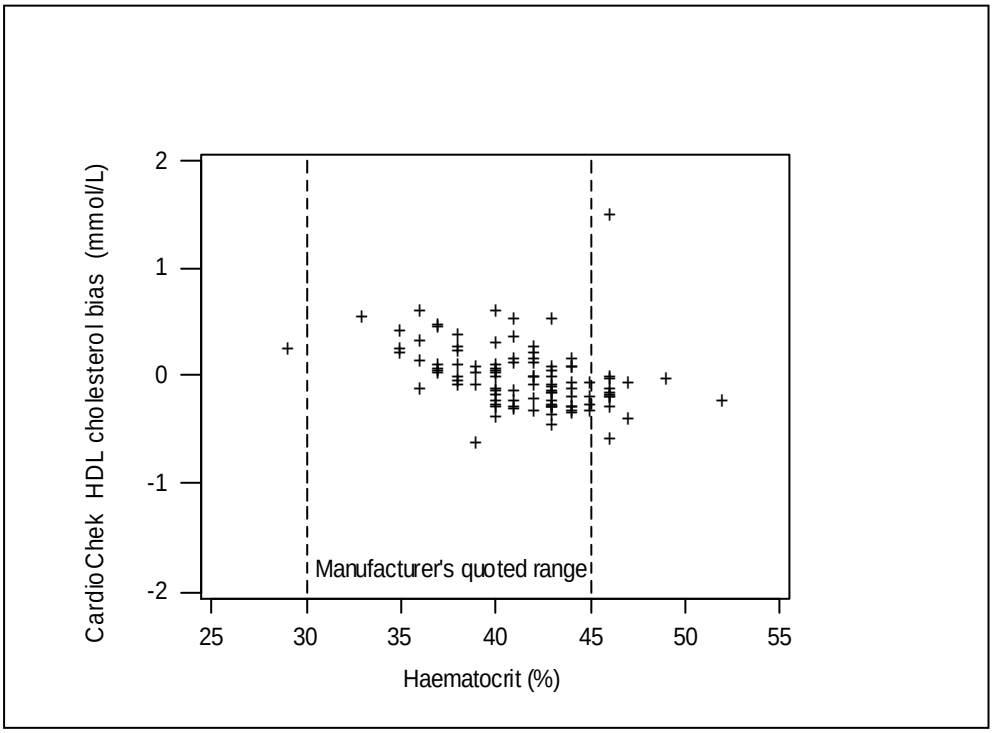
	Intercept (mmol/L)	**Slope**
Estimate (standard error)	-0.06 (0.12)	1.02 (0.09)
95% confidence interval	-0.30 to 0.18	0.84 to 1.20

Table 9: The mean bias of the CardioChek HDL cholesterol results (meter 1) relative to the IL 600 results

IL 600 results (mmol/L)	**Number of results**	**Mean CardioChek bias** mmol/L (**% bias**)	**SD of bias** mmol/L (**% SD**)
0.5 - 1.0	14	0.04 (5 %)	0.22 (24 %)
1.01 - 1.5	60	-0.07 (-6 %)	0.26 (22 %)
1.51 - 2.0	25	0.04 (2 %)	0.24 (14 %)
2.01 - 2.5	2	-0.36 (-16 %)	0.33 (15 %)

Figure 8 shows a strong effect of haematocrit, this time on the bias of the CardioChek HDL cholesterol relative to the IL 600 results. The correlation for the HDL cholesterol bias versus haematocrit is r = -0.52 ($p < 0.001$), with a similar correlation (r = -0.45, $p < 0.001$) evident for the other meter tested. A unit change in haematocrit would be estimated to make a change of 0.04 mmol/L in HDL bias of the CardioCheck.

Figure 8: Scatterplot of bias versus haematocrit for the CardioChek HDL Cholesterol results (meter 1)



Fasting also had an effect on CardioChek HDL cholesterol result, with a mean difference of -0.15 mmol/L in bias ($t_{94} = -2.39$, $p < 0.05$) relative to the IL 600. The mean difference between fasting and non-fasting is greatest with batch 2 test strips, being on average -0.22 mmol/L relative to the IL 600 ($t_{45} = -2.82$, $p < 0.01$).

Comparison of two meters and two batches of test strips for HDL cholesterol

Two CardioChek meters designated 1 and 2 were used in parallel throughout the patient phase of this evaluation. Table 10 records the mean bias in HDL cholesterol readings for the CardioChek relative to the IL 600. For meter 1 there is no significant bias for either batch of test strips, but for meter 2 there is a significant bias with each batch of strips and a significant difference between the bias from the two batches of strips.

Table 10: Mean bias using two CardioChek meters and two different batches of test strips

	Number of results	Meter 1 mean bias (SEM)		Meter 2 mean bias (SEM)	
Batch 1 (lot 4P61)	52	-0.01	(0.04)	-0.10	(0.03)
Batch 2 (lot 4P62)	49	-0.07	(0.04)	-0.20	(0.03)

Note:
SEM = standard error of the mean

Table 11 gives the slope and intercept from a linear regression for meter 1 results against the IL 600 HDL cholesterol readings. Although numerically the slope of the regression lines for the two batches seem quite different, the difference is not significant, partly due to the relatively poor imprecision of HDL results.

Table 11: Regression statistics for HDL cholesterol results from two different batches of CardioChek test strips

	Intercept (SE)		Slope (SE)	
Batch 1 (lot 4P61)	-0.12	(0.15)	1.09	(0.11)
Batch 2 (lot 4P62)	-0.01	(0.18)	0.95	(0.13)

Results comparison for triglyceride assay

Out of a total of 106 triglyceride measurements, one patient's sample gave a value of >5.65 mmol/L with the CardioChek meter, which is outside the manufacturer's stated analytical range. The equivalent Vitros 950 result was 4.98 mmol/L. Correlation obtained on the remaining 105 results from patient specimens using the CardioCheck and the Vitros 950 is shown in figure 9 (correlation coefficient = 0.98). Results were on average 3 % higher than those obtained by the Vitros 950. Table 12 gives the mean triglyceride level obtained for 105 patient specimens using the CardioChek and the Vitros 950. There is a statistically significant overall mean bias of 0.11 mmol/L, with standard error of 0.03 mmol/L (t_{104} = 3.51, p = <0.001).

