Cobas® h 232 POC system

A system for measurement of cardiac biomarkers
and a biomarker for venous thromboembolism
manufactured by Roche Diagnostics GmbH

Report from the evaluation SKUP/2013/97

of NT-proBNP on Cobas h 232

organised by SKUP at the request of

Roche Diagnostics Norway AS

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The report was written by SKUP, April 2013. For more details about SKUP, see attachment 1. Main author was Camilla Eide Jacobsen, SKUP in Norway.

Table of contents

Attachment 7 and 9 with raw data are included only in the copy to Roche Diagnostics Norway AS.

1. Summary

Background
The Cobas h 232 POC system (Cobas h 232) was launched onto the Scandinavian market in 2007. The system is produced by Roche Diagnostics GmbH. The test strips for the meter support diagnosis and assessment of cardiovascular diseases. This evaluation was ordered by Roche Diagnostics Norway and was performed with test strips for NT-proBNP.

The aim of the evaluation
- compare Cobas h 232 results achieved with heparinised venous whole blood in a hospital laboratory and in three primary health care centres with results from serum samples achieved with an established hospital laboratory method for NT-proBNP
- compare the analytical quality of Cobas h 232 with the manufacturer's specifications for imprecision (CV≤15%), trueness versus Elecsys (bias ≤±20%) and accuracy versus Elecsys (a deviation for 95% of the results less than 14 pmol/L in concentration range 7 – 27 pmol/L, less than 52% in concentration range 28 – 142 pmol/L and less than 61% in concentration range 143 – 1062 pmol/L)
- examine the variation between three lots of NT-proBNP test strips
- evaluate the user-friendliness of Cobas h 232 and the user manual

Materials and methods
The evaluation of NT-proBNP on Cobas h 232 was carried out without any specific quality goals set by SKUP. Heparinised venous whole blood samples from 107 hospitalised patients were measured on Cobas h 232 in the hospital laboratory. A total of 95 heparinised venous whole blood samples were tested in three primary health care centres (PHCC). Three lots of NT-proBNP test strips were used. All results from Cobas were compared with the routine method for quantitative determination of NT-proBNP in serum at the hospital laboratory (Elecsys proBNP-II method on Modular Analytics E170). All samples were handled according to the given information about NT-proBNP stability.

Results
- The repeatability CV was approximately 10% in the hospital laboratory and between 5% and 10% in PHCC. The achieved precision fulfils the manufacturer's specifications.
- In the hospital laboratory NT-proBNP on Cobas h 232 showed results in agreement with the comparison method. At the PHCC the Cobas results showed between 14% and 24% higher NT-proBNP results than the comparison method. The bias has so far not been explained. The manufacturer's specification for maximum bias versus the Elecsys porBNP method was not fulfilled for results from PHCC in the concentration range 66-250 pmol/L.
- 100% of the results obtained in the hospital laboratory and 94% of the results obtained by the PHCC were within the manufacturer's specifications for accuracy. The fraction of results inside deviation limits of ±25% were 75% and 58%, respectively.
- The three lots of test strips used in the evaluation seem to give similar results.
- The users were satisfied with the user manual. The time factors and quality control possibilities were assessed as intermediate. This was partly due to the 12 minutes analysis time, the storage conditions for the test strips (refrigerator) and the control material (freezer). The operation facilities were assessed as both satisfactory and intermediate. The needle on the Cardiac pipette makes up a potential risk of injury. It is difficult to avoid air bubbles in the pipette.

– The fraction of technical errors was <2%.

Conclusion

It must be underlined that SKUP had no specific quality goals for this evaluation, and the performance was therefore compared to the manufacturer's specifications. The repeatability CV was between 5% and 10%, and fulfils the manufacturer's specifications (CV≤15%). The results from the hospital laboratory were within the manufacturer's specifications for accuracy. PHCC achieved 94% within these specifications. It was discovered a bias of approximately +20% between the Cobas h 232 results with heparinised whole blood from PHCC and the results from the serum samples sent to the hospital laboratory. This bias was unexpected because the Cobas h 232 results (heparinised whole blood) from the hospital laboratory were in agreement with the comparison method. The response from the evaluation sites about the user-friendliness was acceptable.

Comments from the manufacturer

A letter with comments from Roche Diagnostics is attached to the report.

2. Abbreviations

BLS	Biomedical Laboratory Scientist
BNP	Brain Natriuretic Peptide
CI	Confidence Interval
CK-MB	Creatine Kinase (muscle and brain polypeptide chains)
C-NPU	Committee on Nomenclature, Properties and Units
CMOS	Complementary Metal-Oxide Semiconductor
CV	Coefficient of Variation
DAK-E	Danish Quality Unit of General Practice
EQA	External Quality Assessment
Equalis	External quality assurance in laboratory medicine in Sweden
IFCC	International Federation of Clinical Chemistry and Laboratory Medicine
IUPAC	International Union of Pure and Applied Chemistry
LKB	Laboratory for Clinical Biochemistry
NKK	Norwegian EQA Program for medical Biochemistry
Noklus	Norwegian Quality Improvement of Primary Care Laboratories
NS_EN ISO	Norsk Standard_Europeisk Norm International Organization of Standardization
NT-proBNP	N-Terminal prohormone of Brain Natriuretic Peptide
PHCC	Primary health care centre/centres
POC	Point-of-Care
SD	Standard Deviation
SKUP	Scandinavian evaluation of laboratory equipment for primary health care
TE	Total Error

3. Quality goals

There are no common analytical quality goals for determination of NT-proBNP. Generally, if a point of care test is used as a replacement for the equivalent test in a hospital laboratory, they should have the same analytical quality.

3.1. Analytical quality

Quality goals based on biological variation

Setting quality goals based on biological variation is an acknowledged method [1]. For NT-proBNP the information about biological variation differs substantially. Ricos *et al.* state the intra-individual biological variation (CV_{intra}) as 10% and the inter-individual biological variation (CV_{inter}) as 16% [2]. Other authors discuss findings of CV_{intra} between 30 and 50% [3,4]. Apple *et al.* recommend a desirable total imprecision of <15% at NT-proBNP concentrations within the reference interval, and a CV <10% if the goal is to rely on monitoring of marker trends over time [3].

Precision

Allowable imprecision can be calculated as ≤½ CV_{intra}. Using the various information regarding CV_{intra}, the calculated allowable imprecision will spread from 5 and 25%. A reasonable and specific quality goal for precision is not easily set based on this.

The precision of the comparison method

NT-proBNP on the comparison method, Elecsys proBNP on Modular Analytics E170, is accredited according to NS-EN ISO 15189 (2007) in the measuring range of 10 – 4000 pmol/L (85 – 33898 pg/mL). The requested analytical CV is <8%.

Accuracy

Limits for allowable deviation for the method being evaluated (Cobas h 232) can be calculated based on the bias of Cobas h 232 versus the comparison method, the imprecision of Cobas h 232 and the imprecision of the comparison method.

$$\text{Allowable deviation} = |\text{Bias}_{\text{Cobas}}| + z \times \sqrt{\text{CV}^2_{\text{Cobas}} + \text{CV}^2_{\text{Comparison method}}}$$

Ricos *et al.* state that desirable specifications for bias of NT-proBNP is 4,7% [2]. Using 8% as the imprecision of the comparison method and 5 or 25% as the imprecision of the field method, the calculated limits for allowable deviation for the field method will vary from ±20% to ±48%.

The manufactures quality specifications for test strips CARDIAC proBNP+ on Cobas h 232

Imprecision

SD ≤34 pg/mL for NT-proBNP concentrations ≤225 pg/mL
CV ≤15% for NT-proBNP concentrations from 226 to 1200 pg/mL
CV ≤20% for NT-proBNP concentrations from 1201 to 9000 pg/mL

Trueness

Maximum mean relative bias vs. Elecsys proBNP should be ≤±20%.

Accuracy
95% of the values within the following deviation limit vs. Elecsys proBNP.
Deviation limits: ±117 pg/mL (60 – 225 pg/mL), ±52% (226 – 1200 pg/mL), ±61% (1201 – 9000 pg/mL) = (±14 pmol/L (7 – 27 pmol/L), ±52% (28 – 142 pmol/L), ±61% (143 – 1062 pmol/L))*.

*A factor of 0,118 is used for converting the results from pg/mL to pmol/L.

Lot-to-lot variability
Mean value of relative methodical differences between lots should be ≤20%.

3.2. User-friendliness

The evaluation of user-friendliness is carried out by asking the evaluating persons (end-users) to fill in a questionnaire, see section 5.5.

Specifications regarding fraction of technical errors
SKUP recommends that the percentage of "tests wasted" caused by technical errors should not exceed 2%.

3.3. Principles for the assessments

To qualify for en overall good assessment in a SKUP evaluation, the evaluated system must show satisfactory analytical quality as well as satisfactory user-friendliness.

3.3.1. Assessment of the analytical quality

Precision
The precision of NT-proBNP on Cobas h 232 is presented as the coefficient of variation (CV) with confidence interval (CI) at three different concentration levels.
The decision whether the achieved CV fulfils the manufactures specifications or not is made on a 5% significance level. The distinction between the ratings, and the assessment of precision according to the quality specifications, are shown in table 1.

Table 1. The rating of precision

Distinction between the ratings	**Assessment according to the quality specification**
The CV is lower than the quality specification	The quality specification is fulfilled
The CV is lower than the quality specification (not statistically significant)	Data is inconclusive on fulfilling the quality specification. Most likely the quality specification is fulfilled
The CV is higher than the quality specification (not statistically significant)	Data is inconclusive on fulfilling the quality specification. Most likely the quality specification is not fulfilled
The CV is higher than the quality specification	The quality specification is not fulfilled

Accuracy
The accuracy is illustrated in a difference-plot. The fraction of results within limits of ±25% and limits based on the manufacturer's quality specifications is summarised.

3.3.2. Assessment of the user-friendliness

The user-friendliness is assessed according to the answers and comments given in the questionnaire (see section 5.5.). For each question, the evaluators must choose between three given ratings, as for instance satisfactory, intermediate or unsatisfactory. The responses from the evaluators are reviewed and summed up. To achieve the overall rating ”satisfactory”, the tested equipment must reach the total rating of “satisfactory” in all four sub-areas of characteristics mentioned in section 5.5.
The evaluators register the fraction of error codes and technical errors during the evaluation.

3.4. SKUP´s quality goals in this evaluation

Based on the information about biological variations for NT-proBNP, described in section 3.1, specific quality goals for precision or accuracy are not given in this evaluation. The evaluation of NT-proBNP on Cobas h 232 is carried out as a descriptive study. The results are assessed according to the manufacturer’s specifications for CARDIAC proBNP+ for imprecision, accuracy, trueness and lot-to-lot variability. The imprecision of Cobas h 232 is also compared with the given imprecision of the comparison method.

Imprecision
Requirements used in the hospital laboratory.....CV <8%
Specifications from Roche conc. ≤225 pg/mL.....SD ≤34 pg/mL
conc. 226 – 1200 pg/mL.....CV ≤15%
conc. 1201 – 9000 pg/mL.....CV ≤20%

Trueness vs. Elecsys proBNP
Maximum mean relative bias…….....≤±20%

Accuracy vs. Elecsys proBNP
conc. 60 – 225 pg/mL..……..95% of the values within ±117 pg/mL
conc. 226 – 1200 pg/mL.……...95% of the values within ±52%
conc. 1201 – 9000 pg/mL.…….95% of the values within ±61%

Lot-to-lot variability
Mean value of relative methodical differences…….. ≤20%

Fraction of technical errors .....≤2%

User-friendliness .....Satisfactory

4. Materials and methods

4.1. Definition of the NT-proBNP

NT-proBNP is a physiologically inactive fragment which is released when the active hormone BNP is cleaved from its precursor protein proBNP. BNP and NT-proBNP are synthesized mainly in the ventricular myocardium in response to myocardial wall stress. The NT-proBNP has good in vitro stability and is therefore used in diagnosis of acute congestive heart failure.

