# The Integrated Cardiovascular Clinical Network CHSA


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# Roche cobas b 101 HbA1c and Lipids Evaluation

## July 2013

## Introduction

Cardiovascular disease (CVD) is the leading cause of mortality in Australia, accounting for 31% of all deaths in 2011.[1] Hyperlipidaemia was ranked as the second greatest risk factor contributing to the total burden of disease in 2003.[2] People living in remote areas are amongst the group of patients having the highest rate of hospitalisation and death resulting from CVD in Australia.[3] Hyperlipidaemia is a modifiable risk factor. Several studies have shown that a proportional relationship exists between a decrease in blood cholesterol concentration and reduced risk of coronary heart disease.[4]

A risk factor survey conducted in the rural south-eastern region of South Australia in 2004 reported that significant under testing and under treatment of hyperlipidaemia exists.[5] It has been suggested that point-of-care-testing (PoCT) may assist in combating hyperlipidaemia by increasing screening, diagnosis and monitoring of lipids.[6] Having lipid results available while the patient is having the primary consultation will result in a more complete risk factor assessment and possibly influence the action plan for the patient. This is particularly relevant in rural areas where pathology turnaround times range from 6 to 36 hours if laboratory facilities are not locally available.

Diabetes mellitus is one of the most common non-communicable diseases around the world with 275 new cases being diagnosed every day in Australia.[7] Undetected or poorly controlled diabetes has a major impact on quality of life and life expectancy.[8] Measurement of glycated haemoglobin (HbA1c) is one of the most common methods of monitoring diabetes control with three quarters of diabetic patients receiving this test yearly.[9] Recently, the use of HbA1c testing to diagnose diabetes has been endorsed by the World Health Organisation providing quality assurance programs are in place and assays are standardised to international reference methods.[10] The use of PoCT in diabetes diagnosis and monitoring allows the prevention, early detection and treatment of diabetes related complications and positively impacts the provision of care in diabetic patients.[11]

Method evaluation, validation and verification provides objective evidence that a method is fit for purpose, meaning the particular requirements for a specific intended use are fulfilled. To determine its suitability in non-laboratory settings, in particular in General Practice, the cobas b 101 instrument was evaluated in the iCCnet CHSA laboratory in Adelaide and in 10 primary health care centres in rural and remote South Australia in the period of February to June 2013.

## Instrument Overview

The cobas b 101 system is an in vitro diagnostic test system utilising two types of test discs to measure HbA1c and lipids. The system is intended for professional use in a clinical laboratory setting or point-of-care (PoC) locations. The b 101 runs on mains power and has capabilities for printer, barcode scanner and network connection. The cobas b 101 system has TGA approval.

## Quality Goals

Quality goals used in this study were taken from recommendations by the Standards for Point of Care testing in General Practice.[12]

They are:

- PoCT device measuring HbA1c for use in General Practice in Australia should be able to achieve a minimum imprecision (CV%) of 4 % and ideally meet a desirable imprecision level of 3% or less
- PoCT device measuring cholesterol for use in General Practice in Australia should be able to achieve a minimum imprecision (CV%) of 5 % and ideally meet a desirable imprecision level of 3% or less
- PoCT device measuring triglycerides for use in General Practice in Australia should be able to achieve a minimum imprecision (CV%) of 7.5 % and ideally meet a desirable imprecision level of 5% or less
- PoCT device measuring HDL for use in General Practice in Australia should be able to achieve a minimum imprecision (CV%) of 6 % and ideally meet a desirable imprecision level of 4% or less

| | Desirable Imprecision Goals (%) | Minimum Imprecision Goals (%) | Total Analytical Error Goals (%) |
|---|---|---|---|
| HbA1c | 3 | 4 | 5 |
| CHOL | 3 | 5 | 9 |
| TG | 5 | 7.5 | 15 |
| HDL | 4 | 6 | 12 |

**Table 1**. Summary of Required Accuracy Specifications for PoCT instruments used in General Practice

## Aim of Evaluation

The aim of this study was to test the suitability of the cobas b 101 instrument for the measurement of HbA1c and lipids in General Practice. This was evaluated through precision, linearity and accuracy analysis. Interferences were not evaluated in this study.

Within-practice precision testing (inter assay) was performed by multiple practice nurses at 10 General Practices. Within-practice precision analysis was performed using median CV values as per the Australian RCPA quality assurance programs. Each site tested two levels of quality control material over a minimum of 10 days.

Scientist precision testing (intra assay) was performed by a medical scientist testing 30 replicates of both levels of quality control material over a five hour period in a laboratory setting. All quality control material was supplied by Roche Diagnostics.