Figure 9: Correlation obtained for triglyceride results from 105 patient's fingerstick capillary blood using the CardioChek (meter 1)

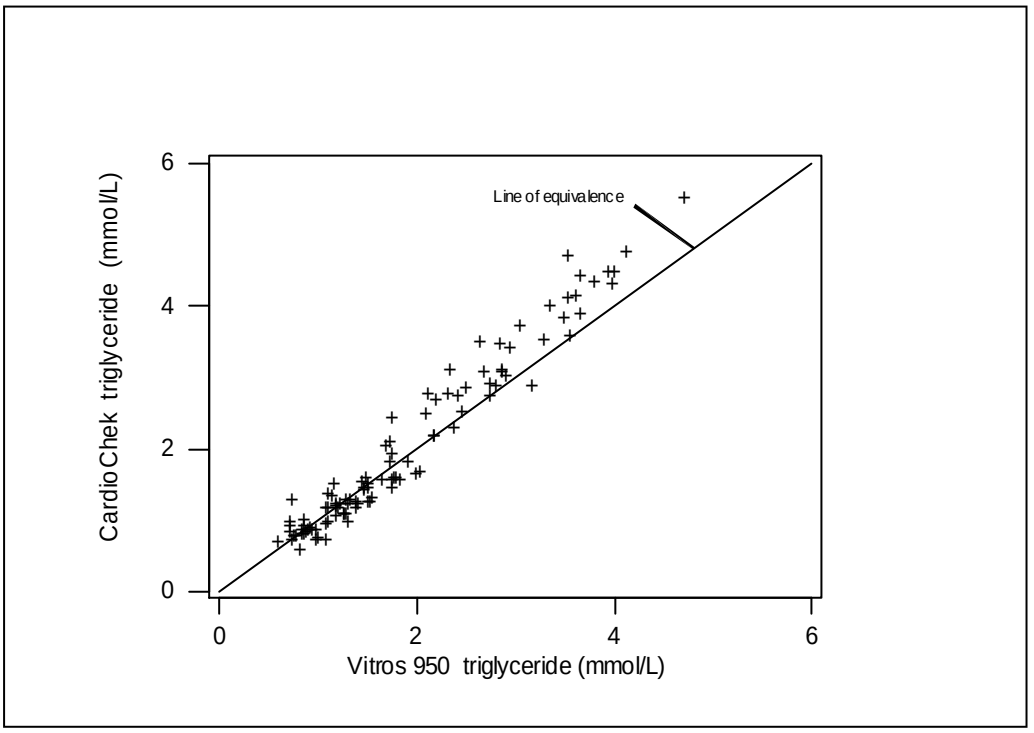


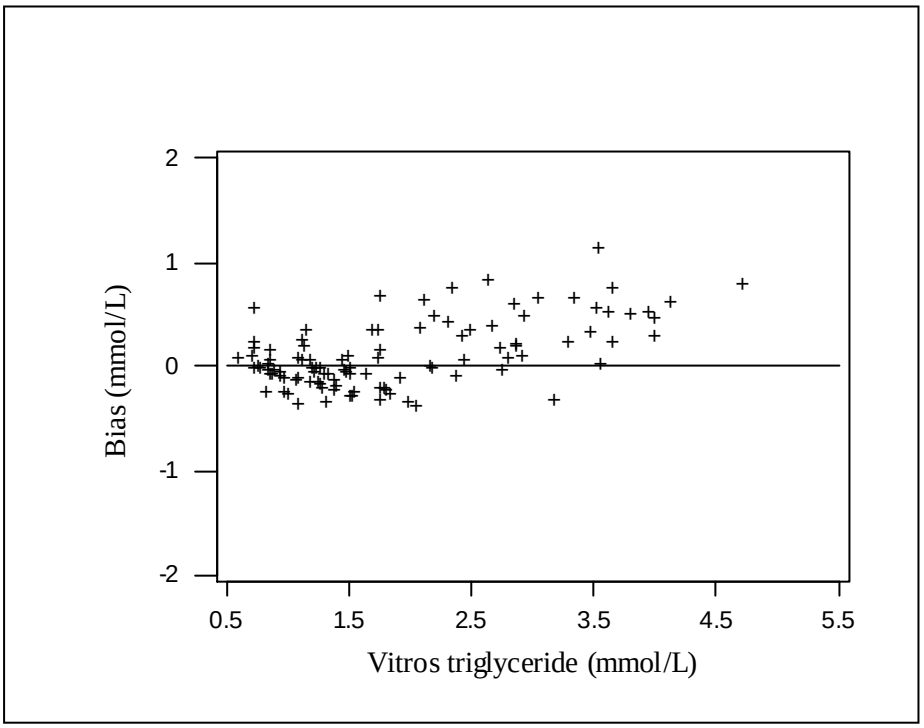
Table 12: Summary statistics of triglyceride concentrations (mmol/L) obtained by the CardioChek and Vitros 950 (n = 105)

	CardioChek (capillary blood)	Vitros 950 (venous serum)	CardioChek - Vitros 950
Mean	2.01	1.90	0.11
SD	1.21	1.00	0.32

Figure 10 shows the differences between the triglyceride results from the CardioChek and the Vitros 950 plotted against the Vitros 950 result. Perfect agreement between the two sets of results would give a horizontal line of points