The International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) and International Union of Pure and Applied Chemistry (IUPAC) work in a joint Committee on Nomenclature, Properties and Units (C-NPU). The descriptions of clinical laboratory tests are listed in the ”NPU database” [5]. In the database the full name is given for the measurand together with which unit the result should be reported in, see table 2. In this report the term “NT-proBNP” will be used for the measurand.

Table 2. Name, code and unit for NT-proBNP tests according to C-NPU

NPU code	Full name of test according to NPU	Short name	Unit
NPU21571	P—Pro-brain natriuretic peptide(1-76); mass concentration	Pro-BNP	ng/L
NPU26811	P—Pro-brain natriuretic peptide(1-76); substance concentration	Pro-BNP	pmol/L

Results for NT-proBNP on Cobas h 232 are given as mass concentration with the unit of pg/mL. The numerical values of these results are the same as the numerical values of results given with the unit ng/L. Results for NT-proBNP of the comparison method, Elecsys proBNP on Modular Analytics E170, are given as substance concentration with the unit pmol/L. All calculations in this report are carried out with results in pmol/L, except for calculation of repeatability on Cobas h 232 (table 6 and 8). A factor of 0,118 is used for converting the results from pg/mL to pmol/L.

4.2. The evaluated measurement system Cobas h 232

The instrument Cobas h 232 (figure 1) is designed for near-patient-testing of cardiac biomarkers and a biomarker for venous thromboembolism. The test for N-terminal prohormone of brain natriuretic peptide (NT-proBNP) on Cobas h 232 is intended as a tool for diagnosing or exclusion of heart failure. The test strips (CARDIAC proBNP+) contains monoclonal and polyclonal antibody against epitopes of the NT-proBNP molecule of which one is gold-labelled and the other biotinylated. Test strips for Troponin T, Creatinin Kinase-muscle and brain polypeptide chains (CK-MB), Myoglobin and D-Dimer are also available. In the test strip detection zone there are two lines; a signal line and a control line. The signal line indicates if the substance is present in the blood sample. The sample material is heparinised venous blood. The optical system of the instrument detects and measures the intensity of the signal line by means of a CMOS-camera sensor (Complementary Metal-Oxide Semiconductor). The control line indicates that the test is valid. The system is automatically calibrated when a test strip is inserted. Each lot of the Roche CARDIAC proBNP+ test strips is calibrated against the Elecsys proBNP test.

Figure 1. Cobas h 232

For technical data about NT-proBNP assay on Cobas h 232, see table 3. For more information about Cobas h 232 POC-system and name of the manufacturer and the suppliers in the Scandinavian countries, see attachment 2 and 3. For product information, see attachment 4.

Table 3. Technical data for NT-proBNP on Cobas h 232

Technical data	Description
Sample material	Heparinised venous whole blood (lithium or sodium heparin)
Sample volume	150 µL
Measuring time	12 minutes
Measuring range	60 – 9000 pg/mL (7 – 1062 pmol/L)
Storage capacity	500 patient test results
Electrical power supply	Specially-designed handheld battery pack or power supply adapter

4.3. The selected comparison method

A selected comparison method is a fully specified method which, in the absence of a Reference method, serves as a common basis for the comparison of a field method.

4.3.1. The selected comparison method in this evaluation

The selected comparison method in this evaluation is the routine method for quantitative determination of NT-proBNP in human serum in the Laboratory for Clinical Biochemistry (LKB) at Haukeland University Hospital. The Elecsys proBNP II-method is implemented on two Modular Analytics E170 instruments from Roche Diagnostics hereafter called "the comparison method on Modular E1 and Modular E5". LKB can document good analytical quality of the method through participation in an external analytical quality assessment program. The method is accredited after NS_EN ISO 15189 (2007).

4.3.2. Verification of the analytical quality of the comparison method

Precision

The analytical component of NT-proBNP is accredited in the measuring range 10 to 4000 pmol/L (85 – 33898 pg/mL). The requested analytical CV is <8%.

Internal quality control

Internal quality control material Seronorm 2 from SERO (target 240 pmol/L) and a proBNP serum pool from approximately 100 hospitalised patients (target 16,4 pmol/L), were analysed daily in the evaluation period.

External Quality Assessment (EQA)

LKB participates in the external analytical assessment program for NT-proBNP from the NKK (Norwegian EQA Program for Medical Biochemistry) / Labquality. Four times a year LKB receives control material in two concentration levels of NT-proBNP. The controls have consensus values based on calculation of results from 50 to 70 participants with analytical systems from Roche.

4.4. The evaluation

4.4.1. Planning of the evaluation

Background for the evaluation

The Cobas h 232 POC system was launched onto the Scandinavian market in 2007. At present there are a few users of the test strip for NT-proBNP in Norway. According to Roche this cardiac biomarker will be an interesting tool for diagnosis and assessment of heart failure in primary health care in the future.

Inquiry about an evaluation

Liv-Janne Øvrebust, Roche Diagnostics Norway AS, applied to SKUP in June 2012 for an evaluation of Cobas h 232. In October 2012 Roche decided that the evaluation should be performed only with the test strip for NT-proBNP. SKUP accepted to carry out this evaluation.

Protocol, arrangements and contract

Roche and SKUP signed a contract for the evaluation in November 2012, and the protocol for the evaluation was approved in December 2012. LKB, Haukeland University Hospital, agreed to do the practical work with the evaluation under standardised and optimal conditions. At the same time three primary health care centres agreed to represent the end-users in this evaluation.

Preparations, training program and practical work

The biomedical laboratory scientist (BLS) Camilla Eide Jacobsen from SKUP started the preparations for the evaluation in October 2012. The Advisory BLS Stein Binder, Noklus, agreed to administrate the practical work with the evaluation in the primary health care centres (PHCC). The equipment for the evaluation was received in January 2013. Shortly after, Liv-Janne Øvrebust from Roche demonstrated the Cobas h 232 system for Camilla and two BLSs from LKB. Afterwards Camilla went through the evaluation procedure and demonstrated the Cobas h 232 system for Stein Binder, and they co-operated in the training of the three PHCC. The practical work was carried out during eight weeks at LKB and at the three PHCC, ending in April 2013.

4.4.2. Evaluation sites and persons involved

LKB, Haukeland University Hospital, has 250 employees of which approximately 150 are BLSs.
PHCC1, Oasen Legesenter, has five physicians, three health secretaries and two medical secretaries.
PHCC2, Fenring Legesenter, has 8 physicians, 7 nurses and one BLS.
PHCC3, Øyrane Legekontor, has four physicians and four health secretaries.

An overview of the persons responsible for the various parts of the evaluation is given in table 4.

Table 4. Persons responsible for various parts of the evaluation

Name	Title	Place	Responsibility
Liv-Janne Øvrebust	Product manager	Roche Diagnostics Norway	Ordered the evaluation
Camilla Eide Jacobsen	BLS Master of Science	SKUP/Noklus	Responsible for the evaluation and statistical calculations, author of the report
Stein Binder	Advisory BLS	Noklus	Guiding and supporting the PHCC
Kristin Haagensen Siw Anette Busk Solveig Haugstad	BLSs	LKB, Haukeland University Hospital	Practical work with the evaluation
Eldbjørg Hunderi Gunn Håvik Gowri Suganthan	Health secretaries	PHCC1 Oasen	Practical work with the evaluation
Randi Lutchen Lehn	BLS	PHCC2 Fenring	Practical work with the evaluation
Jane Eide Marianne Løvgren Elin Thomassen Karina V. Lexander	Nurses		
Lise Torkjell Grethe Teigland Olsnes	Health secretaries	PHCC3 Øyrane	Practical work with the evaluation

4.4.3. The evaluation model

The SKUP evaluation

SKUP evaluations for quantitative methods are based upon the fundamental guidelines in the book "Utprøving av analyseinstrumenter. En veiledning spesielt beregnet for utprøving av instrumenter for primærhelsetjenesten" [6]. The evaluation consists of two parallel parts. One part of the evaluation is carried out under standardised and optimal conditions by laboratory educated personnel in a hospital laboratory. This part documents the quality of the system under conditions as favourable as possible for achieving good analytical quality. The other part of the evaluation is carried out among the end-users in different primary health care centres. This part documents the quality of the system under real-life conditions.

The aim of the evaluation

The evaluation of NT-proBNP on Cobas h 232 comprises the following studies:

- An examination of the repeatability of NT-proBNP on Cobas h 232 achieved with approximately 100 heparinised venous whole blood samples, performed by two BLSs in a hospital environment
- An examination of the repeatability of NT-proBNP on Cobas h 232 achieved with approximately 80 heparinised venous whole blood samples, performed in three primary health care centres
- A comparison of the analytical quality of Cobas h 232 (heparinised whole blood samples) with the comparison method (serum samples) regarding imprecision

- An examination of the accuracy of NT-proBNP by comparing the results from Cobas h 232 (heparinised whole blood samples analysed at LKB and PHCC) with the results from the comparison method at LKB (serum samples), Haukeland University Hospital
- A comparison of the analytical quality of Cobas h 232 with CARDIAC proBNP+ test strips according to the manufactures specifications for imprecision, trueness and accuracy
- An examination of the variation between three lots of test strips
- An evaluation of the user-friendliness of Cobas h 232

Blood sampling
All samples for measurements on Cobas h 232 were collected from hospitalised patients or outpatients who were to take a routine sample for NT-proBNP at the evaluation sites. The heparinised venous whole blood samples were measured in duplicates using one Cobas h 232 instrument and test strips with the same lot number. A special pipette from Roche was used to transfer 150 µL blood from the sample tube to the sample application area at the test strip. In the user's manual a procedure with perforating the cap with the needle holding the sample tube upside down is shown. An alternative method with removing the cap from the sample tube and placing the needle downwards in the tube was presented by Roche as an option in the training session. The measurements were performed within eight hours after sampling, as stated in the method specification.

Handling of samples for the comparison method
The samples for the comparison method were taken before the samples for Cobas h 232. Venous whole blood was collected using gel tubes. The samples were treated according to the procedure at the evaluation sites, and centrifuged for 10 minutes at 1880 g (3000 rpm) within two hours after sampling. Serum was used for the analysing of NT-proBNP on the comparison method at LKB. The measurements of the comparison method were not performed in duplicate.

4.4.4. The evaluation procedure under standardised and optimal conditions

Internal analytical quality control
LKB had two Cobas h 232 instruments and used three lot of test strips. To monitor the quality of the test strips during the evaluation period, the control material Roche CARDIAC Control proBNP level 1 and 2 was used. The instruments were checked by means of the control solutions every second day they were in use; instrument 1 was checked the first day, instrument 2 was checked the second day, instrument 1 was checked the third day and so on. The reconstituted control serum was stored in the freezer at approximately -20°C. Level 1 was used for the first six days, level 2 for the next six days and so on. The reconstituted control serum can be thawed and frozen up to five times in the original vial.

Recruitment of patients
Blood samples were collected from hospitalised patients who should have their NT-proBNP measured routinely. Patients were recruited mostly from the Emergency Department, the Department of Heart Disease and the Department of Medical intensive care.

Handling of specimens and measurements
After the sampling of the routine sample for NT-proBNP (serum gel tube) the patients had one heparinised (sodium) venous whole blood sample taken. The sample for Cobas h 232 was kept at

room temperature and, within one to five hours from sampling, analysed in duplicate on either Cobas h 232 instrument 1 or 2 using one of the three lot numbers of test strips.

Recording of results
All results, together with the patient's gender and age, were registered in a form provided by SKUP and signed by the evaluators. If one of the Cobas h 232 instruments showed an error code while analysing a sample, a new measurement was made. All error codes were recorded.

The precision of Cobas h 232
Repeatability was calculated from the results of approximately 100 heparinised venous blood samples measured in duplicate on Cobas h 232 instrument 1 and 2. Formula 1 in attachment 5 was used for the calculation. The results are divided into three concentration intervals, and the CV is given with a 90% confidence interval.