Lipids linearity was evaluated by testing the RCPA 2012 general serum chemistry program in duplicate. HbA1c linearity was determined by testing the RCPA 2012 glycated haemoglobin program in duplicate. Each program was tested in one session.

Accuracy was evaluated in 10 rural and remote primary health care settings by testing capillary whole blood samples from 15 patients at each site on the cobas b 101 in parallel with venous samples sent to the local laboratory. Both levels of quality control material were tested in the morning of each day that patient testing was performed.

All practices were invited to participate in a survey designed to investigate their thoughts on the b 101 instrument.

This study was approved by the Southern Adelaide Clinical human Research Ethics Committee.

**Product Description**

The HbA1c disc quantitatively determines the percent HbA1c (DCCT/NGSP) and mmol/mol (IFCC) in human capillary and venous whole blood. An estimated average glucose level (eAG) is also calculated by the system using the ADAG equation.[13] Approximately 2 µL of blood is applied to the disc and results are generated via photometric transmission measurement in under 6 minutes. The b 101 system measures results from 4-14% (DCCT/NGSP) or 20-130 mmol/mol (IFCC). The HbA1c method is standardised against the IFCC reference method for the measurement of HbA1c in human blood and can be transferred by calculation to results traceable to DCCT/NGSP. Lot-specific calibration data is read from barcodes on each disc, eliminating the need for user calibration. Caution should be used when interpreting HbA1c results from patients with haemoglobin variants, haemolytic anaemia or other haemolytic disease, homozygous sickle cell trait, pregnancy, high amounts of HbF and recent significant or chronic blood loss as results may be affected by these conditions. In patients with haemoglobin levels below 60 g/L or above 200 g/L no HbA1c result is reported.

The package insert states no significant interference was found for unconjugated/conjugated bilirubin up to 1000 µmol/L, intralipid concentration up to 5.65 mmol/L, glucose up to 111 mmol/L, rheumatoid factor up to 750 IU/mL and common drug panels at therapeutic concentrations. For diagnostic purposes, the results should always be assessed in conjunction with the patient's medical history, clinical examination and other findings.

The lipids disc quantitatively determines the total cholesterol (CHOL), triglycerides (TG) and HDL cholesterol (HDL) in human capillary and venous whole blood or

plasma. Calculated values for low-density lipoprotein (LDL), Non-HDL and the CHOL/HDL ratio are also provided by the b 101 system. Approximately 19 µL of blood or plasma is applied to the disc and results are generated via photometric transmission measurement in around 6 minutes. The b 101 system measures total cholesterol results from 1.28-12.95 mmol/L, triglycerides from 0.50-7.35 mmol/L and HDL cholesterol from 0.38-2.60 mmol/L. The lipids method for total cholesterol and HDL cholesterol are traceable to the designated CDC reference methods and triglycerides are traceable to the ID/MS method. Lot-specific calibration data is read from barcodes on each disc, eliminating the need for user calibration.

The package insert states no significant interference was found for conjugated bilirubin up to 1326 µmol/L, unconjugated bilirubin up to 2652 µmol/L, haemolysis up to a haemoglobin concentration of 5.65 mmol/L, intralipid concentrations up to 5.65 mmol/L, triglycerides up to 11.29 mmol/L, ascorbic acid up to 0.06 mmol/L, common drug panels at therapeutic concentrations and haematocrit concentrations between 30-55%. For accurate triglyceride and LDL testing patients must fast for 9-12 hours before the sample is collected. Hand creams or soaps can contain fatty substances which may lead to false high triglyceride results. Abnormal liver function may cause inaccurate lipid results due to the effects on lipid metabolism. For diagnostic purposes, the results should always be assessed in conjunction with the patient's medical history, clinical examination and other findings.

Test discs do not require refrigeration and are stored at room temperature. Quality control material does require refrigeration and is to be performed with cobas HbA1c control and cobas Lipid Control respectively for HbA1c and lipids discs. Each kit of quality control material contains a lot-specific QC info disc containing target values and ranges read by the b 101. Applicable regulations and guidelines should be followed for frequency of quality control testing but the AACB PoCT guidelines stating one quality control sample per month should be followed[14]. Quality control materials are based on human sera and should be disposed of according to your facilities infection control guidelines.

No maintenance is required for the b 101 other than routine cleaning of spills inside and on the outside of the instrument. Any spills should be cleaned immediately using a soft cotton swab or cloth dampened with 70% ethanol or isopropyl alcohol and dried with a soft dry cloth. Gloves must be worn and the instrument turned off before any maintenance is performed.

**Evaluation preparation**

Clinical Network Scientists at iCCnet were trained by Roche Diagnostics staff on the operation of the cobas b 101 system. Each primary health care centre involved was then trained face to face by iCCnet scientists on the operation of the instrument, evaluation protocol, consenting of patients and collection and reporting of results. Every b 101 instrument had both of levels of quality control tested and passed before being used in the evaluation.