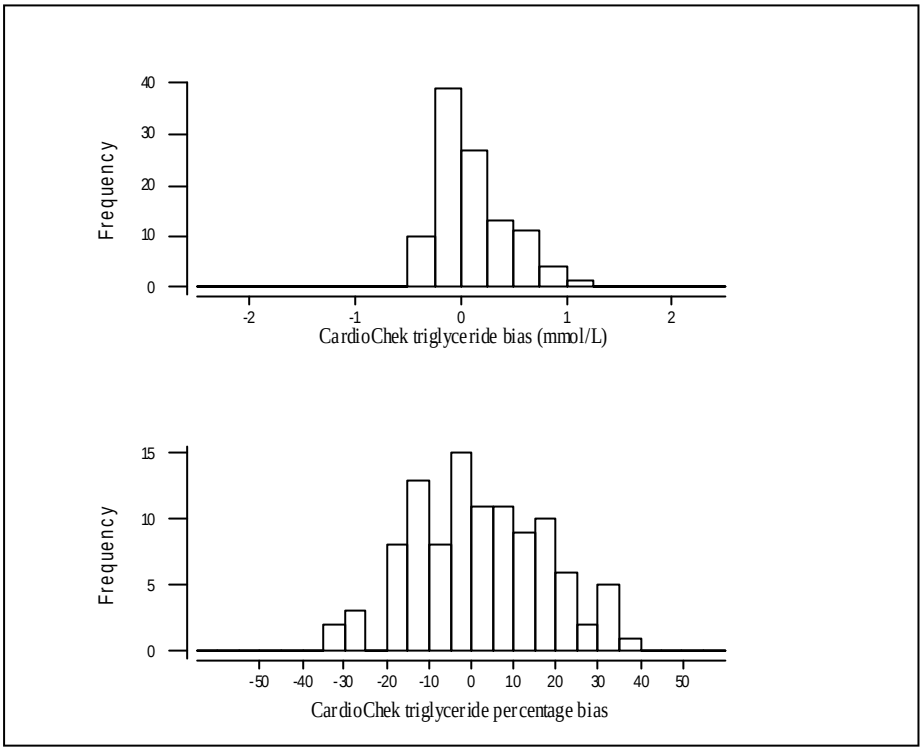
passing through zero on the y axis and a persistent trend away from that general pattern would indicate some variation in bias. The pattern evident in figure 10 suggests an increasingly positive bias with increasing concentration.

Figure 10: Differences between the CardioChek (meter 1) and the Vitros 950 triglyceride results plotted against the Vitros 950 result



Visual evidence of this overall bias is provided in figure 11, which displays in histogram form the bias and percentage bias of each of the 105 results. There is an overall tendency for a positive bias. The corresponding plot of percentage bias shows 53 % of results from the CardioChek having a positive bias relative to the Vitros 950 results.

Figure 11: Histogram of the bias and percentage bias in CardioChek triglyceride results



The regression statistics presented in table 13 show that the slope of the regression line differs significantly from 1 (t_{103} = 7.28, $p < 0.001$), suggesting that there is a concentration dependent bias in the CardioChek results. This is more evident in detail in table 14, which presents the mean bias of the CardioChek results at 5 different concentration levels. Thus the CardioChek would appear to give minimal bias at low concentrations, but an increasingly positive bias with increasing concentration. Also presented in table 14 is the standard deviation of bias, which should reflect the imprecision of the CardioChek . This would suggest imprecision of around 15 %, and this is confirmed by the linear regression analysis reported in table 13, which gave an 'about line' standard deviation of 0.26 mmol/L (a CV of 14 %).

Table 13: Regression statistics for triglyceride results on the CardioChek versus Vitros 950 (n = 105)

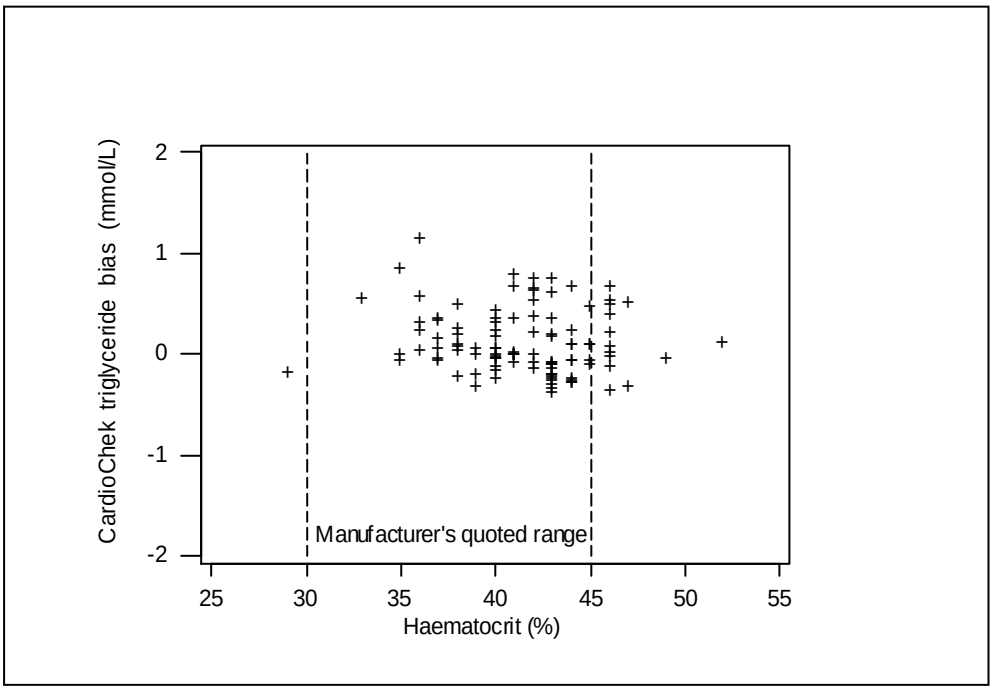
	Intercept (mmol/L)	**Slope**
Estimate (standard error)	-0.24 (0.05)	1.19 (0.03)
95% confidence interval	-0.34 to -0.14	1.13 to 1.25