Comparison of Cobas h 232 versus Modular
The comparison of Cobas h 232 versus Modular was carried out with results from approximately 100 heparinised venous blood samples on the two Cobas h 232 instruments and results from single measurements of serum samples from the comparison method Modular E1.

Evaluation of user-friendliness
After the practical work was completed, the BLSs at LKB evaluated the user-friendliness of Cobas h 232 by means of the questionnaire composed by SKUP, see section 5.5.

4.4.5. Evaluation procedure among the end-users in primary health care

Internal analytical quality control
Each PHCC had one Cobas h 232 instrument and one of the three lots of test strips to their disposal. To monitor the quality of the test strips during the evaluation period, the control material Roche CARDIAC Control proBNP was used. The instrument at PHCC1 and PHCC2 was checked by means of the control solution every third day they were in use. PHCC1 used control level 1 and PHCC2 used control level 2. The reconstituted control serum was stored in the freezer at approximately -20°C. PHCC3 had no access to a freezer and could therefore not analyse the control material during the evaluation period. The Advisory BLS checked the instrument at PCCH3 with control material at the beginning and in the end of the evaluation period.

Recruitment of patients
Each primary health care centre was supposed to recruit 30 patients. Patients, who the physicians ordered to take a NT-proBNP sample, were invited to participate in the evaluation. They were asked if they were willing to give an extra blood sample for measurements on Cobas h 232. Participation was voluntarily, and verbal consent was considered sufficient.

Handling of specimens and measurements
After the sampling of the routine sample for NT-proBNP (serum gel tube) all patients had one heparinised (sodium) venous whole blood sample taken. The sample for Cobas h 232 was kept at room temperature and analysed in duplicate on Cobas h 232 within zero to five hours from sampling.

The samples for the comparison method
The sample for the comparison method (serum gel tube) was treated according to the procedure at the centres, and centrifuged for 10 minutes within two hours after sampling. The centrifuged gel tube was transported to LKB, Haukeland University Hospital, and analysed for NT-proBNP at Modular E1 or E5 the same day they were taken or at the latest the following day. The result from LKB was reported electronically to the centres.

Recording of results
All results, together with the patient's gender and age were registered in a form provided by SKUP and signed by the evaluators. If the Cobas h 232 instrument showed an error code while analysing a sample, a new measurement was made. All error codes were recorded.

The precision of Cobas h 232
Repeatability was calculated from the results of approximately 80 heparinised venous blood samples measured in duplicates on Cobas h 232 at the three PHCC. Formula 1 in attachment 5 was used for the calculation. The results are divided into three concentration intervals, and the CV is given with a 90% confidence interval.

Comparison of Cobas h 232 versus Modular
The comparison of Cobas h 232 versus Modular was carried out with results from approximately 80 heparinised venous blood samples on the Cobas h 232 instruments at PHCC and results from single measurements of serum samples from the comparison method Modular E1 and E5.

Evaluation of user-friendliness
After the practical work was completed, the staff at the three PHCC evaluated the user-friendliness of Cobas h 232 by means of the questionnaire composed by SKUP, see section 5.5.

5. Results and discussion

Statistical expressions and calculations used by SKUP are shown in attachment 5.

5.1. Number of samples

In the hospital evaluation a total of 107 samples for NT-proBNP were collected; 55 heparinised samples were analysed in duplicates on Cobas h 232 instrument 1 and 52 samples on instrument 2. Single measurements of 107 serum samples were made with the comparison method on Modular E1.

In the primary health care evaluation the PHCC1 recruited 33 patients, PHCC2 recruited 30 patients and PHCC3 recruited 32 patients. A total of 95 samples were analysed in duplicates on Cobas h 232 (heparinised venous blood). Two of these samples failed with error codes; ID 2 and 8 at PHCC2. Single measurements of 93 serum samples were made with the comparison method on Modular E1 and Modular E5.

5.1.1. Excluded and missing results

Hospital laboratory

- ID 47 on Cobas h 232 instrument 1 and ID 9 on instrument 2 got both their results outside the measuring range, >9000 and <60 pg/mL, respectively. The results were in accordance with the results of the comparison method and thus, considered correct. However, the results from these two samples are not included in the calculation of repeatability, trueness, accuracy and lot variation.
- Four blood samples measured on Cobas h 232 had one of the duplicate results outside the measuring range (>9000 pg/mL). These four samples are not included in the calculation of repeatability, but the reported single results from the samples are included in the calculation of trueness, accuracy and lot variation.

Primary health care centres

- Seven blood samples got both results over the upper measuring range (>9000 pg/mL), and six samples got both results below the lower measuring range (<60 pg/mL) on Cobas h 232. The results were in accordance with the results of the comparison method for 12 of these 13 samples and thus, considered correct. However, these 13 samples are not included in the calculation of repeatability, trueness, accuracy and lot variation.
- Two samples measured on Cobas h 232 had one of the duplicate results outside the measuring range; one sample with a result <60 pg/mL and one sample with a result >9000 pg/mL. These two samples are excluded from the calculation of repeatability, but the reported single results are included in the calculation of trueness, accuracy and lot variation.
- ID 11 at PHCC2 was classified as an outlier according to Burnett's model in the calculation of repeatability on Cobas h 232 and was removed before calculation of trueness and lot variation, but was included in the calculation of accuracy.
- ID 8 at PHCC1 was classified as an outlier according to Burnett's model in the calculation of trueness on Cobas h 232 and was removed before calculation of lot variation, but was included in the calculation of accuracy.

5.1.2. Failed measurements

The BLSs performed 107x2 measurements on Cobas h 232 and no error codes were registered. The primary health care centres performed 95x2 measurements on Cobas h 232, and two samples (four measurements) failed with error codes E402 (test strip faulty) and E403 (dosing error).

Total fraction of technical errors was: (4/404) x 100 = 1,0%

Conclusion

The quality goal for fraction of technical errors <2% was fulfilled for Cobas h 232.

5.2. Analytical quality of the selected comparison method

5.2.1. Internal quality control

In daily operation of the comparison method, the analytical quality of NT-proBNP is monitored with the internal quality control Seronorm 2 (target 249 pmol/L) and a serum pool (target 16,4 pmol/L). All control results from the evaluation period were inside the limits of the target values for the controls. The raw data is not shown.

5.2.2. The precision of the comparison method

Modular E1 was used to analyse all samples from the hospital laboratory. For analysing the samples from the three primary health care centres, both Modular E1 and Modular E5 were used.

Repeatability

Separate imprecision studies for the comparison method on Modular E1 and E5 were not performed in this evaluation. LKB documents a CV <8%.

Reproducibility

The reproducibility of the comparison method is shown in table 5.

Table 5. Reproducibility of the comparison method

Instrument	Control	n	Mean NT-proBNP (pmol/L)	CV (90% CI) %
Modular E1	Serum pool	68	15,8	3,9 (3,4 – 4,6)
	Seronorm 2	65	242,3	3,8 (3,3 – 4,5)
Modular E5	Serum pool	67	16,2	3,1 (2,7 – 3,6)
	Seronorm 2	79	241,6	3,6 (3,2 – 4,1)

Discussion

In the evaluation period the reproducibility CV achieved with internal quality control material was <4% for both Modular E1 and E5. The result fulfils the imprecision CV <8% documented by LKB.

5.2.3. The trueness of the comparison method

There is no standard reference material to verify the trueness of methods for determination of NT-proBNP in human serum. LKB participates in the external analytical assessment program for NT-proBNP from NKK/Labquality. During the period from November 2012 to February 2013 the comparison method at LKB showed a bias from -8% to +4% compared to the consensus values from the entire group of Roche systems (n = 50 – 70).

5.3. Analytical quality of Cobas h 232 in a hospital laboratory

5.3.1. Internal quality control

The two Cobas h 232 instruments used by the BLSs were checked with the manufacturer's control solution Roche CARDIAC Control proBNP level 1 and 2 every second day they were used. The test strips have lot-specific target values for the controls. The reproducibility CV for level 1 was <10% for all three lots of test strips, and between 8% and 17% for level 2. All results were within the control range given by Roche. Raw data is shown in attachment 6.

5.3.2. Comparison of the 1st and 2nd measurement

One venous heparinised sample was taken of each person for duplicate measurements on Cobas h 232. For the calculation of imprecision, all results have been checked to meet the imposed condition for using formula 1 in attachment 5. There were no systematic differences pointed out between the paired measurements (data not shown).

5.3.3. The precision of Cobas h 232

Repeatability under standardised and optimal conditions in a hospital laboratory

The repeatability of Cobas h 232 obtained by the BLSs with venous heparinised blood samples, is shown in table 6. The results from Cobas h 232 instrument 1 and 2 are combined, sorted and divided into three concentration intervals of NT-proBNP according to the mean of the duplicate measurements on Cobas h 232. Raw data is shown in attachment 7.

Table 6. Repeatability, NT-proBNP on Cobas h 232. Results achieved in the hospital laboratory

NT-proBNP interval Cobas h 232, pg/mL	n	Excluded results	Mean value NT-proBNP, pg/mL (pmol/L)	CV (90% CI) %
71 – 550	34	0	274 (32)	9,5 (7,9 – 11,9)
551 – 2111	33	0	1079 (127)	8,5 (7,1 – 10,7)
2112 – 7842	34	0	4315 (509)	10,7 (8,9 – 13,5)

In addition two samples on Cobas h 232 got both their results outside the measuring range >9000 and <60 pg/mL, respectively.

Discussion

The repeatability CV for NT-proBNP on Cobas h 232, obtained under standardised and optimal conditions at LKB, was approximately 10%. The achieved precision was better than the manufactures quality specifications. Compared to the documented imprecision of the comparison method (<8%), Cobas h 232 showed significantly higher CV than the comparison method for NT-proBNP concentrations ≥2112 pg/mL (250 pmol/L).

The reproducibility CV achieved with internal quality control material from Roche was <10% for level 1 and between 8% and 17% for level 2.

5.3.4. The trueness of Cobas h 232

The mean deviation (bias) of NT-proBNP on Cobas h 232 instrument 1 and 2 from the comparison method was calculated from the results achieved in the hospital laboratory with three lots of test strips. The results are combined, sorted and divided into three concentration intervals of NT-proBNP according to the results of the comparison method on Modular E1. The trueness of Cobas h 232 is shown in table 7. Raw data from the comparison method is shown in attachment 7.

Table 7. Trueness, NT-proBNP on Cobas h 232. Results achieved in the hospital laboratory

NT-proBNP interval Comparison method, pmol/L	n	Excluded results	Mean value Comparison method, pmol/L	Mean value Cobas h 232, pmol/L	Bias (95% CI), pmol/L	Bias, %
9 – 65	33	0	31,7	32,2	0,5 ((–1,9) – (+3,0))	1,7
66 – 250	39	0	138,7	148,4	9,7 ((–2,8) – (+22,2))	7,0
251 - 1357	33	0	620,4	590,3	–30,1 ((–73,3) – (+13,1))	–4,9

In addition two samples on Cobas h 232 got both their results outside the measuring range >9000 and <60 pg/mL, respectively. The results were in accordance with the results of the comparison method, and considered correct.

Discussion

NT-proBNP on Cobas h 232 showed results in agreement with the comparison method. No significant bias was pointed out.

5.3.5. The accuracy of Cobas h 232

To evaluate the accuracy of NT-proBNP results on Cobas h 232, the agreement between Cobas h 232 and the comparison method on Modular E1 is illustrated in two accuracy plots. The plots show the deviation of single measurement results on Cobas h 232 from the comparison method, and give a picture of both random and systematic deviation, reflecting the total measuring error on Cobas h 232. The accuracy is demonstrated for the first measurement of the paired results, only.