## Precision

| | Scientist Control Testing | | | Within-Practice Control Testing | | |
|---|---|---|---|---|---|---|
| **Analyte** | **Mean** | **SD** | **CV %** | **Mean** | **SD** | **Median CV % (mean)** |
| HbA1c (mmol/mol) | 39 | 0.77 | 2.0 | 39 | 1.05 | 2.7 (3.2) |
| CHOL (mmol/L) | 3.75 | 0.06 | 1.6 | 3.63 | 0.06 | 1.6 (1.7) |
| TG (mmol/L) | 1.11 | 0.01 | 1.4 | 1.11 | 0.02 | 1.5 (1.5) |
| HDL (mmol/L) | 0.99 | 0.02 | 2.3 | 0.92 | 0.03 | 2.8 (2.9) |

**Table 2**. cobas b 101 precision analysis for Quality Control Level 1

| | Scientist Control Testing | | | Within-Practice Control Testing | | |
|---|---|---|---|---|---|---|
| **Analyte** | **Mean** | **SD** | **CV %** | **Mean** | **SD** | **Median CV % (mean)** |
| HbA1c (mmol/mol) | 87 | 1.36 | 1.6 | 87 | 1.48 | 1.7 (1.7) |
| CHOL (mmol/L) | 6.8 | 0.12 | 1.8 | 6.74 | 0.11 | 1.6 (1.7) |
| TG (mmol/L) | 4.4 | 0.04 | 0.9 | 4.38 | 0.05 | 1.2 (1.2) |
| HDL (mmol/L) | 1.7 | 0.03 | 2.1 | 1.69 | 0.04 | 2.4 (2.6) |

**Table 3**. cobas b 101 precision analysis for Quality Control Level 2

| | Level 1 Control | | Level 2 Control | |
|---|---|---|---|---|
| **Analyte** | cobas b 101 CV (%) | GP Trial CV (%)* | cobas b 101 CV (%) | GP Trial CV (%)* |
| HbA1c | 2.7 | 2.7 | 1.7 | 3.1 |
| CHOL | 1.6 | 2.7 | 1.6 | 3.0 |
| TG | 1.5 | 4.5 | 1.2 | 4.6 |
| HDL | 2.8 | 6.1 | 2.4 | 4.4 |

* CV results for the GP trial were taken as an average across the two lot numbers used. Means for each control were not reported in the GP trial so could not be compared in this table

**Table 4.** Comparison of the median within-practice precision results obtained in this trial to the Australian Government's Point of Care Testing in General Practice Trial[15]

All analytes showed excellent precision, meeting both the minimum and desirable imprecision goals. Comparison of the within-practice and scientist control testing demonstrates that practice nurses can achieve similar precision results within a clinical setting to a controlled laboratory setting.

Apart from the low level HbA1c control where results were the same, the cobas b 101 performed better than the results achieved in the Australian Government's Point of Care Testing in General Practice Trial. The instruments used in the General Practice Trial were the DCA 2000 for HbA1c and the Cholestech LDX for lipids.

## Linearity

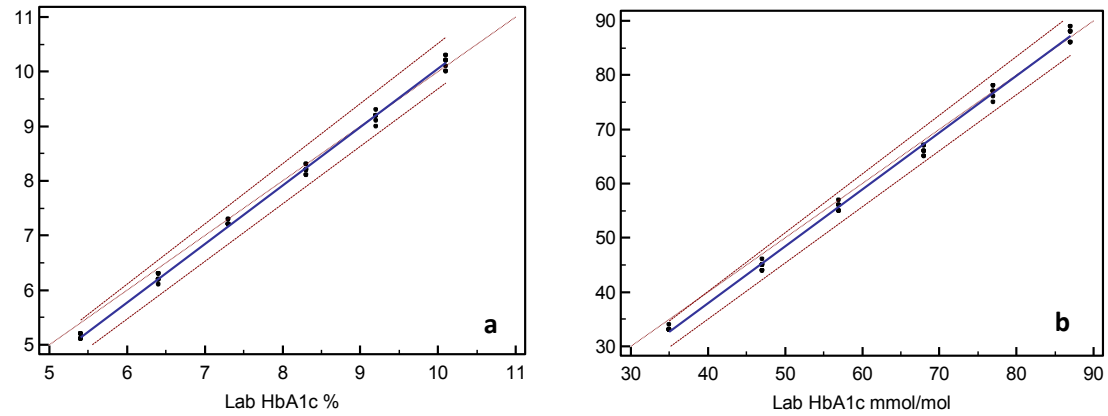


**Figure 1**. Passing Bablok evaluation of HbA1c in % (a) and mmol/mol (b) for the cobas b 101 using the glycated haemoglobin RCPA QAP program