Table 14: The mean bias of the CardioChek triglyceride results relative to the Vitros 950 results

Vitros 950 results (mmol/L)	**Number of results**	**Mean CardioChek bias** mmol/L (**% bias**)	**SD of bias** mmol/L (**% SD**)
0 - 1	21	0.01 (1 %)	0.18 (22 %)
1 - 2	45	-0.06 (-4 %)	0.21 (15 %)
2 - 3	22	0.27 (11 %)	0.30 (12 %)
3 - 4	15	0.44 (12 %)	0.34 (9 %)
4 - 5	2	0.70 (15 %)	0.11 (2 %)

Figure 12 illustrates the variation in concentration of triglyceride level with haematocrit for the CardioChek meter 1. Correlation between the haematocrit level and the CardioChek triglyceride results relative to the Vitros 950 is not significant for the two meters tested (meter 1, r = -0.12, p = 0.22 and meter 2, r = -0.07, p = 0.49).

Figure 12: Scatterplot of bias versus haematocrit for the CardioChek triglyceride results (meter 1)



Fasting has a significant effect on the bias of the CardioChek triglyceride results relative to the Vitros 950, with a bias of 0.18 mmol/L (t_{98} = 2.74, p < 0.01). However, whilst in the same direction (0.12 mmol/L) the bias with batch 2 strips is not significant (t_{47} = 1.41, p = 0.17).

Comparison of two meters and two batches of test strips for triglyceride

Two CardioChek meters designated 1 and 2 were used in parallel throughout the patient phase of this evaluation. Table 15 shows the mean bias for CardioChek results relative to the Vitros 950 for meters 1 and 2 on the two batches of test strips used. There is a significant bias for meter 2 with both batches of strips and for meter 1 with batch 4P61 test strips. There is also a significant difference in bias between meters and between batches of test strips.

Table 15: Mean bias for triglyceride (mmol/L) using two CardioChek meters and two different batches of test strips

	Number of results	Meter 1 mean bias (SEM)		Meter 2 mean bias (SEM)	
Batch 1 (lot 4P61)	54	0.21	(0.04)	0.52	(0.05)
Batch 2 (lot 4P62)	51	0.00	(0.04)	0.26	(0.04)

Note:
SEM = standard error of the mean

For the regression statistics in table 16, there is a significant concentration dependence in bias in both batches of test strips for meter 1 and meter 2.

Table 16: Regression statistics for triglyceride (mmol/L) from two different batches of test strips

	Intercept (SE)		Slope (SE)	
Batch 1 (lot 4P61)	-0.16	(0.08)	1.18	(0.04)
Batch 2 (lot 4P62)	-0.31	(0.07)	1.17	(0.03)

Classification of results

When assessing an individual for risk of coronary heart disease using lipid profile results, other positive risk factors also need to be considered. These are: smoking habit, hypertension, presence of cardiovascular disease, obesity, diabetes, family history of coronary heart disease, physical inactivity and age and sex [6-8]. A full lipid profile consisting of total cholesterol, HDL cholesterol and triglyceride, and calculated LDL measured on a fasting blood sample gives a useful risk assessment. However, because of cost implications, in the majority of cases, total cholesterol measurement is performed initially to assess the risk. The recommendation [6-8] is that if total cholesterol is greater than 6.2 mmol/L, or greater than 5.2 mmol/L in the presence of other risk factors, then a full lipid profile on a fasting sample of blood should be performed.

For this study it was necessary to assess the accuracy of the results across the entire analytical range, therefore volunteers were not asked to fast for the recommended 12 hours. However, for total and HDL cholesterol, dietary fat has minimal effect [6] and patients are not required to fast. All other precautions when obtaining blood samples and performing the measurement were observed.

The risk assessment based on the results obtained with the CardioChek can be performed using the total cholesterol result alone or using the total cholesterol to HDL cholesterol ratio. The CardioCheck's ability to correctly classify patients was assessed by placing the CardioCheck and Vitros 950 results into the appropriate categories based on the National Cholesterol Education Programme Adult treatment Panel III (NCEP ATP III) recommendations [6] for classifying total cholesterol, HDL cholesterol and triglyceride. These are:

Total cholesterol:

desirable	< 5.20 mmol/L (200 mg/dl)
borderline high	5.20 - 6.19 mmol/L (200 - 239 mg/dl)
high risk	≥ 6.20 mmol/L (≥ 240 mg/dl)