The accuracy of NT-proBNP on Cobas h 232, with three lots of test strips, under standardised and optimal measuring conditions is shown for the entire concentration range in figure 2. Figure 3 shows the same results as figure 2, highlighting the concentrations up to 300 pmol/L. The results for the three lots of test strips are illustrated with different symbols in the plots. Deviation limits given by the manufacturer are shown in the plots as intact lines. Deviation limits of ±25%, based on calculation with values partly obtained in this evaluation using the formula in section 3.1, are shown in the plots as stippled lines.

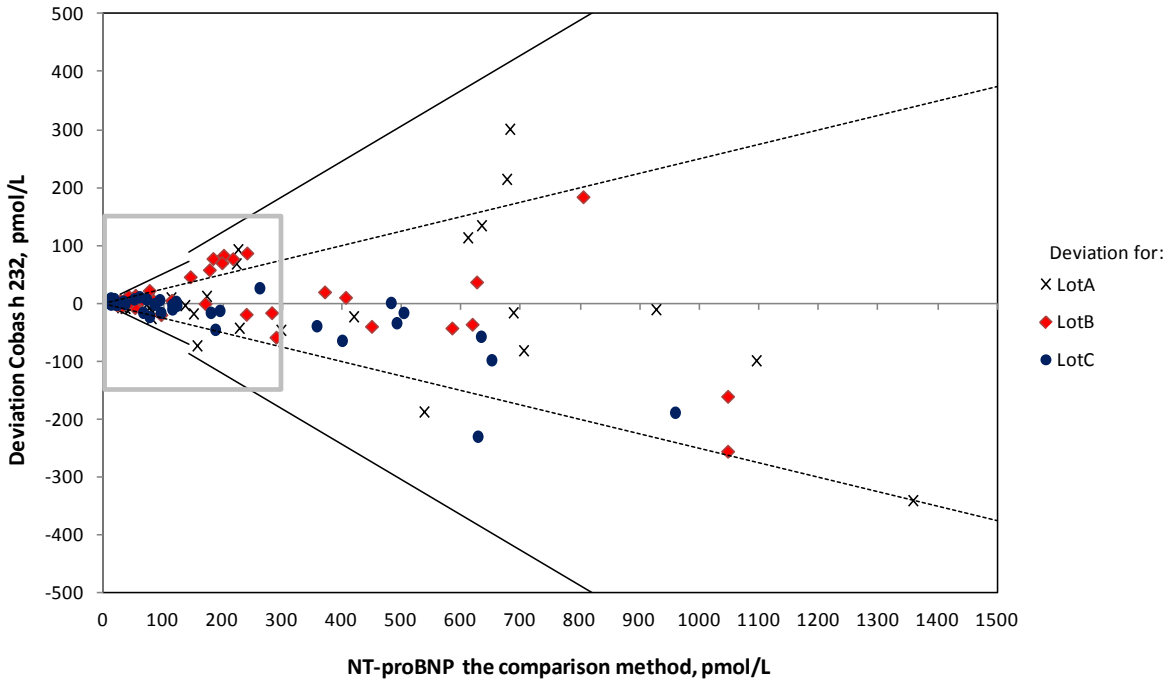

Figure 2. Accuracy. NT-proBNP on Cobas h 232 (three lots of test strips) under standardised and optimal measuring conditions in a hospital laboratory. The x-axis represents the result of the comparison method on Modular. The y-axis shows the difference between the first measurement on Cobas h 232 and the result on the comparison method. The deviation for Cobas h 232 lot A is represented with the symbol ×, lot B with ◆ and lot C with ●. Intact lines represent deviation limits given by the manufacturer (±14 pmol/L (7 – 27 pmol/L), ±52% (28 – 142 pmol/L), ±61% (143 – 1062 pmol/L)). Stippled lines represent deviation limits of ±25%, calculated by SKUP. n = 105.
The area marked with a square in grey is enlarged and shown in figure 3.

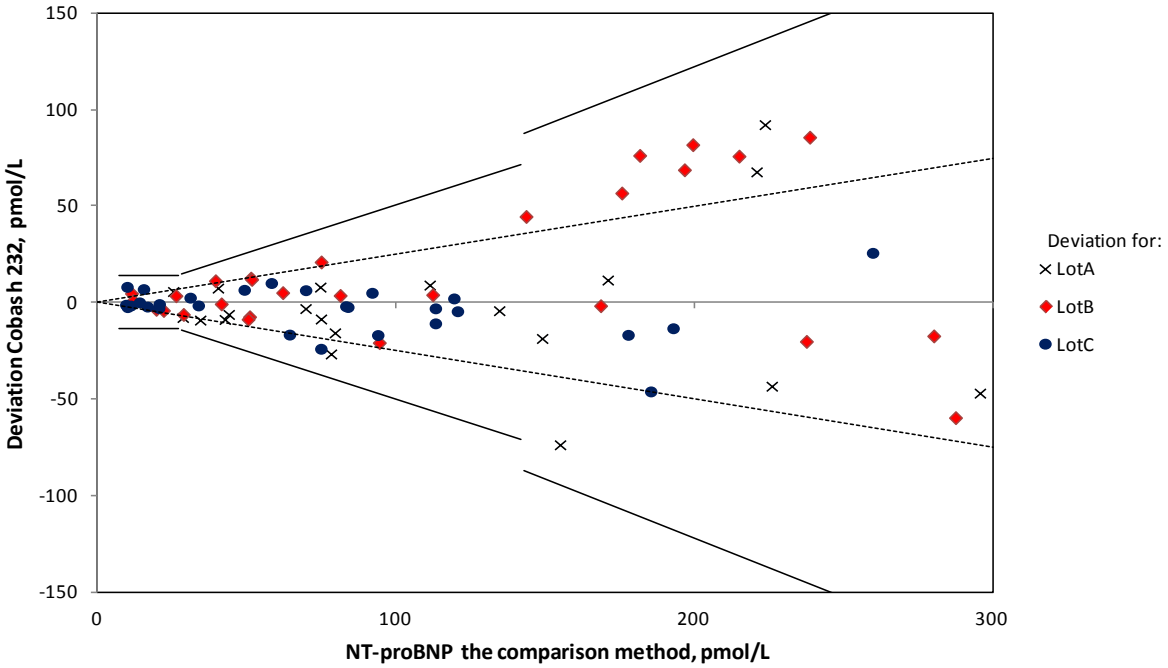

Figure 3. Accuracy. NT-proBNP on Cobas h 232 (three lots of test strips) under standardised and optimal measuring conditions in a hospital laboratory. The x-axis represents the result of the comparison method on Modular in the range 0 – 300 pmol/L. The y-axis shows the difference between the first measurement on Cobas h 232 and the result of the comparison method. The deviation for Cobas h 232 lot A is represented with the symbol ×, lot B with ◆ and lot C with ●. Intact lines represent deviation limits given by the manufacturer (±14 pmol/L (7 – 27 pmol/L), ±52% (28 – 142 pmol/L), ±61% (143 – 1062 pmol/L)). Stippled lines represent deviation limits of ±25%, calculated by SKUP.

Discussion

Figure 2 and 3 show that 100% of the results obtained by the BLSs were within the manufacture's quality specifications for accuracy. These specifications have wide limits for accuracy. 75% of the results were inside the deviation limits of ±25% calculated partly using the values for imprecision and bias obtained in the evaluation. Table 8 shows the number of results within fixed limits of ±30% and ±20% as well. These results are for information only. In addition two samples on Cobas h 232 got both results outside the measuring range >9000 and <60 pg/mL, respectively. The results were in accordance with the results of the comparison method and thus, considered correct.

Table 8. Accuracy of NT-proBNP on Cobas h 232

Measurements performed by	**n**	**Number of results (%) within the limits**		
		±30%	**±25%**	**±20%**
LKB	105	82	75	68

Cobas h 232 instrument 1 and 2, used in the hospital evaluation, gave results in agreement with each other (data not shown).

5.3.6. Variation between three lots of test strips for NT-proBNP

The measurements on Cobas h 232 instrument 1 and 2 were performed with three different lots of test strips from three productions. Figure 2 and 3 in section 5.3.5 show that there is no distinct difference in the results from the three lots of test strips used in the evaluation. The three lots of test strips seem to be in agreement. Separate lot calculations are not shown.

5.4. Analytical quality of Cobas h 232 in primary health care

5.4.1. Internal quality control

The Cobas h 232 instruments used by PHCC1 and PHCC2 were checked with one level of the manufacturer's control solution Roche CARDIAC Control proBNP every third day they were used. PHCC3 had no access to a freezer and could not analyse the control material during the evaluation period. The instrument at PCCH3 was therefore only checked with control material at the beginning and in the end of the evaluation period. All results from PHCC were within the control range given by Roche. Raw data is shown in attachment 8.

5.4.2. Comparison of the 1st and 2nd measurement

One venous heparinised sample was taken of each person for duplicate measurements on Cobas h 232. For the calculation of imprecision, all results have been checked to meet the imposed condition for using formula 1 in attachment 5. There were no systematic differences pointed out between the paired measurements (data not shown).

5.4.3. The precision of Cobas h 232

Repeatability achieved at three primary health care centres

The repeatability of Cobas h 232 obtained at three primary health care centres with venous heparinised blood samples is shown in table 9. The results from three Cobas h 232 instruments are combined, sorted and divided into three concentration intervals of NT-proBNP according to the mean of the duplicate measurements on Cobas h 232. Raw data is shown in attachment 9.

Table 9. Repeatability, NT-proBNP on Cobas h 232. Results achieved in three primary health care centres

NT-proBNP interval Cobas h 232, pg/mL	n	Excluded results	Mean value NT-proBNP, pg/mL (pmol/L)	CV (90% CI) %
70 – 550	30	0	235 (28)	5,9 (4,9 – 7,6)
551 – 2111	25	0	1034 (122)	5,3 (4,3 – 7,0)
2112 – 6954	23	1*	3570 (421)	10,0 (8,0 – 13,5)

The given numbers of results (n) are counted before exclusion of outliers. Mean and CV are calculated after exclusion of outliers. In addition 13 samples on Cobas h 232 got both their results outside the measuring range, >9000 or <60 pg/mL.

*One statistical outlier (ID 11 at PHCC2) according to Burnett's model.

Discussion

The repeatability CV for NT-proBNP on Cobas h 232, obtained by the three primary health care centres, was <6% for concentrations <2112 pg/mL (250 pmol/L) and 10% for concentrations ≥2112 pg/mL. The achieved precision was better than the manufacturer's quality specifications.

The primary health care centres achieved significantly better repeatability for NT-proBNP concentrations <2112 pg/mL compared to the hospital laboratory. This is an unexpected finding. The pre-analytical procedure and the measurement procedure probably are less standardised at PHCC than in the hospital laboratory. In PHCC more persons were involved in the practical work with the evaluation and three Cobas h 232 instruments were used.

The major difference between the evaluation performed at the hospital and at PHCC is the procedure for drawing of blood from the sample tube using the Cardiac pipette. PHCC followed the user's manual and perforated the cap with the needle holding the sample tube upside down. The BLSs at LKB had problems with this technique, and chose the alternative method removing the cap from the sample tube and placing the needle downwards in the tube. The occupational group working in PHCC seems more familiar with the "upside down" drawing technique then the BLSs.

There is no calculation of reproducibility because of few internal quality results from PHCC and different target values for the three lots of test strips.

5.4.4. The trueness of Cobas h 232 in primary health care

The mean deviation (bias) of NT-proBNP on Cobas h 232 from the comparison method was calculated from the results achieved by three primary health care centres with three lots of test strips on three Cobas h 232 instruments. The results are combined, sorted and divided into three concentration intervals of NT-proBNP according to the results of the comparison method on Modular E1 and E5. The trueness of Cobas h 232 is shown in table 10. Raw data from the comparison method is shown in attachment 9.