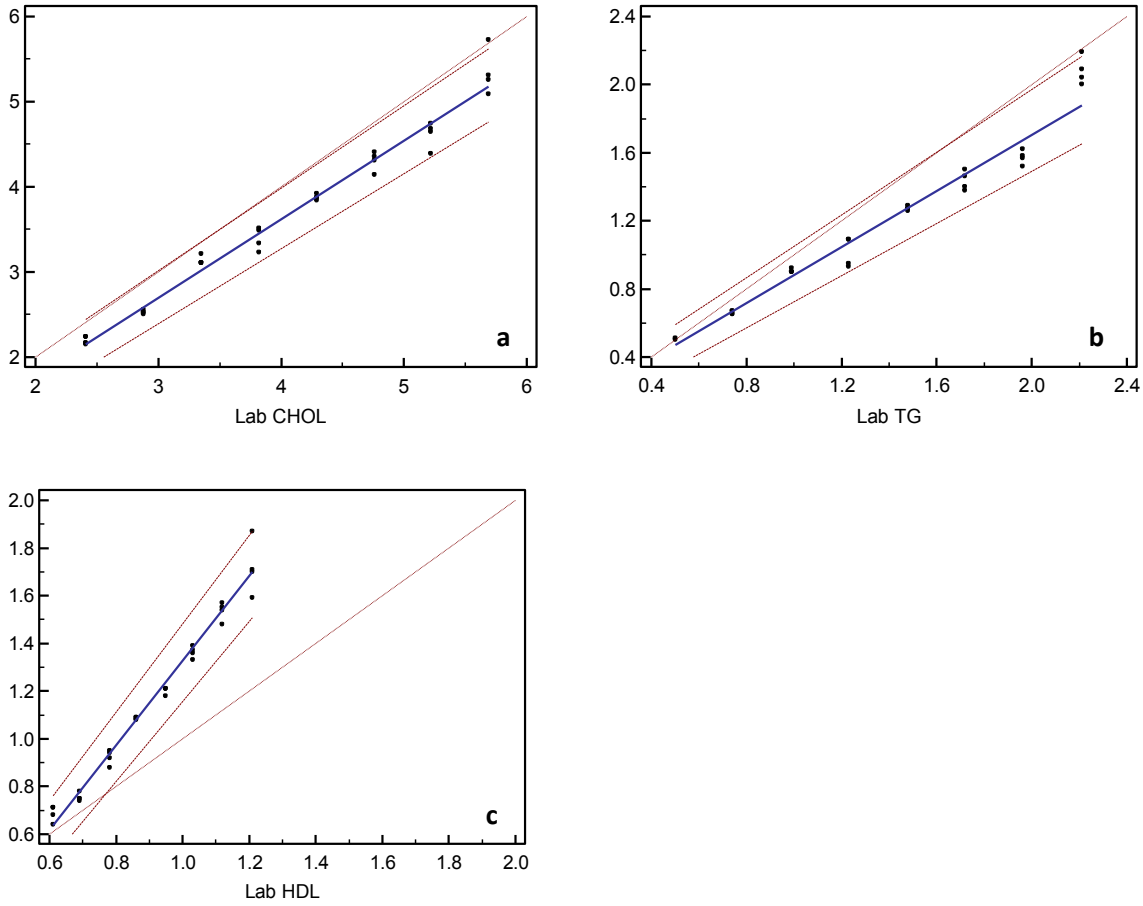


**Figure 2**. Passing Bablok evaluation of CHOL (a), TG (b) and HDL (c) for the cobas b 101 using the general serum chemistry RCPA QAP program

| Glycated Haemoglobin Program | | | | |
|---|---|---|---|---|
| Analyte | Equation | r Value | Mean Bias# % | p value |
| HbA1c (%) | y = 1.07x - 0.66 | 0.999 | -1.15 | 0.36 |
| HbA1c (mmol/mol) | y = 1.00x - 4.10 | 0.999 | -1.94 | 0.13 |

# Mean Bias was calculated from the Bland-Altman Data

**Table 5**. Passing Bablok evaluation of HbA1c for the cobas b 101 using the glycated haemoglobin RCPA QAP program

| General Serum Chemistry Program | | | | |
|---|---|---|---|---|
| Analyte | Equation | r Value | Mean Bias# % | p value |
| CHOL | y = 0.92x - 0.08 | 0.990 | -9.27 | 0.67 |
| TG | y = 0.82x + 0.06 | 0.979 | -12.86 | 0.58 |
| HDL | y = 1.77x - 0.44 | 0.990 | +27.43 | 0.65 |

**Table 6**. Passing Bablok evaluation of CHOL, TG and HDL for the cobas b 101 using the general serum chemistry RCPA QAP program

All analytes showed good correlation to the RCPA QAP samples ($r \geq 0.98$). No significant deviation from linearity was seen with all p values >0.10. HDL cholesterol displayed a significant slope of 1.77 and bias of +27.43% which resulted in overestimation of HDL results as the level increased. The HDL overestimation appears to be a matrix effect with the RCPA QAP samples as a slope closer to 1 was seen in the patient comparisons.