HDL cholesterol

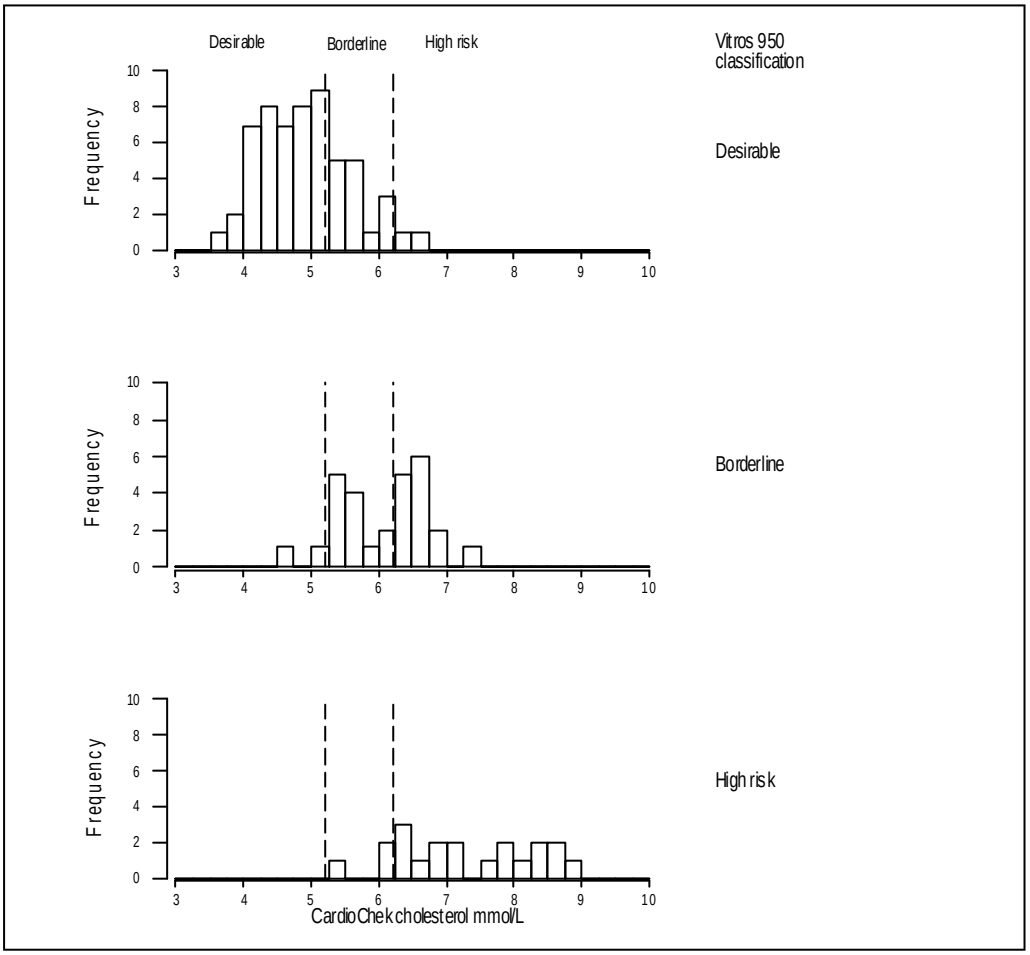
low result	< 1.04 mmol/L
desirable	≥1.04 mmol/L

Triglycerides

normal	<1.70 mmol/L
borderline high	1.7 - 2.25 mmol/L
high	2.25 - 5.6 mmol/L
Very high	>5.6 mmol/L

Classification of the 106 total cholesterol results obtained using capillary blood on the CardioChek and Vitros 950 is shown in table 17. The results show that 67% (71 out of 106) of the CardioChek cholesterol results were correctly classified.

Table 17: Classification of the CardioChek and Vitros 950 total cholesterol results using the NCEP APT III guidelines



	CardioChek total cholesterol (mmol/L)					
Vitros 950 Cholesterol (mmol/L)	**n**	**£ 5.20 mmol/L**	**5.20 - 6.19 mmol/L**	**³ 6.20 mmol/L**	**Mean**	**SD**
Desirable ≤ 5.20 mmol/L	58	41*	14	3	4.92	0.67
Borderline high 5.20 - 6.19 mmol/L	28	1	13*	14	6.05	0.63
High risk ≥ 6.20 mmol/L	20	0	3	17*	7.27	1.00

Notes: *Patients classified correctly

Sensitivity, specificity and predictive value of the CardioChek total cholesterol assay

The sensitivity, specificity and predictive value [9] of cholesterol results obtained using the CardioChek are shown in table 18. These calculations assume that cholesterol values determined by the Vitros 950 using venous serum samples, correctly categorise the subjects studied.

Using a total cholesterol cut off level of 6.2 mmol/L the CardioChek identified 85% of high risk subjects. Thus the test sensitivity, the proportion of true positive results in subjects classified as high risk by the reference method, was 85 % (i.e. 15 % false negatives). The specificity, the proportion of true negative results in subjects not at high risk was 80% (i.e. 20 % false positive). Using a cut off level of 5.2 mmol/L, the CardioChek identified 98% of the borderline high/high risk subjects (ie sensitivity 98 %) with a specificity of 71 %.

Table 18: Sensitivity, specificity and predictive value of CardioChek total cholesterol assay

	High risk (> 6.2 mmol/L)	**Borderline high and high risk** (> 5.2 mmol/L)
Sensitivity	85 % (15 % FN)	98 % (2 % FN)
Specificity	80 % (20 % FP)	71 % (29 % FP)
Predictive value of positive CardioChek results (PPV)	50 %	73 %
Predictive value of negative CardioChek results (NPV)	96 %	98 %
Efficiency	81 %	83 %
Prevalence of those at risk in population studied	19 %	45 %

NOTES:

TP = true positive results, TN = True negatives, FN = false negatives, FP = false positives.

$$\text{Sensitivity} = \frac{TP}{(TP + FN)} \times 100$$

$$\text{Specificity} = \frac{TN}{(TN + FP)} \times 100$$

$$\text{PPV} = \frac{TP}{(TP + FP)} \times 100$$

$$\text{NPV} = \frac{TN}{(TN + FN)} \times 100$$

$$\text{Efficiency} = \frac{(TP + TN)}{\text{Total}} \times 100$$

Note that PPV and NPV are effected by the prevalence and thus are population dependent.

Classification, sensitivity and specificity using HDL cholesterol

HDL cholesterol levels are indicative of the risk of coronary heart disease, low levels indicating high risk and, conversely, high levels indicating low risk. The HDL cholesterol levels need to be taken into consideration when assessing risk due to high levels of cholesterol and triglyceride [6-8].

Previous guidelines have been based on the ratio of total cholesterol to HDL cholesterol with a cut-off of 5.0 being recommended [10, 11]. However, more recent NCEP APT III guidelines [6] do not mention use of such a ratio and instead a HDL cholesterol level of ≥1.04 mmol/L is recommended. The CardioChek PA meter does provide a calculated total cholesterol to HDL cholesterol ratio if a lipid panel measurement is carried out.