Table 10. Trueness, NT-proBNP on Cobas h 232. Results achieved in three primary health care centres

NT-proBNP interval Comparison method, pmol/L	n	Excluded results	Mean value Comparison method, pmol/L	Mean value Cobas h 232, pmol/L	Bias (95% CI), pmol/L	Bias, %
2 – 65	35	0	27,7	32,5	4,8 ((+2,3) – (+7,3))	17,3
66 – 250	26	0	128,0	158,3	30,3 ((+16,3) – (+44,3))	23,7
251 – 1029	18	1*	418,5	478,5	59,9 ((+26,9) – (+93,0))	14,3

The given numbers of results (n) are counted before exclusion of outliers. Mean and bias are calculated after exclusion of outliers. In addition 13 samples on Cobas h 232 got both their results outside the measuring range, >9000 or <60 pg/mL. 12 of these results were in accordance with the results of the comparison method, and are considered correct.
*One statistical outlier (ID 8 at PHCC1) according to Burnett's model.

Discussion

In primary health care Cobas h 232 showed significantly higher NT-proBNP results than the comparison method in all three concentration intervals. The bias was between 14% and 24%. This bias was unexpected because the Cobas h 232 results from LKB were in agreement with the comparison method. The differences in bias between results from LKB and PHCC can be due to the stability of NT-proBNP concentration in either the heparinised sample tube or the gel tube for serum samples.

The PHCC analysed the heparinised sample tube on Cobas h 232 within zero to five hours after sampling. LKB analysed the Cobas h 232 samples within one to five hours after sampling. All evaluation sites have mixed the samples before analysing both of the duplicates. Roche states that

the heparinised sample for analysis of NT-proBNP is stable for eight hours after sampling. All evaluation sites have stored the test strips in 2 – 8°C, as stated in the test strip insert.
The serum gel tube from PHCC were transported to the hospital laboratory and analysed on either Modular E1 or E5 the same day the samples were taken or within the next day. LKB reports a stability of NT-proBNP in serum for three days at room temperature or six days if the samples are stored in a refrigerator. LKB has performed experiments with stability in cooled samples, while the information about stability at room temperature is reported from Roche [7]. According to the given information about the NT-proBNP sample stability, the bias that arose cannot be explained by this. Further investigations are necessary.

5.4.5. The accuracy of Cobas h 232 in primary health care

To evaluate the accuracy of NT-proBNP results on Cobas h 232 in primary health care, the agreement between Cobas h 232 and the comparison method on Modular E1 and E5 is illustrated in two accuracy plots. The plots show the deviation of single measurement results on Cobas h 232 from the comparison method, and give a picture of both random and systematic deviation, reflecting the total measuring error on Cobas h 232. The accuracy is demonstrated for the first measurement of the paired results, only.

The accuracy of the NT-proBNP on Cobas h 232, at three primary health care centres with three lots of test strips, is shown for the entire concentration range in figure 4. Figure 5 shows the same results as figure 4, highlighting the concentrations up to 300 pmol/L. Deviation results for the three primary health care centres (three lots of test strips) are illustrated with different symbols in the plots. Deviation limits given by the manufacturer are shown in the plots as intact lines. Deviation limits of ±25%, based on calculation with values partly obtained in this evaluation using formula in section 3.1, are shown in the plots as stippled lines.

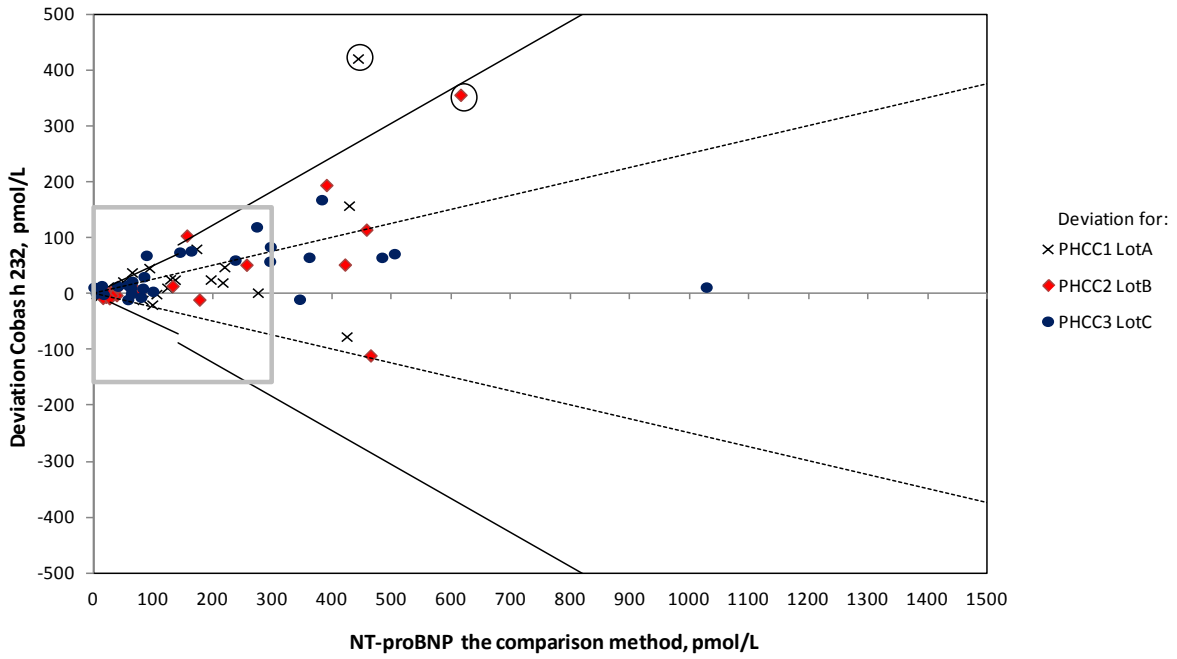

Figure 4. Accuracy. NT-proBNP on Cobas h 232 (three lots of test strips) in three primary health care centres. The x-axis represents the result of the comparison method on Modular. The y-axis shows the difference between the first measurement on Cobas h 232 and the result of the comparison method. The deviation for Cobas h 232 at PHCC1 (lot A) is represented with the symbol ×, PHCC2 (lot B) with ◆ and PHCC3 (lot C) with ●. Intact lines represent deviation limits given by the manufacturer (±14 pmol/L (7 – 27 pmol/L), ±52% (28 – 142 pmol/L), ±61% (143 – 1062 pmol/L)). Stippled lines represent deviation limits of ±25%, calculated by SKUP. ID 11 at PHCC2 and ID 8 at PHCC1, statistical outliers from the calculation of repeatability and trueness, respectively, are represented with a circle around the symbols. n = 80.
The area marked with a square in grey is enlarged and shown in figure 5.

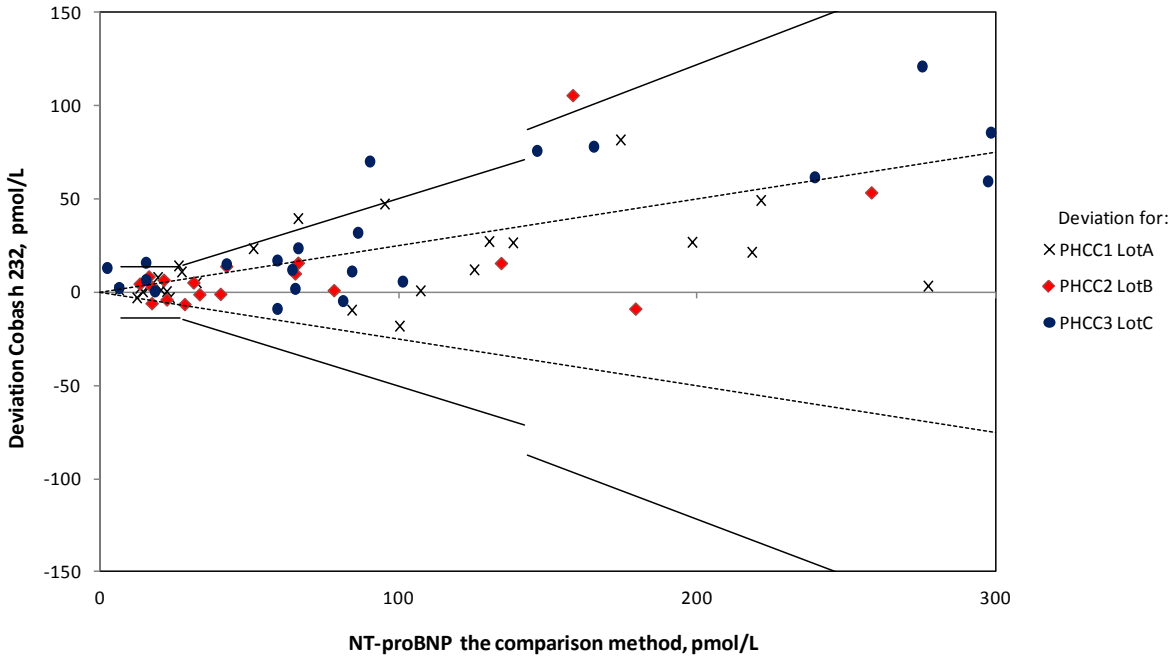

Figure 5. Accuracy. NT-proBNP on Cobas h 232 (three lots of test strips) in three primary health care centres. The x-axis represents the result of the comparison method on Modular in the range 0 – 300 pmol/L. The y-axis shows the difference between the first measurement on Cobas h 232 and the result of the comparison method. The deviation for Cobas h 232 at PHCC1 (lot A) is represented with the symbol ×, PHCC2 (lot B) with ◆ and PHCC3 (lot C) with ●. Intact lines represent deviation limits given by the manufacturer (±14 pmol/L (7 – 27 pmol/L), ±52% (28 – 142 pmol/L), ±61% (143 – 1062 pmol/L)). Stippled lines represent deviation limits of ±25%, calculated by SKUP.

Discussion

In figure 4 and 5, five out of 80 results (6%) obtained by the PHCC were outside the manufacturer's quality specifications for accuracy. These specifications have wide limits for accuracy. 58% of the results were inside the deviation limits of ±25% calculated partly using the values for imprecision and bias obtained in the evaluation. Table 11 shows the number of results within fixed limits of ±30% and ±20% as well. These results are for information only. In addition 13 samples on Cobas h 232 got both their results outside the measuring range, >9000 or <60 pg/mL. 12 of these results were in accordance with the results of the comparison method and thus, are considered correct.

Table 11. Accuracy of NT-proBNP on Cobas h 232

Measurements performed by	**n**	**Number of results (%) within the limits**		
		±30%	**±25%**	**±20%**
PHCC	80	64	58	39

5.4.6. Variation between three lots of test strips for NT-proBNP

The measurements on Cobas h 232 in three primary health care centres were performed with three different lots of test strips from three productions; one lot at each centre. The results from the three lots of test strips seem to be in agreement. Separate lot calculations are not shown.

5.5. Evaluation of user-friendliness

5.5.1. Questionnaire to the evaluators

The most important response regarding user-friendliness comes from the users themselves. The end-users often emphasize other aspects than those pointed out by more extensively trained laboratory personnel.

At the end of the evaluation period, the persons at the evaluation sites cooperated to fill in the questionnaire about the user-friendliness of the instrument. The questionnaire is divided into four sub-areas:

- Rating of the information in the manual
- Rating of time factors for the measurement and preparation
- Rating of quality control possibilities (rated only by SKUP)
- Rating of operation facilities

The questionnaire and the expressed opinions are presented in tables 10 to 13. The first column shows what is up for consideration. The second column shows the rating by the users at the evaluation sites. The third to fifth column show the rating options. Coloured frames mark the cells with the overall ratings from all evaluating sites. The last row in each table summarises the total rating in the table. The total rating is an overall assessment of the described property, and not necessarily the arithmetic mean of the rating in the rows. Consequently, a single poor rating can justify an overall poor rating, if this property seriously influences on the user-friendliness of the system.
Unsatisfactory and intermediate ratings will be marked with an asterisk and explained below the table.

Comment
In this evaluation, the user-friendliness was assessed by four evaluation sites; three primary health care centres and one hospital laboratory in the rating order PHCC, PHCC, PHCC and LKB.