## Method Comparison

A total of 158 patients were enrolled in this study with 141 HbA1c and 140 lipids results.

HbA1c

| Analyte | Equation | r Value | Range | Mean Bias % | N |
|---|---|---|---|---|---|
| HbA1c % | y = 1.10x - 0.36 | 0.972 | 5.1 - 10.6 | +4.62 | 141 |
| HbA1c mmol/mol | y = 1.10x - 1.29 | 0.971 | 32 - 92 | +6.60 | 141 |

**Table 7**. Passing Bablok analysis of HbA1c for patient results with the cobas b 101 and all laboratory results

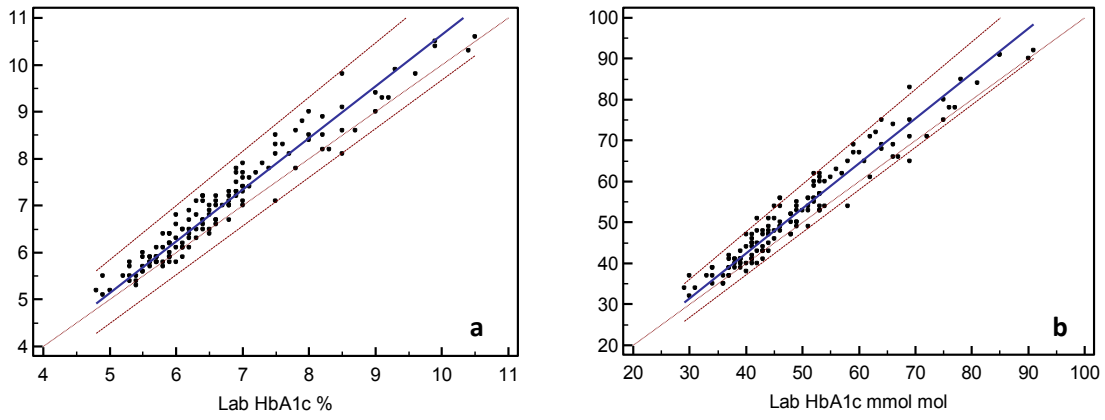


**Figure 3**. Passing Bablok analysis of HbA1c in % (a) and mmol/mol (b) for patient results with the cobas b 101 and all laboratory results

| Analyser | Units | Equation | r Value | N |
|---|---|---|---|---|
| Integra | % | y = 1.29x - 1.47 | 0.984 | 33 |
| | mmol/mol | y = 1.29x - 9.70 | 0.985 | |
| cobas 502 | % | y = 1.03x + 0.21 | 0.981 | 27 |
| | mmol/mol | y = 1.00x + 4.00 | 0.981 | |
| BioRad Variant II | % | y = 1.04x - 0.05 | 0.972 | 81 |
| | mmol/mol | y = 1.04x + 0.44 | 0.971 | |

**Table 8**. Instrument specific Passing Bablok analysis of HbA1c in % and mmol/mol for patient results with the cobas b 101 and laboratory instruments used