Table 19 gives the sensitivity and specificity of the CardioChek to various cut-offs involving HDL cholesterol which have been suggested in previous publications [10, 11].

Table 19: Sensitivity and specificity of the total cholesterol/ HDL cholesterol ratio for classification of lipid results

	Sensitivity	Specificity
TC/ HDL Ratio >5.0	90%	74 %
Total cholesterol ≥ 5.2 and/or **TC/HDL ratio >5.0**	98 %	55 %
Total cholesterol ≥ 5.2 and **TC/HDL ratio >5.0**	93%	85%
HDL < 1.04 mmol/L	75%	79%

Imprecision

The imprecision of the CardioChek system was determined on two meters on venous blood samples obtained from three laboratory workers at various concentrations of total cholesterol, HDL cholesterol and triglyceride. Blood was collected into lithium heparin vacutainer tubes (Becton Dickinson). The spiked blood sample was aliquoted into 23 x 0.5 ml plastic tubes. An aliquot was selected randomly and used once only for lipid measurements on two CardioChek meters using test strip lot number 4P61, and five times on the Vitros 950 and IL 600 to obtain the definitive result.

Results are summarised in tables 20a, 20b and 20c. The US NCEP and the NIH have issued guidelines [12, 13] for imprecision and total system error. The imprecision figures are: total cholesterol ≤ 3%, HDL cholesterol ≤ 4% and triglyceride ≤ 5% (these guidelines were set to apply to all testing methods regardless of instrument size or testing location). The CardioChek fails to meet these criteria for total cholesterol, HDL cholesterol and triglycerides at all levels tested. In the case of triglyceride there is a substantial meter to meter component of imprecision in addition to the imprecision from a single meter.

The US NCEP and the NIH guidelines for total system error [12, 13] are: total cholesterol ≤ 8.9%, HDL Cholesterol ≤ 13% and Triglyceride ≤15%. The CardioChek total cholesterol met these criteria at two of the three levels. However, the CardioChek failed to meet the citeria applicable to HDL cholesterol and triglycerides at all levels tested.

In the clinical study the imprecision for total cholesterol was 12%, exceeding the NCEP total system error of 8.9%. ncluding the bias component as estimated in table 4 the total error for the CardioChek system is around 20% at a concentration of between 3 and 4 mmol/L. For HDL cholesterol the imprecision estimated in the clinical study is 19% and again this exceed the NCEP total system error. At the lowest concentration interval studied (0.5 - 1.5 mmol/L) total error is estimated at 30%. For triglyceride the imprecision is 14% and the NCEP guideline for total error limit is 15%. Typically at the lowest concentration group (see table 14) the total error would be estimated at 22%.

In the laboratory study imprecision was assessed using venous whole blood samples collected by a biomedical scientist. If capillary whole blood is collected by unskilled operators the overall assay imprecision may deteriorate further as shown with other analysers [14, 15]. For the clinical study imprecision was assessed from a variety of patient samples, where a whole range of haematocrits would be encountered.

Table 20a: Imprecision of the CardioChek total cholesterol assay at three concentrations

	Level 1	Level 2	Level 3
Vitros 950 results (mmol/L)	4.12	6.01	7.91
CardioChek Mean (mmol/L)	4.03	5.61	7.09
SD_d (mmol/L)	0.22	0.22	0.34
CV_d (%)	5.4 %	3.7 %	4.3 %
SD_m (mmol/L)	NS	NS	NS
CV_t (%)	5.4 %	3.7 %	4.3 %
Total error (%)	5.8 %	7.6 %	11.2 %

Notes:

SD_d = replicate standard deviation (n = 22 on each of 2 meters)
CV_d = replicate coefficient of variation
SD_m = meter to meter standard deviation (2 meters)
CV_t = total (duplicate and meter) coefficient of variation
Total variance = $(SD_d)^2 + (SD_m)^2 + (bias)^2$
Total error (%) = 100 x $(total\ variance)^{1/2}$ / mean reference total cholesterol
NS = Not significant

Table 20b: Imprecision of the CardioChek HDL cholesterol assay at three concentrations

	Level 1	Level 2	Level 3
Vitros 950 results (mmol/L)	0.99	1.67	2.09
Mean (mmol/L)	0.69	1.31	1.79
SD_d (mmol/L)	0.07	0.10	0.16
CV_d (%)	7.5%	5.7%	7.7%
SD_m (mmol/L)	0.03	0.06	0.09
CV_t (%)	8.2 %	6.9%	8.7 %
Total error (%)	31.4%	22.6%	16.7%

Notes:

SD_d = replicate standard deviation (n = 22 on each of 2 meters)
CV_d = replicate coefficient of variation
SD_m = meter to meter standard deviation (2 meters)
CV_t = total (duplicate and meter) coefficient of variation
Total variance = $(SD_d)^2 + (SD_m)^2 + (bias)^2$
Total error (%) = 100 x $(total\ variance)^{1/2}$ / mean reference HDL cholesterol

Table 20 c: Imprecision of the CardioChek triglyceride assay at three concentrations

	Level 1	Level 2	Level 3
Vitros 950 results (mmol/L)	0.95	1.26	2.80
Mean (mmol/L)	0.91	0.92	3.08
SD_d (mmol/L)	0.07	0.11	0.20
CV_d (%)	7.4%	8.7 %	7.1 %
SD_m (mmol/L)	0.20	0.15	0.32
CV_t (%)	22.3%	14.8 %	13.5 %
Total error (%)	22.7%	30.8 %	16.8 %

Notes:

SD_d = replicate standard deviation (n = 22 on each of 2 meters)
CV_d = replicate coefficient of variation
SD_m = meter to meter standard deviation (2 meters)
CV_t = total (duplicate and meter) coefficient of variation
Total variance = $(SD_d)^2 + (SD_m)^2 + (bias)^2$
Total error (%) = 100 x $(total\ variance)^{1/2}$ / mean reference triglyceride

Operator dependency

Analytical systems for use by non-laboratory operators should have a minimal number of complex manoeuvres, to reduce the risk of obtaining incorrect results. A major operator-dependent step inherent to all analytical systems using capillary whole blood is in obtaining an adequate volume of free flowing blood. Another user-dependent step is related to ensuring that reagents are stored correctly following manufacturer's instructions and that they have not passed their expiry date.