Table 10. Assessment of the information in the manual

Information in the manual	**Ratings**	**Red**	**Yellow**	**Green**
General impression	G,Y[1],G	Unsatisfactory	**Intermediate**	**Satisfactory**
Table of contents	G,G,G	Unsatisfactory	Intermediate	**Satisfactory**
Preparations / Pre-analytic procedure	G,G,G	Unsatisfactory	Intermediate	**Satisfactory**
Specimen collection	G,G,-	Unsatisfactory	Intermediate	**Satisfactory**
Measurement / Reading	G,G,G	Unsatisfactory	Intermediate	**Satisfactory**
Measurement principle (rated by SKUP)	G	Unsatisfactory	Intermediate	**Satisfactory**
Sources of error	G,G,R[2]	**Unsatisfactory**	Intermediate	**Satisfactory**
Fault-tracing / Troubleshooting	G,Y[3],Y[3]	Unsatisfactory	**Intermediate**	**Satisfactory**
Keyword index	G,G,G	Unsatisfactory	Intermediate	**Satisfactory**
Readability / Clarity of presentation	G,Y[4],G	Unsatisfactory	**Intermediate**	**Satisfactory**
Available insert in Danish, Norwegian, Swedish (rated by SKUP)	G	Unsatisfactory	Intermediate	**Satisfactory**
Others comments about information in the manual (please specify)	-	Unsatisfactory	Intermediate	Satisfactory
Rating for the information in the manual			Intermediate	**Satisfactory**

PHCC1 did not rate the manual.

[1]The size of the manual is too large. Comments from SKUP: The evaluation sites received the manual printed in A4 format as a copy of the original manual in A5 format
[2]We have observed error message that is not described
[3]There is no chapter in the manual regarding explanation of error codes
[4]The size of the text in the manual is too small

Table 11. Assessment of time factors

Time factors	**Ratings**	**Red**	**Yellow**	**Green**
Time for preparations / Pre-analytical time	G,G,G,G	>10 min	6 to 10 min.	**<6 min.**
Analysis time	Y,Y,Y[1],Y	>20 min	**10 to 20 min**.	<10 min.
Required training time	G,G,G,G	>8 hours	2 to 8 hours	**<2 hours**
Stability of test, unopened package (rated by SKUP)	R[2]/G[2]	**<3 months**	3 to 5 months	**>5 months**
Stability of test, opened package (rated by SKUP)	R[3]	**<14 days**	14 to30 days	>30 days
Other comments about time factors, please specify (rated by SKUP)		Unsatisfactory	Intermediate	Satisfactory
Rating of time factors			**Intermediate**	Satisfactory

[1]The analysis time of 12 minutes is regarded as long, but the space of time can be used for other tasks
[2]The test strips must be stored in the refrigerator to be stable until the printed expiration date. In room temperature the stability of the test strip unopened is up to one week
[3]The test must be used within 15 minutes once the pouch has been opened

Negative comments
The results disappear too fast from the Cobas display.

Table 12. Assessment of quality control possibilities (rated by SKUP)

Quality control	**Ratings**	**Red**	**Yellow**	**Green**
Internal quality control	G	Unsatisfactory	Intermediate	**Satisfactory**
External quality control	G	Unsatisfactory	Intermediate	**Satisfactory**
Stability of quality control material, unopened	G	<3 months	3 to5 months	**>5 months**
Stability of quality control material, opened	R[1]/G[1]	**≤1 day**	2 to 6 days	**>6 days or disposable**
Storage conditions for quality control materials, unopened	Y	–20°C	**+2 to +8°C**	+15 to +30°C
Storage conditions for quality control materials, opened	R[1]/G[1]	**–20°C**	+2 to +8°C	**+15 to +30°C**
Usefulness of the quality control	Y[2]	Unsatisfactory	**Intermediate**	Satisfactory
Other comments about quality control (please specify)		Unsatisfactory	Intermediate	Satisfactory
Rating of quality control			**Intermediate**	

[1]Stability of the components in reconstituted control serum is 12 weeks at ≤ -20 °C and only 24 hours at 2-25°C. The reconstituted control serum can be frozen up to 5 times in the original vial
[2]The control material has different matrix than the patient samples. The reproducibility CV of the control material level 2 was between 8% and 17% in this evaluation

Table 13. Assessment of the operation facilities

Operation facilities	**Ratings**	**Red**	**Yellow**	**Green**
To prepare the test / instrument	G,G,G,G	Unsatisfactory	Intermediate	**Satisfactory**
To prepare the sample	G,G,G,R[1]	**Unsatisfactory**	Intermediate	**Satisfactory**
Application of specimen	Y[2],Y[2],G,Y[3]	Unsatisfactory	**Intermediate**	**Satisfactory**
Specimen volume	G,Y[4],G,G	Unsatisfactory	**Intermediate**	**Satisfactory**
Number of procedure step	G,G,G,G	Unsatisfactory	Intermediate	**Satisfactory**
Instrument / test design	G,G,G,Y[3-4]	Unsatisfactory	**Intermediate**	**Satisfactory**
Reading of the test result	G,Y[5],G,Y[6]	Difficult	**Intermediate**	**Easy**
Sources of errors	G,Y[7],G,G	Unsatisfactory	**Intermediate**	**Satisfactory**
Cleaning / Maintenance	G,G,G,G	Unsatisfactory	Intermediate	**Satisfactory**
Hygiene, when using the test	G,G,G,Y[1]	Unsatisfactory	**Intermediate**	**Satisfactory**
Storage conditions for tests, unopened package (rated by SKUP)	Y	–20°C	**+2 to +8°C**	+15 to +30°C
Storage conditions for tests, opened package (rated by SKUP)	G	–20°C	+2 to +8°C	**+15 to +30°C**
Environmental aspects: waste handling	Y[8],Y[8],Y[8],Y	Special precautions	**Sorted waste**	No precautions
Intended users (rated by SKUP)	Y[9]	Biomedical laboratory scientists	**Laboratory experienced**	GP personnel or patients
Size and weight of package	G,G,G,G	Unsatisfactory	Intermediate	**Satisfactory**
Other comments about operation facilities (please specify)	-	Unsatisfactory	Intermediate	Satisfactory
Rating of operation			**Intermediate**	**Satisfactory**

[1]Risk to injure oneself on the needle when using the Cardiac pipette
[2]Difficult to avoid air bubbles in the Cardiac pipette when drawing blood from the sample tube
[3]The time for the blood to be absorbed at the application area on the test strip was a little long
[4]Sample volume of 150 µL is a bit too much

[5]The results disappear to fast from the Cobas display
[6]Some numbers in the display were difficult to differentiate
[7]There is no explanation for error codes
[8]The pipette must be discarded as special precautions because of the needle
[9]Some laboratory experience can be an advantage because of the sampling technique and the handling of the Cardiac pipette

Positive comments
You don't have to remove the cap from the sample tube to absorb the blood sample into the pipette because the pipette has a needle.

Negative comments
One of the primary health care centres thought the Cobas h 232 instrument was a bit too big and the measuring range was restricted.
The instrument did not always register the test strip at first attempt.

5.5.2. Assessment of the user-friendliness

Assessment of the information in the manual (table 10)
The information in the manual is assessed as satisfactory despite of the comments from the evaluation sites about the fact that there is no explanation of error codes in the manual. The manual has a chapter concerning troubleshooting. This chapter describes how the instrument continually checks the system for unexpected and unwanted conditions. A message appears in the display as a status message or an error message. The system gives a description of the error and a possible solution.

Assessment of time factors (table 11)
The time factors are assessed as intermediate due to the 12 minutes analysis time, and the fact that the test strips must be stored in the refrigerator to be stable for more than one week and have to be used within 15 minutes once the pouch has been opened.

Assessment of quality control possibilities (table 12)
The quality control possibilities are assessed as intermediate. To gain stability for the internal control material for more than 24 hours the users must have access to a freezer of -20°C. Not all primary health care centres have a freezer or have enough space to install a freezer. The control material is an aqueous solution and has different matrix than the patient samples.

Assessment of the operation facilities (table 13)
The operation facilities are assessed as both satisfactory and intermediate. It is a potential risk to injure oneself on the Cardiac pipette because of the needle. In addition, the pipette must be handled as special precautions. It was difficult to avoid air bubbles when drawing blood from the sample tube using the pipette. To operate the Cobas h 232 system it can be an advantage to have some laboratory experience because of the sampling technique with use of the Cardiac pipette. The test strips must be stored in a refrigerator. The results disappear too fast from the Cobas display. This cannot be adjusted by the operator.

6. References

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3. Apple FS, Panteghini M, Ravkilde J *et al*. Quality Specifications for B-Type Natriuretic Peptide Assays. Clin Chem 2005; 51(3): 486-493.
4. Clerico A, Zucchelli GC, Pilo A *et al*. Clinical relevance of biological variation: the lesson of brain natriuretic peptide (BNP) and NT-proBNP assay. Clin Chem Lab Med 2006; 44(4): 366-378.
5. http://www.ifcc.org/ifcc-scientific-division/sd-committees/c-npu/npusearch/
6. Christensen N.G, Monsen G, Sandberg S. *Utprøving av analyseinstrumenter*. 1997: Alma Mater Forlag.
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The organisation of SKUP

Scandinavian evaluation of laboratory equipment for primary health care, *SKUP*, is a co-operative commitment of Noklus[1] in Norway, DAK-E[2] in Denmark, and Equalis[3] in Sweden. SKUP was established in 1997 at the initiative of laboratory medicine professionals in the three countries. SKUP is led by a Scandinavian *steering committee* and the secretariat is located at Noklus in Bergen, Norway.

The purpose of SKUP is to improve the quality of near patient testing in Scandinavia by providing objective and supplier-independent information on analytical quality and user-friendliness of laboratory equipment. This information is generated by organising SKUP *evaluations*.

SKUP offers manufacturers and suppliers evaluations of equipment for primary health care and also of devices for self-monitoring. Provided the equipment is not launched onto the Scandinavian market, it is possible to have a confidential pre-marketing evaluation. The company requesting the evaluation pays the actual testing costs and receives in return an impartial evaluation.

There are *general guidelines* for all SKUP evaluations and for each evaluation a specific *SKUP protocol* is worked out in co-operation with the manufacturer or their representatives. SKUP signs *contracts* with the requesting company and the evaluating laboratories. A *complete evaluation* requires one part performed by experienced laboratory personnel as well as one part performed by the intended users.

Each evaluation is presented in a *SKUP report* to which a unique *report code* is assigned. The code is composed of the acronym SKUP, the year and a serial number. A report code, followed by an asterisk (*), indicates a special evaluation, not complete according to the guidelines, e.g. the part performed by the intended users was not included in the protocol. If suppliers use the SKUP name in marketing, they have to refer to www.skup.nu and to the report code in question. For this purpose the company can use a logotype available from SKUP containing the report code.

SKUP reports are published at www.skup.nu.

[1] Noklus (Norwegian Quality Improvement of Primary Care Laboratories) is an organisation founded by Kvalitetsforbedringsfond III (Quality Improvement Fund III), which is established by The Norwegian Medical Association and the Norwegian Government. Noklus is professionally linked to “Seksjon for Allmennmedisin” (Section for General Practice) at the University of Bergen, Norway.