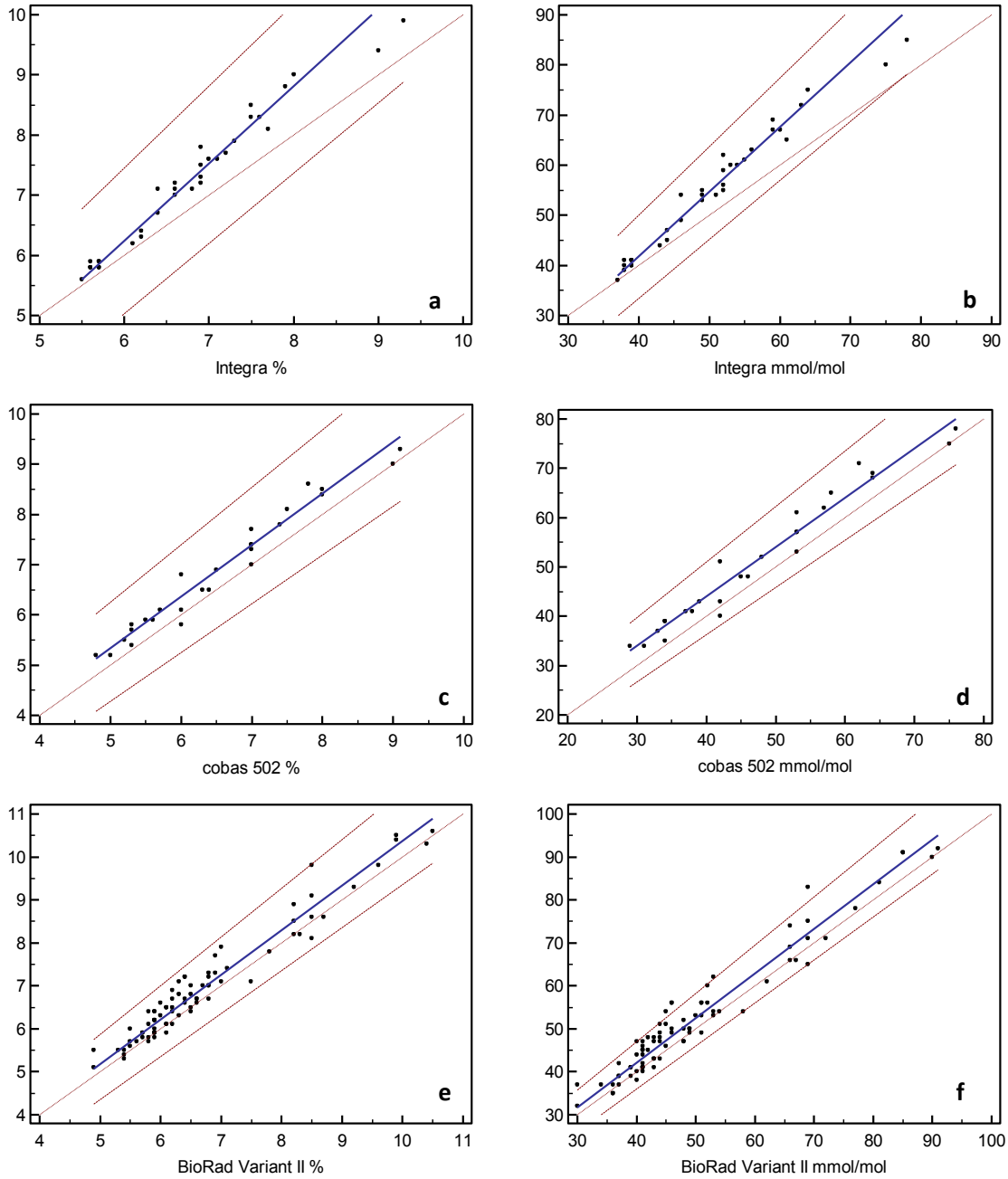


**Figure 4**. Instrument specific Passing Bablok analysis of HbA1c for the Integra % (a) and mmol/mol (b), cobas 502 % (c) and mmol/mol (d) and BioRad Variant II % (e) and mmol/mol (f)

| Laboratory Instrument | Mean Bias % b 101 | Within-Practice Imprecision %[$] b 101 | Total Analytical Error % b 101* | Goal |
|---|---|---|---|---|
| Overall | +6.6 | 2.2 | 10.2 | 5 |
| Integra | +9.6 | 2.2 | 13.2 | 5 |
| cobas 502 | +7.6 | 2.2 | 11.2 | 5 |
| Bio-Rad Variant II | +5.2 | 2.2 | 8.8 | 5 |

[$] Within practice imprecision calculated as an average of the level 1 and level 2 control
* Total analytical error = %Bias + 1.65 x imprecision

**Table 9.** Mean bias, within-practice imprecision and total analytical error for HbA1c separated into instrument type compared to the quality goals listed in table 1

HbA1c showed good correlation when compared to all laboratory methods used (r=0.97). An overall positive bias of up to +6.6% was seen, however the amount of bias varied for the different laboratory method used.

As this study used different laboratory methods a comparison to the gold standard reference method was not available. HbA1c exceeded the quality goals for total analytical error. When compared to the different laboratory methods, each exceeded the quality goal. However, the amount of bias seen was dependent on the laboratory method used. A higher bias was seen for the Integra and cobas 502 analysers which contributed to greater analytical error.

The Scandinavian evaluation of laboratory equipment for primary health care (SKUP) has set a total analytical error of 10% as allowable for HbA1c.[16] The cobas b 101 did meet this goal when compared to the Bio-Rad Variant II, but did not meet it for all instruments combined, the Integra or the cobas 502.