Additional operator dependent steps identified for the the CardioChek system are:

- ensuring that the reagents are not subjected to extremes of temperature or humidity
- checking that the meter is calibrated for the correct batch number of strips and all steps are taken to ensure that the lot code on the test strip vial, memo chip and analyser display match. If the operator fails to insert the correct calibration code chip into the meter it may be possible to obtain misleading results
- avoiding introduction of air bubbles into the capillary pipette whilst collecting capillary blood samples, so that the appropriate sample volume for the measurement is applied
- avoiding storing or using the analyser in direct light, such as sunlight, spotlight, under a lamp or by a window. The manufacturer states that “direct light may adversely effect test results”
- ensuring that the patient’s hands are clean in accordance with the the manufacturer’s instructions
- ensuring that the system is set to the correct units of measurement for the UK (mmol/L). Although there is the facility for users to change the unit of measurement, it is not easily done as a number of complex steps to access the appropriate menu have to be taken.

Instructions for use

Instructions for use of the meter included a 31-page user guide. Although the instructions are concise and understandable for non-technical users [16, 17] and are illustrated with black and white diagrams, they would benefit from colour pictures and a larger font size. Instruction sheets in English as well as various other languages are also provided in the reagent pack, and give details for carrying out the appropriate measurements on the meter. The intended use of the device is not clearly stated in any one place within the instructions for use. Both the user's guide and the instructions for use provided contact and helpline numbers for the USA but not for the UK.

Costings

The cost of the CardioChek meter is £479.00 excluding VAT. The price for 25 reagent test strips for total cholesterol, HDL cholesterol or triglyceride is £57.50, £67.00 and £67.25 respectively (excluding VAT). A pack of fifteen Lipid Panel test strips for simultaneous measurement of total cholesterol, HDL cholesterol, and triglyceride is £149.85 excluding VAT. Multichemistry and HDL control solutions (2 mL) at two levels are available at a cost of £30.00 and £22.99 respectively . The instrument comes with a 1 year warranty.

Cost of a cholesterol test

The cost of carrying out a cholesterol test per person is the sum of capital cost, labour and consumables. They are calculated as:

Capital cost

The CardioChek system costs £479.00 excluding VAT. Assuming the life span of the instrument is 3 years, the capital cost is £159.66 per year (£3.08 per week).

Labour

Assuming that a test requires an average of 15 minutes, and includes allowing the patient to sit initially for 5 minutes, performing a control test, setting up the instrument, maintenance and blood collection, for a healthcare professional on a salary of £26,650 per year (excluding employers contributions), the cost of labour is approximately equivalent to £3.42 per test.

Consumables

Consumables include cost of the reagent test strips, control solutions, alcohol swab, gauze, capillary pipette and sharps bin.

Reagent cost
The reagent cost will differ, depending on whether individual tests for total cholesterol, HDL cholesterol, triglyceride or Lipid Profile test strips are used.

A pack of 25 cholesterol and HDL cholesterol test strips is £57.50 and £67.00 respectively (excluding VAT) . The cost per test strip measuring total cholesterol or HDL cholesterol is £2.30 and £2.68 respectively.

A pack of 15 Lipid Panel test strips is £149.85 excluding VAT. The cost per test strip simultaneously measuring total cholesterol, HDL cholesterol and triglyceride is £9.99.

Expenditure on control materials will vary depending on the frequency of use, and the number of assays done on each 2 mL vial at two levels. The costs for the multi Chemistry

solution is £30.00 and £22.99 for the HDL control solution (excluding VAT). If HDL cholesterol requires to be monitored then both quality control solutions will need to be purchased. The manufacturer states that the control materials are stable up to the expiration date printed on the label even after it is opened. If the material is used daily, one level will be sufficient for approximately 40 tests. This will give the cost of the control material per test as £0.38. The cost of the test strip used for the quality control measurement will depend on the frequency at which it is carried out. Assuming that both levels one and two are measured once for every ten patient samples, this will give a cost per patient sample of £0.46 for total cholesterol assay.

There are other minor miscellaneous costs for lancet, alcohol swab, gauze, capillary pipette, sharps bin, which comes to approximately £0.55 per patient specimen.

Table 21 gives an indication of the overall cost per test for a site performing 100 to 3000 tests per year. Thus for a site testing twenty patients per week for total cholesterol, the cost per patient sample is approximately £7.27. No allowance is made for rent, space, power supply and profit.

Table 21: Overall cost per total cholesterol test

Total number of tests		Cost per test			Overall cost per test
Per year	Per week	Capital cost	Labour	Consumables	
100	2	£1.60	£3.42	£3.69	£8.71
250	5	£0.64	£3.42	£3.69	£7.75
500	10	£0.32	£3.42	£3.69	£7.43
1000	20	£0.16	£3.42	£3.69	£7.27
2000	40	£0.08	£3.42	£3.69	£7.19
3000	60	£0.05	£3.42	£3.69	£7.16

The cost per patient for measuring a lipid panel (total and HDL cholesterol and triglyceride) will differ as the cost of the test strip is increased to £9.99 per test. The cost of the control solutions and the test strips used for measuring the QC materials (two levels x2) will also be increased to £4.67. The capital cost and cost of the consumables will be the same. For a primary care site testing twenty patients a week for a lipid panel, the cost per patient will be approximately £18.79.