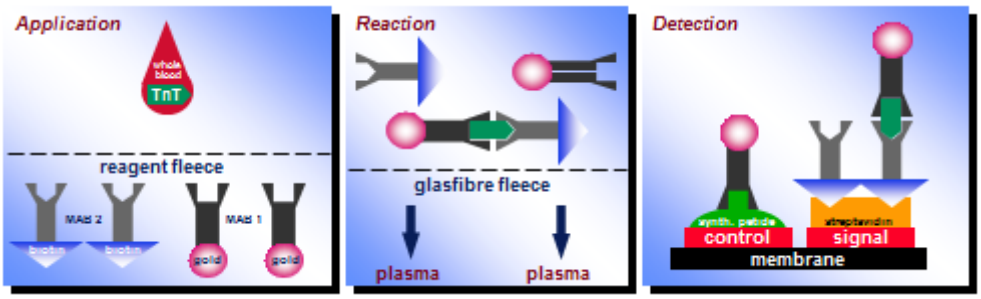
[2] SKUP in Denmark is placed in Hillerød Hospital. SKUP in Denmark reports to DAK-E (Danish Quality Unit of General Practice), an organisation that is supported by KIF (Foundation for Quality and Informatics) and Faglig udvalg (Professional Committee), which both are supported by DR (The Danish Regions) and PLO (The Organisation of General Practitioners in Denmark).

[3] Equalis AB (External quality assurance in laboratory medicine in Sweden) is a limited company in Uppsala, Sweden, owned by “Sveriges Kommuner och Landsting” (Swedish Association of Local Authorities and Regions), “Svenska Läkaresällskapet” (Swedish Society of Medicine) and IBL (Swedish Institute of Biomedical Laboratory Science).

Facts about the Cobas h 232 POC system

Parts of this form are filled in by Roche Diagnostics Norway AS.

Table 1. Basic facts

Name of the measurement system:	Roche Cobas h 232 system
Dimensions and weight:	Width: 102 mm Length: 275 mm Height: 55 mm Weight: 650 g (incl. battery pack)
Components of the measurement system:	Meter, test strips, code chip, handheld battery pack, handheld base unit, AC/DC adapter
Measurand:	NT-proBNP (also available: Troponin T, D-dimer, Myoglobin, CK-MB)
Sample material:	Heparinised whole blood
Sample volume:	150 µL
Measuring principle:	 Immunological (“double sandwich” principle with antibodies labeled with gold and biotin). Optical detection (CMOS camera sensor).
Traceability:	Calibrated against Elecsys proBNP, which is standardized against reference standards by weighing pure synthetic NT-proBNP (1-76 amino acids) into equine serum matrix
Calibration:	Calibration done via code key with the lot specific data
Measuring range:	60-9000 pg/mL
Linearity:	60-9000 pg/mL
Measurement duration:	12 minutes
Operating conditions:	Operating temp.: +18°C - +32°C. Humidity: 10-85%
Electrical power supply:	100V – 240V (+/- 10%), 50/60 Hz. AC/DC adapter or rechargeable battery pack
Recommended regular maintenance:	None except cleaning
Package contents:	Instrument, power supply, user manual (ENG), CD-ROM with user manual for other languages)

Necessary equipment not included in the package:	• Pipette (150 µL) • Optional: Rechargeable battery pack • Optional: Base unit

Table 2. Post analytical traceability

Is input of patient identification possible?	Yes, via integrated barcode reader or via touch screen
Is input of operator identification possible?	Yes, via integrated barcode reader or via touch screen
Can the instrument be connected to a bar-code reader?	Integrated barcode reader
Can the instrument be connected to a printer?	Yes
What can be printed?	Results, time/date, IDs, comments
Can the instrument be connected to a PC?	Yes, directly or via data management system (e.g Cobas IT 1000)
Can the instrument communicate with LIS (Laboratory Information System)? If yes, is the communication bidirectional?	Yes, bidirectional communication possible
What is the storage capacity of the instrument and what is stored in the instrument?	500 results with time/date and comments. In addition is up to 200 code key-files stored
Is it possible to trace/search for measurement results?	Yes

Table 3. Facts about the reagent/test strips/test cassettes

Name of the reagent/test strips/test cassettes:	Roche Cardiac proBNP test strip
Stability in unopened sealed vial:	18 months (+2°C - +8°C)
Stability for opened test strip pouch:	15 minutes
Package contents:	10 single packed test strips, code key, packet inserts

Table 4. Quality control

Electronic self check:	Yes
Recommended control materials and volume:	150 µL Roche Cardiac Control proBNP
Stability in unopened sealed vial:	18 months (+2°C - +8°C)
Stability in opened vial:	After reconstitution: • 24 h at +2°C - +25°C • 12 weeks at -20°C (can be frozen up to 5 times in original bottle)
Package contents:	4 bottles of freeze dried serum (2 level I, 2 level II), code key with lot specific target values, packet inserts

Information about manufacturer, retailers and marketing

Table 1. Marketing information

Manufacturer:	Roche Diagnostics GmbH Sandhofer Strasse 116 68305 Mannheim, Germany
Retailers in Scandinavia:	Denmark: Roche Diagnostics Denmark A/S Industriholmen 59 2650 Hvidovre-Copenhagen Norway: Roche Diagnostics Norway AS Postboks 6610 Etterstad 0607 Oslo Sweden: Roche Diagnostics Sweden AB Karlsbodavägen 30 Box 147 SE-16126 Bromma
In which countries is the system marketed:	Globally X Scandinavia ☐ Europe ☐
Date for start of marketing the system in Scandinavia:	2007
Date for CE-marking:	15. Feb. 2007
In which Scandinavian languages is the manual available:	All

Product information, Cobas h 232

SKUP/2013/97

Cobas h 232 serial numbers

Instrument	Serial number	Used by
Cobas h 232 (called instrument 1)	0211803	LKB
Cobas h 232 (called instrument 2)	0211867	LKB
Cobas h 232 (called instrument 3)	0211871	PHCC1 (Oasen)
Cobas h 232 (called instrument 4)	0211846	PHCC2 (Fenring)
Cobas h 232 (called instrument 5)	0211823	PHCC3 (Øyrane)

NT-proBNP test strips

Roche CARDIAC proBNP+ test strips	Lot number	Expiry date	Used by
Test strips lot A	28138715	2013-06	LKB, PHCC1
Test strips lot B	28142315	2013-08	LKB, PHCC2
Test strips lot C	28130215	2013-06	LKB, PHCC3

Other equipment used in the evaluation

Other equipment	Lot number	Expiry date	Used by
Roche CARDIAC Control proBNP	169 921-02	2013-11	LKB (level 1+2) PHCC1 (level 1) PHCC2 (level 2)
Roche CARDIAC pipettes 150 µL	70095543	2017-10	All evaluation sites
4 mL Sodium Heparin tubes, Vacuette Greiner Bio-One (used for Cobas h 232)	A120501Q	2013-11	PHCC
	A121104X	2014-05	LKB
4 mL serum Gel tubes, Vacuette Greiner Bio-One	Used for Modular Analytics E170	2014-04 2014-05	LKB, PHCC

Statistical expressions and calculations

This chapter with standardised text deals with the statistical expressions and calculations used by SKUP. The chapter is a short extract of the comprehensive SKUP-document "Statistics in SKUP reports", presented at www.skup.nu**,** under the option "The SKUP evaluation". The statistical calculations will change according to the type of evaluation. The descriptions in section 4.2 are valid for evaluations of quantitative methods with results on the ratio scale.

Statistical terms and expressions

The definitions in this section come from the ISO/IEC Guide 99; International Vocabulary of Metrology, VIM [a].

Precision

Definition: Precision is the closeness of agreement between measured quantity values obtained by replicate measurements on the same or similar objects under stated specified conditions.

Precision is measured as *imprecision*. Precision is descriptive in general terms (good, poor e.g.), whereas the imprecision is expressed by means of the standard deviation (SD) or coefficient of variation (CV). SD is reported in the same unit as the analytical result. CV is usually reported in percent.

To be able to interpret an assessment of precision, the precision conditions must be defined.
Repeatability is the precision of consecutive measurements of the same component carried out under identical measuring conditions (within the measuring series).
Reproducibility is the precision of discontinuous measurements of the same component carried out under changing measuring conditions over time.

Trueness

Definition: Trueness is the closeness of agreement between the average of an infinite number of replicate measured quantity values and a reference quantity value.

Trueness is inversely related to systematic measurement error. Trueness is measured as *bias*. Trueness is descriptive in general terms (good, poor e.g.), whereas the bias is reported in the same unit as the analytical result or in percent.

Accuracy

Definition: Accuracy is the closeness of agreement between a measured quantity value and the true quantity value of a measurand.

Accuracy is not a quantity and cannot be expressed numerically. A measurement is said to be more accurate when it offers a smaller measurement error. Accuracy can be illustrated in a difference-plot. Accuracy is descriptive in general terms (good, poor e.g.).

a. ISO/IEC Guide 99:2007, International vocabulary of metrology – Basic and general concepts and associated terms, VIM, 3rd edition, JCGM 200:2008

Statistical calculations

Statistical outliers

The criterion promoted by Burnett [b] is used for the detection of outliers. The model takes into consideration the number of observations together with the statistical significance level for the test. The significance level is set to 5%. The segregation of outliers is made with repeated truncations, and all results are checked. Where the results are classified according to different concentration levels, the outlier-testing is carried out at each level separately. Statistical outliers are excluded from the calculations.

Calculation of imprecision

The precision of the field method is assessed by use of paired measurements of genuine patient sample material. The results are divided into three concentration levels, and the estimate of imprecision is calculated for each level separately, using the following formula [c,d]:

$$SD = \sqrt{\frac{\sum d^2}{2n}}$$

d = difference between two paired measurements
n = number of differences

(formula 1)

This formula is used when the standard deviation can be assumed reasonable constant across the concentration interval. If the coefficient of variation is more constant across the concentration interval, the following formula is preferred:

$$CV = \sqrt{\frac{\sum (d/m)^2}{2n}}$$

m = mean of paired measurements

(formula 2)

The two formulas are based on the differences between paired measurements. The calculated standard deviation or CV is still a measure of the imprecision of single values. The imposed condition for using the formulas is that there is no systematic difference between the 1st and the 2nd measurement of the pairs. The CV is given with a 90% confidence interval.

Calculation of bias

The mean deviation (bias) at different concentration levels is calculated based on results achieved under optimal measuring conditions. A paired t-test is used with the mean values of the duplicate results of the comparison method and the mean values of the duplicate results on the field method. The mean difference is shown with a 95% confidence interval.

Assessment of accuracy

The agreement between the field method and the comparison method is illustrated in a difference-plot. The x-axis represents the mean value of the duplicate results of the comparison method. The y-axis shows the difference between the first measurement on the field method and the mean value of the duplicate results of the comparison method. The number of results within the quality goal limits is counted and assessed.

b. Burnett RW, "*Accurate Estimation of Standard Deviations for Quantitative Methods Used in Clinical Chemistry*". Clinical Chemistry 1975; **21** (13): 1935 – 1938
c. Saunders, E. Tietz textbook of clinical chemistry and molecular diagnostics. 2006. Chapter 14, Linnet, K., Boyd, J. "*Selection and analytical evaluation of methods – with statistical techniques*", ISBN 0-7216-0189-8
d. Fraser, C.G, Biological variation: *From principles to practice*. 2006. Chapter 1 "*The Nature of Biological Variation*". AACC Press. ISBN 1-890883-49-2

Raw data NT-proBNP, internal quality control, Cobas h 232 in a hospital laboratory

Roche CARDIAC Control proBNP	Lot-no	Expiry	Roche CARDIAC porBNP+ test strips	Target value NT-proBNP, pg/mL
Level 1	169 921-02	2013-11	28138715 (lot A)	108 (62 – 154)
			28142315 (lot B)	110 (61 – 159)
			28130215 (lot C)	146 (73 – 218)
Level 2			28138715 (lot A)	684 (342 – 1025)
			28142315 (lot B)	760 (380 – 1139)
			28130215 (lot C)	903 (451 – 1354)

Control Solution analysed on the biomedical laboratory scientists' instrument 1 and 2

Date	Roche CARDIAC Control proBNP Level 1, pg/mL		
	Lot-no	Value	Instrument
22.jan	a	95	1
28.jan	a	102	1
04.feb	b	118	1
11.feb	b	95	1
15.feb	c	133	1
19.feb	c	139	1
21.feb	c	147	1
05.mar	a	104	1
13.mar	a	92	1
19.mar	b	103	1
22.jan	a	90	2
28.jan	a	113	2
01.feb	b	106	2
06.feb	b	114	2
08.feb	b	108	2
11.feb	b	105	2
22.feb	c	168	2
04.mar	c	147	2
05.mar	a	114	2
19.mar	b	93	2