Lipids

| Analyte | Equation | r Value | Range | Mean Bias % | N |
|---|---|---|---|---|---|
| CHOL | y = 0.96x - 0.05 | 0.981 | 1.94 - 6.74 | -5.71 | 140 |
| TG | y = 0.97x + 0.08 | 0.959 | 0.56 - 6.02 | +3.50 | 137 |
| HDL | y = 1.23x - 0.31 | 0.955 | 0.46 - 2.56 | -1.43 | 140 |

**Table 10**. Passing Bablok analysis of CHOL, TG and HDL for patient results with the cobas b 101 and all laboratory results

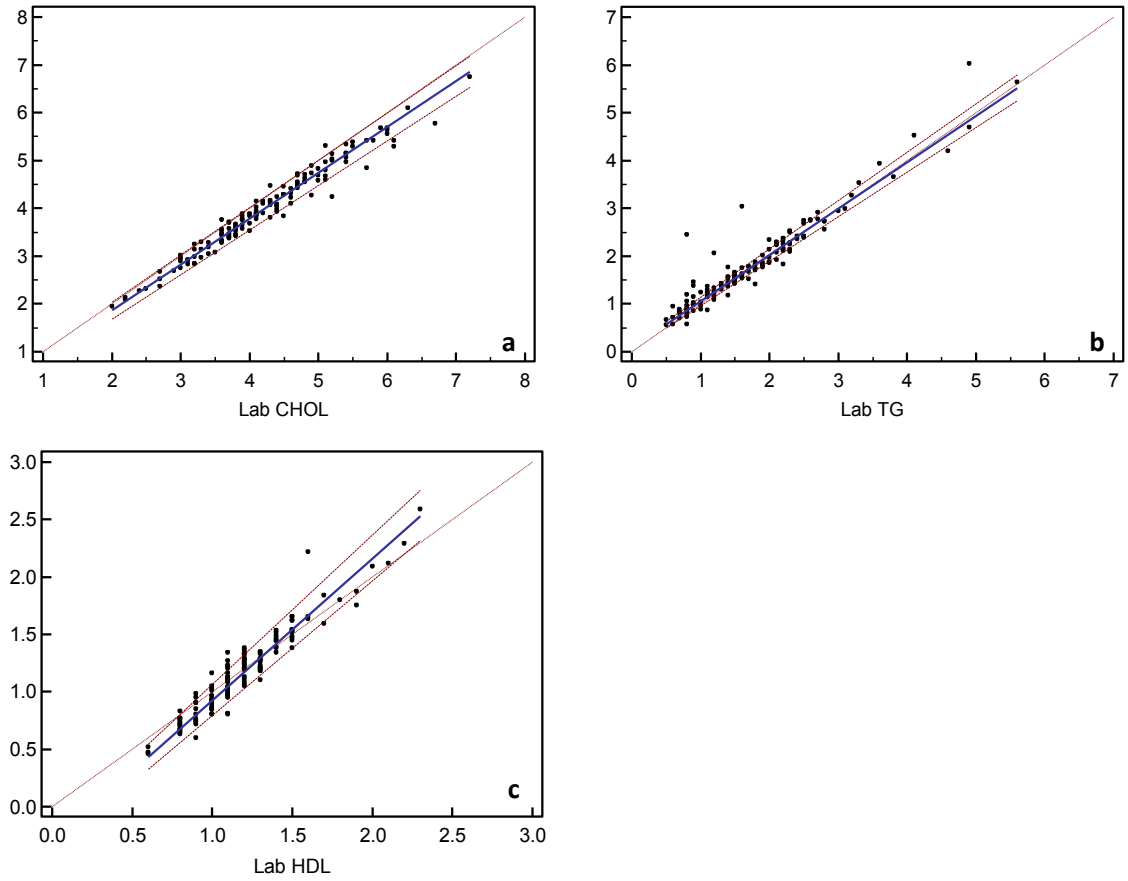


**Figure 5**. Passing Bablok analysis of CHOL (a), TG (b) and HDL (c) for patient results with the cobas b 101 and all laboratory results

| Analyser | Analyte | Equation | r Value | N |
|---|---|---|---|---|
| Siemens Dimension RXL | CHOL | y = 0.98x + 0.02 | 0.987 | 33 |
| | TG | y = 0.97x + 0.14 | 0.980 | |
| | HDL | y = 1.35x - 0.32 | 0.979 | |
| cobas 701 | CHOL | y = 0.99x - 0.22 | 0.989 | 30 |
| | TG | y = 1.06x + 0.08 | 0.950 | |
| | HDL | y = 1.14x - 0.25 | 0.988 | |
| Advia 2400 | CHOL | y = 0.96x - 0.04 | 0.989 | 35 |
| | TG | y = 0.95x + 0.06 | 0.863 | |
| | HDL | y = 1.30x - 0.41 | 0.960 | |
| Olympus AU640 | CHOL | y = 0.93x - 0.01 | 0.981 | 42 |
| | TG | y = 0.96x + 0.02 | 0.989 | |
| | HDL | y = 1.37x - 0.47 | 0.935 | |