Discussion and conclusions

For screening purposes, a relatively quick, simple cholesterol assay is invaluable in helping correctly classifying those individuals at risk from coronary heart disease. The CardioChek lipid analyser has several features such as portability, use of capillary whole blood samples, speed and ease of use, which would appear to make it suitable for use in extra-laboratory testing. The system has a number of advantages, the main one being that a full lipid profile is available within 2 minutes on a 40 µl capillary whole blood sample. The lipid panel test strip for total cholesterol, HDL cholesterol and triglyceride was used in this evaluation. The instrument is relatively easy to use which is important when the system is intended for use by non-laboratory personnel. The system is pre-calibrated, and requires minimal maintenance.

Samples were taken from 106 patients or volunteers for analysis by the CardioChek and the reference method - the Vitros 950 for total cholesterol and triglyceride and the IL 600 for HDL cholesterol. Correlation between the CardioChek and the reference methods were 0.86, 0.74 and 0.98 for total cholesterol, HDL cholesterol and triglyceride respectively. The relatively poor correlation for HDL cholesterol reflected the level of imprecision observed in these results. There was an overall significant bias in total cholesterol and triglyceride results from the CardioChek relative to the Vitros 950 of 0.23 and 0.11 mmol/L, but in both analytes there was a strong influence of concentration on the magnitude of the bias. In the case of total cholesterol this took the form of an increasingly negative bias (+13 to - 10 %) with increasing concentration whereas for triglyceride there was an increasingly positive bias (-4 to + 12 %) with increasing concentration. The overall bias in HDL cholesterol results is not significant, nor is there a significant trend in bias with concentration.

Haematocrit had a strong association with the bias for total cholesterol and HDL cholesterol reflected in correlations of -0.57 and -0.37. This leads to an estimated 0.11 mmol/L reduction in total cholesterol bias per unit increase in haematocrit and 0.03 mmol/L reduction in HDL cholesterol. Fasting also had an effect on the bias shown for all three analytes and there was significant variation from batch to batch of test strips in HDL cholesterol and triglyceride results.

Imprecision of the CardioChek system was estimated in the clinical study to be between 9 and 14% for total cholesterol, between 15 and 24 % for HDL cholesterol and between 9 and 22 % for triglyceride. In the laboratory phase of the evaluation Imprecision varied between 4 and 5 % for total cholesterol, 7 and 9 % for HDL cholesterol and 14 and 22 % for triglyceride. NCEP guidelines for imprecision are ≤ 3 % for total cholesterol, ≤ 4 % for HDL cholesterol and ≤ 5 % for triglyceride. The CardioChek did not meet these criteria.

In the laboratory phase of the evaluation total error varied between 6 and 11% for total cholesterol and 17 and 31% for both HDL cholesterol and triglyceride. NCEP guidelines for acceptable total error are ≤8.9 % for total cholesterol, ≤13 % for HDL cholesterol and ≤ 15 % for triglyceride. The CardioChek did not meet these criteria except for two out of three of the total cholesterol levels studied.

In the population studied using total cholesterol results alone, sensitivity and specificity for detecting individuals at high risk of coronary heart disease (with a 6.2 mmol/L cut-off, as defined by the US NCEP ATP III guidelines) were 85 % and 80 % respectively. Using HDL cholesterol alone (with <1.04 mmol/L cut-off, US NCEP ATP III guidelines) gives sensitivity and specificity of 75% and 79% respectively.

The manufacturer (PTS) and distributor (BHR) state that the system is marketed as a first-line screening tool in the UK rather then a diagnostic method, and outline it's intended use in the following comment box.

Manufacturer's statement on intended use:

Following this evaluation the manufacturer clarified intended use as follows:

The system is intended for in vitro diagnostic use by health care professionals for primary prevention. Results should be used in conjunction with other cardiac risk factors to assess and classify patients into essentially three risk categories, low, medium and high. The manufacturer recommends that "Practice guidelines for Cholesterol Testing" published by the Royal Pharmaceutical Society of Great Britain in June 2003 should be adhered to. These guidelines state that:

"It should be stressed that a single elevated cholesterol measurement, even under the most rigorous quality control, does not establish the diagnosis of high blood cholesterol, for which two or more cholesterol measurements are needed."

The manufacturer also recommends that patients classified as being in the high risk category should have additional test(s) performed under appropriate conditions e.g. fasting by a laboratory before initiating therapy. Those in the medium risk category should be retested at 6 or 12 months.

Evaluator's comments:

The intended use of the device is not clearly stated in any one place within the instructions for use. Care is needed to avoid misinterpretation in intended use as the 'Users Guide' describes the system as "accurate" and" capable of lipid screening". The lipid panel test strip insert mentions "lipid measurements are used in diagnosis and treatment" and states "the test is designed for use by healthcare professionals"; the test strip packaging indicates "suitable for self-testing". The instructions for use would benefit from revision in this respect.

In conclusion, in the hands of experienced healthcare professionals the CardioChek PA lipid system with the lipid panel test strips was relatively easy to operate. However, attention should be drawn to the level of imprecision.

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Appendix

Manufacturer's comments

The following comments on this report have been received from Mr Hans Fredman, Sales Director Europe at Polymer Technology Systems, Inc:

> We would like to thank the staff at Wolfson Research Laboratories for their efforts to evaluate the CardioChek™ PA and Lipid Panel Test Strips.
>
> In any scientific evaluation or survey, the choice of methods, as well as the analyses and interpretations of results will vary. PTS Inc. firmly believes it is imperative that results and interpretations in this report are not viewed in isolation. Data must be reviewed in combination with the product's intended use, and in combination with the advantages a hand-held, easy to use Point-of-Care analyzer can offer.
>
> Since this study was performed, several improvements to the CardioChek System have been implemented, including further refinement of the test strips as well as introduction of an updated software version of the CardioChek PA, resulting in enhanced performance of the system.