Date	Roche CARDIAC Control proBNP Level 2, pg/mL		
	Lot-no	Value	Instrument
23.jan	a	676	1
29.jan	a	647	1
31.jan	b	746	1
05.feb	b	688	1
07.feb	b	813	1
12.feb	b	733	1
18.feb	c	509	1
27.feb	c	832	1
01.mar	c	798	1
12.mar	a	534	1
20.mar	b	688	1
24.jan	a	607	2
30.jan	a	570	2
04.feb	b	705	2
14.feb	b	599	2
	c	838	2
20.feb	c	895	2
28.feb	c	818	2
12.mar	a	563	2
18.mar	a	575	2
21.jan	c	901	2

Raw data NT-proBNP, internal quality control, Cobas h 232 in primary health care

Roche CARDIAC Control proBNP	Lot-no	Expiry	Roche CARDIAC porBNP+ test strips	Target value NT-proBNP, pg/mL
Level 1	169 921-02	2013-11	28138715 (lot A)	108 (62 – 154)
			28142315 (lot B)	110 (61 – 159)
			28130215 (lot C)	146 (73 – 218)
Level 2			28138715 (lot A)	684 (342 – 1025)
			28142315 (lot B)	760 (380 – 1139)
			28130215 (lot C)	903 (451 – 1354)

Control Solution analysed at three primary health care centres

Date	Roche CARDIAC Control proBNP Level 1, pg/mL		
	Lot-no	Value	PHCC
30/1	a	110	1
7/2	a	98	1
13/2	a	120	1
25/2	a	125	1
6/3	a	108	1
12/3	a	108	1
21/3	c	135	3
2/3	c	129	3

Date	Roche CARDIAC Control proBNP Level 2, pg/mL		
	Lot-no	Value	PHCC
30/1	b	671	2
11/2	b	740	2
18/2	b	602	2
6/3	b	763	2
12/3	b	782	2
22/3	b	850	2
29/1	c	918	3

SKUP-info

Cobas h 232 POC system fra Roche Diagnostics,
et instrument for måling av spesifikke hjerte- og tromboemboliske markører.
Sammendrag fra en utprøving av NT-proBNP i regi av SKUP.

Konklusjon
Måling av NT-proBNP på Cobas h 232 viste en upresishet på mellom 5 % og 10 % og oppfyller produsentens spesifikasjon for CV ≤ 15 %. Prøvene som ble analysert på Cobas h 232 på sykehuset ga resultat som samsvarte med sykehusets rutinemetode. Det var derfor uventet at det ble funnet et avvik på ca. 20 % mellom NT-proBNP resultat fra Cobas h 232 i primærhelsetjenesten (heparinblod) og serumprøvene som ble sendt inn til analysering på sykehusets rutinemetode. Dette avviket kan på nåværende tidspunkt ikke forklares. Holdbarheten på serumprøver til NT-proBNP skal undersøkes nærmere. Brukervennligheten var akseptabel.

Cobas h 232 er et instrument for kvantitativ bestemmelse av ulike spesifikke hjerte- og tromboemboliske markører; Troponin T, D-Dimer, NT-proBNP, CK-MB og Myoglobin. Instrumentet benytter teststrimler til engangsbruk. Teststrimlene kalibreres automatisk. Prøvemateriale er heparinisert venøst fullblod. Prøvevolum er 150 µL. Analysetid er 8 eller 12 minutter avhengig av hvilken komponent som analyseres. Cobas h 232 kan lagre 500 resultater.

Utprøvingen ble utført under optimale betingelser i et sykehuslaboratorium og på tre legekontor i primærhelsetjenesten. Det ble tatt blodprøver av 107 personer på sykehuset og 95 personer på de tre legekontorene. NT-proBNP- resultat fra Cobas h 232 (heparinblod) ble sammenlignet med rutinemetoden for måling av NT-proBNP i sykehuset (serum). Serumprøvene tatt på sykehuset ble analysert på rutinemetoden kort tid etter prøvetaking. Serumprøvene fra primærhelsetjenesten ble sendt til sykehuset og analysert på sykehusets rutinemetode innen to døgn etter prøvetaking (oppgitt holdbarhet er tre døgn).

Resultater. Analysen viste en upresishet på ca. 10 % når målingene ble utført av bioingeniører på sykehuslaboratoriet, og ca. 5 % på målinger utført av brukerne i primærhelsetjenesten. Prøvene som ble analysert på Cobas h 232 på sykehuslaboratoriet, ga resultat som samsvarte med serumprøver analysert på laboratoriets rutinemetode. Da serumprøvene fra primærhelsetjenesten ble analysert på sykehuslaboratoriet, fremkom en forskjell mellom laboratoriets rutinemetode og Cobas-resultater i primærhelsetjenesten på 14 til 24 %. Så langt er det ikke funnet en forklaring på denne forskjellen. Holdbarheten på serumprøver til NT-proBNP, som skal transporteres fra primærhelsetjenesten til sykehuslaboratoriet, skal undersøkes nærmere.

Brukervennlighet. Brukerne var fornøyde med brukermanualen. Brukervennligheten til instrumentet ble oppsummert som akseptabel. Brukerne hadde kommentarer til at analysetiden på 12 minutter var lang. Teststrimlene må oppbevares i kjøleskap. Oppløst internt kvalitetskontrollmateriale kan brukes flere ganger hvis den oppbevares i –20 °C. CARDIAC pipetten, som benyttes for å suge opp prøvematerialet fra prøveglasset, har en nål som utgjør en risiko for stikkskade.

Tilleggsinformasjon. Den fullstendige rapporten fra utprøvingen av NT-proBNP på Cobas h 232, SKUP/2013/97, finnes på SKUPs nettside www.skup.nu. Opplysninger om pris fås ved å kontakte leverandør. Laboratoriekonsulentene i Noklus kan gi råd om analysering av NT-proBNP på legekontor. De kan også orientere om det som finnes av alternative metoder/utstyr.

List of previous SKUP evaluations

Summaries and complete reports from the evaluations are found at www.skup.nu. In addition, SKUP reports are published at www.skup.dk, where they are rated according to the national Danish quality demands for near patient instruments used in primary health care. SKUP summaries are translated into Italian by Centre for Metrological Traceability in Laboratory Medicine (CIRME), and published at http://users.unimi.it/cirme. SKUP as an organisation has no responsibility for publications of SKUP results on these two web-sites.

Recent SKUP evaluations

Evaluation no.	Component	Instrument/testkit	Producer
SKUP/2013/97	NT-proBNP	Cobas h 232 POC system	Roche Diagnostics GmbH
SKUP/2013/99*	Glucose	Accu-Chek Mobile	Roche Diagnostics
SKUP/2013/98*	Glucose	Accu-Chek Aviva	Roche Diagnostics
SKUP/2013/96	Haemoglobin	DiaSpect Hemoglobin T	DiaSpect Medical GmbH
SKUP/2012/95	Glucose[1]	Mendor Discreet	Mendor Oy
SKUP/2012/94	Glucose[1]	Contour XT	Bayer HealthCare
SKUP/2011/93*	Glucose	Accu-Chek Performa	Roche Diagnostics
SKUP/2013/92	CRP	Eurolyser smart 700/340 CRP	Eurolyser Diagnostica GmbH
SKUP/2012/91	HbA1c	Quo-Test A1c	Quoient Diagnostics Ltd
SKUP/2011/90	CRP	*i*-Chroma	BodiTech Med. Inc.
SKUP/2010/89*	Glucose	FreeStyle Lite	Abbott Laboratories
SKUP/2010/88*	HbA1c	*Confidential*	
SKUP/2011/86	Glucose[1]	OneTouch Verio	LifeScan, Johnson & Johnson
SKUP/2013/85	Glucose	StatStrip	Nova Biomedical
SKUP/2011/84*	PT-INR	Simple Simon PT and MixxoCap	Zafena AB
SKUP/2010/83*	Glucose	*Confidential*	
SKUP/2010/82*	Glucose, protein, blood, leukocytes, nitrite	Medi-Test URYXXON Stick 10 urine test strip and URYXXON Relax urine analyser	Macherey-Nagel GmBH & Co. KG
SKUP/2010/81*	Glucose	mylife PURA	Bionime Corporation
SKUP/2010/80	PT (INR)	INRatio2	Alere Inc.
SKUP/2010/79*	Glucose, protein, blood, leukocytes, nitrite	CombiScreen 5SYS Plus urine test strip and CombiScan 100 urine analyser	Analyticon Biotechnologies AG
SKUP/2010/78	HbA1c	In2it	Bio-Rad
SKUP/2011/77	CRP	*Confidential*	
SKUP/2009/76*	HbA1c	*Confidential*	
SKUP/2009/75	Glucose	Contour	Bayer HealthCare
SKUP/2009/74	Glucose[1]	Accu-Chek Mobile	Roche Diagnostics
SKUP/2010/73	Leukocytes	HemoCue WBC	HemoCue AB
SKUP/2008/72	Glucose[1]	*Confidential*	
SKUP/2009/71	Glucose[1]	GlucoMen LX	A. Menarini Diagnostics
SKUP/2011/70*	CRP	smartCRP system	Eurolyser Diagnostica GmbH
SKUP/2008/69*	Strep A	Diaquick Strep A test	Dialab GmbH
SKUP/2013/68	Allergens	ImmunoCap Rapid	Phadia AB
SKUP/2010/67	Allergens	*Confidential*	
SKUP/2008/66	Glucose[1]	DANA DiabeCare IISG	SOOIL Developement co. Ltd
SKUP/2008/65	HbA1c	Afinion HbA1c	Axis-Shield PoC AS
SKUP/2007/64	Glucose[1]	FreeStyle Lite	Abbott Laboratories
SKUP/2007/63	Glucose[1]	*Confidential*	
SKUP/2007/62*	Strep A	QuikRead	Orion Diagnostica Oy
SKUP/2008/61	CRP	i-CHROMA	BodiTech Med. Inc.

*A report code followed by an asterisk indicates evaluations at special request from the supplier, or evaluations that are not complete according to SKUP guidelines, e.g. the part performed by the intended users was not included in the protocol.
[1] Including a user-evaluation among diabetes patient.

SKUP
Box 6165
5892 Bergen

Oslo, 28.08.2013

Roche Professional Diagnostics response to the

"Report from the evaluation SKUP/2013/97 of NT-proBNP on cobas h 232".

This is a very professional report describing the Roche **cobas h** 232 point of care system and NT-proBNP assay in a proper and correct way.

Comparing the NT-proBNP test results from the two **cobas h** 232 Point of Care systems in the Hospital environment with the Roche Lab system showed clear alignment between the tests as specified in the product documentation.

Also for the primary health care settings most of the results were within the specifications, and the very good precision at these three sites showed that the users performed the tests as good as in the hospital setting. The bias between the **cobas h** 232 results from the primary health care sites and the results from the samples sent to the hospital laboratory, was unexpected and difficult to explain. There were a couple of minor differences in the pre-analytical phase, but the main difference was only the transport of the samples to the lab, and the time before they were analyzed on the Roche Lab system.

After the final report was done, the remaining test materials from the evaluation were used to do some additional testing. The results showed that there was no difference between the 5 instruments and they all also showed alignment with the test results from the Lab system (the same reference method as in the evaluation was used).

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This supports that the minor differences in the pre-analytical phase, the time and the transportation has influenced the bias in some way in the pre-hospital setup. Roche has not been able to identify this influence more exactly.

The Cardiac pipette which was used in the evaluation is now redesigned to meet EU needlestick safety legislation. The new version was available from August 2013.

Best regards,

Roche Diagnostics International Ltd.

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