**Table 11**. Instrument specific Passing Bablok analysis of CHOL, TG and HDL for patient results with the cobas b 101 and laboratory instruments used

| Test | Mean Bias % b 101 | Within-Practice Imprecision %[$] b 101 | Total Analytical Error % b 101* | Goal |
|---|---|---|---|---|
| CHOL | -5.7 | 1.6 | 8.3 | 9 |
| TG | +3.5 | 1.4 | 5.8 | 15 |
| HDL | -1.4 | 2.6 | 5.7 | 12 |

[$] Within practice imprecision calculated as an average of the level 1 and level 2 control
* Total analytical error = %Bias + 1.65 x imprecision

**Table 12.** Mean bias, within-practice imprecision and total analytical error for CHOL, TG and HDL compared to the quality goals

All lipid analytes showed good correlation when compared to all laboratory methods used (r≥0.96). Triglycerides had a bias positive bias of 3.50%. Negative bias was seen for total cholesterol (-5.71%) and HDL cholesterol (-1.43%). Total analytical error for cholesterol, HDL and triglycerides met the quality goals.

**Qualitative User Survey on the cobas b 101**

| b 101 User Evaluation - Ease of Use | Very Easy | Easy | Difficult |
|---|---|---|---|
| Filling a disc | 17% | 67% | 17% |
| Putting a disc into the b 101 | 83% | 17% | 0% |
| Reading results on the b 101 | 67% | 33% | 0% |
| Hearing the alarm | 67% | 33% | 0% |
| All in all, the operation of the instrument | 50% | 33% | 17% |

**Table 13**. b 101 ease of use evaluation

| b 101 User Evaluation - Technical Aspects | Strongly Agree | Agree | Neutral | Disagree |
|---|---|---|---|---|
| The lipids sample volume was acceptable | 0% | 83% | 0% | 17% |
| The HbA1c sample volume was acceptable | 50% | 50% | 0% | 0% |
| I liked the layout of the instrument | 33% | 67% | 0% | 0% |
| I liked the layout of the discs | 17% | 67% | 17% | 0% |
| The menus were easy to navigate | 33% | 50% | 17% | 0% |
| The error codes made it easy to understand the problem | 50% | 17% | 33% | 0% |
| Dual testing of lipids and HBA1c was a benefit | 33% | 33% | 17% | 17% |

**Table 14**. b 101 technical aspects evaluation

60% of practices responded to the survey. For the duration of the trial only 2 errors were reported; a single episode of disc failure and one site reported a fill error with comment “Test disc hard to fill until I got used to it”. When asked about potential improvements to the instrument, the only request was to have a printer available. Printers are available for the b 101, but weren’t used for this trial.

Five out of the six practices reported that they had confidence in the results generated by the b 101, while one of the sites observed that for HbA1c the discrepancy between the laboratory increased for higher results. This is possibly due to the particular laboratory method used by this site as the different methods demonstrated large variations. Five out of six practices believed using the b 101 had an advantage to using their local laboratory (in most cases located in a different town). All of these advantages reported were around the availability of results immediately while the patient was still in the practice assisting patient management. The major barrier to implementing the b 101 in their practice was the lack of Medicare rebates available to GP practices without costly full accreditation.

## Conclusions

The Roche cobas b 101 showed good precision with all analytes meeting the desirable imprecision goals. The b 101 exhibited good linearity as confirmed by the RCPA QAP samples and correlated well with laboratory results.

Although all analytes correlated well with the laboratory methods for patient testing, only the lipids (total cholesterol, triglycerides and HDL cholesterol) met the Point of Care Standards in General Practice quality goals for total analytical error. HbA1c exceeded the total analytical error goal which is mainly attributable to the bias seen when comparing patient testing to non-reference laboratory methods. This can in part be explained by the significant differences seen in laboratory methods used, showing a lack of standardisation across different methods.

Operators of the b 101 in General Practice are able to achieve precision results similar to those achieved by a scientist and generally found the instrument easy to use. Sites reported the lack of a Medicare rebate in General Practice as a barrier to on-going implementation.

Results of this study suggest that the Roche cobas b 101 is a suitable point of care instrument to use in non-laboratory settings for HbA1c and lipid analysis. Implementation in rural and remote areas may assist with improving under testing and under treatment of hypercholesterolemia that has been reported in rural areas of Australia and in reducing the burden of diabetes disease on patient quality of life.

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