ACCU-CHEK® Aviva

A meter designed for glucose self-measurement manufactured by Roche

Report from an evaluation organised by

SKUP

The evaluation was ordered by Roche Diagnostics Norge AS

SKUP/2005/44

SKUP in Norway, NOKLUS, Division of General Practice, University of Bergen, 5009 Bergen, www.SKUP.nu

Summary

Background
Accu-Chek Aviva is a meter designed for glucose self-measurements by diabetic patients. The meter is produced by Roche and is supplied in Scandinavia by Roche Diagnostics. Accu-Chek Aviva has not been launched onto the Norwegian market yet.

In order to give reimbursement for the test strips, The National Social Insurance Office (*Rikstrygdeverket*) in Norway instructs the companies to carry out an evaluation that includes a user-evaluation among diabetic patients. The evaluation of Accu-Chek Aviva is done under the direction of SKUP during the spring of 2005.

The aim of the evaluation
The aim of the evaluation of Accu-Chek Aviva is to

- reflect the analytical quality under standardised and optimal conditions (performed by two biomedical laboratory scientists)
- reflect the analytical quality by the users (79 diabetics)
- compare the analytical quality among diabetics with and without training
- compare the analytical quality among diabetics before and after three weeks of practise
- check the variations between three lots of test strips
- examine if hematocrit interferes with the measurements
- evaluate Accu-Chek Aviva regarding user-friendliness
- evaluate the Accu-Chek Aviva user-manual

Materials and methods
79 diabetic patients took part in the evaluation. 40 participants had two consultations (the "training group") and 39 participants had one consultation (the "postgroup"). At the first consultation the "training group" was given a standardised instruction about the Accu-Chek Aviva before they did a finger prick and performed two measurements on the meter. The biomedical laboratory scientist also took capillary samples of the diabetic patients and measured twice at Accu-Chek Aviva. In addition, two capillary samples were taken to a designated comparison method. The "postgroup" received Accu-Chek Aviva by post and no training was given. Both groups of diabetics carried out a practice period of approximately three weeks at home, before they were called for a final consultation. The blood glucose sampling and measurement procedures at the first consultation were repeated, and in addition a sample for hematocrit was taken. Three different lots of test strips were used in the evaluation. All the participants finally answered questionnaires about the user-friendliness and the user-manual of Accu-Chek Aviva.

Results

- Accu-Chek Aviva shows acceptable precision. The CV is < 5 % under standardised and optimal measuring conditions and approximately 5 % when the measurements are performed by diabetic patients.
- The agreement with a designated comparison method is good. Quality goals set in ISO 15197 are achieved under standardised and optimal measuring conditions. When handled by the diabetic patients, Accu-Chek Aviva also shows good results. 97 % of these results

are within the "adjusted ISO-goal" and 96 % are also within the quality goals set in ISO 15197.
- Two of the three lots of test strips that were used showed significantly higher values then the comparison method. The measured differences have no clinical importance.
- Glucose measurements on Accu-Chek Aviva do not seem to be affected by hematocrit values between 28 – 49 %. Hematocrit outside this range has not been tested.
- The diabetic patients summarise the Accu-Chek Aviva device as easy to use. As a whole they were pleased with the device. The patients that had used the user manual were satisfied with the manual.

Conclusion

Glucose measurements on Accu-Chek Aviva have acceptable precision. The results obtained under standardised and optimal measuring conditions are within the quality goals set in the ISO-guide 15197. The measurements performed by the diabetic patients are also within the ISO-goal. The glucose results in this evaluation are not affected by hematocrit. The users say that the Accu-Chek Aviva device is easy to use and they are quite satisfied with the device.

USER-EVALUATION
ACCU-CHEK AVIVA Blood Glucose Meter System

Table of contents

Attachments with raw data are included only in the copy to Roche Diagnostics.

1. The organisation of SKUP

Scandinavian evaluation of laboratory equipment for primary health care, SKUP, is a cooperative venture by Norway, Sweden and Denmark. SKUP was established in the autumn of 1997 at the initiative of professionals and health authorities in the three countries. SKUP is led by a Scandinavian expert group. The secretariat is located at NOKLUS Centre in Bergen, Norway.

The goal of SKUP is to produce objective and independent information concerning the quality and user-friendliness of laboratory equipment for physicians' offices outside the hospital. This information is generated by organizing SKUP's own evaluation program.

The SKUP evaluation is standardised according to SKUP's general evaluation guidelines. The evaluation follows a protocol based on these guidelines, but the protocol is always adjusted to the actual evaluation in cooperation with the supplier. The SKUP evaluation consists of two comparable parts. One part of the evaluation is done under standardised and optimal measuring conditions and the other part is performed by the users the equipment is produced for. Primarily, SKUP evaluates equipment intended for the primary health care, but SKUP can also offer evaluations of equipment for self monitoring blood glucose (SMBG). The evaluations of SMBG are conducted under standardised and optimal conditions and among diabetic patients.

SKUP personnel are financed with funds from their respective countries, while the actual testing is funded by the equipment suppliers. For suppliers this offers an opportunity to have their equipment subjected to standardised testing all over Scandinavia. For consumers it means easy access to objective information on equipment, and health care authorities will be able to gain an overview of the equipment (and its quality) available on the market at any given time.

SKUP distributes information about evaluated equipment to physicians' offices, laboratory medical councils, laboratory advisors and health political authorities. The evaluation reports are presented at www.skup.nu.

A unique evaluation code number is assigned to every SKUP evaluation report. The code is composed of the name SKUP, and the year and number of the evaluation. This applies for all evaluations following the complete SKUP standard evaluation procedure. Pre marketing evaluations, evaluations without the user's contribution, supplementary evaluations and special evaluations on request from the producer/supplier are in addition marked with a star in connection to the evaluation number. If the company makes use of SKUP's name in the marketing of an instrument, they have to refer to www.skup.nu and the actual evaluation number at the same time. If required, the company can get access to a SKUP logo where this information is an integral part.

2. Planning of the evaluation

Mette Engebretsen from Roche, Norway, applied to SKUP in the autumn of 2004 for an evaluation of the glucose meter Accu-Chek Aviva. In October 2004 SKUP gave a written offer, and in Mars 2005 a preliminary suggestion regarding how to organise the evaluation was sent. The protocol for the evaluation of Accu-Chek Aviva was accepted by Roche in April 2005. A contract was set up between Roche and SKUP in June 2005. The Laboratory at Haraldsplass Diaconal Hospital (HDH) accepted to carry out the analytical part of the evaluation dealing with the reference samples.

The Accu-Chek Aviva system was launched onto the Norwegian market in july 2005. SKUP carried out the user-evaluation of Accu-Chek Aviva blood glucose meter system during the spring of 2005.

SKUP evaluations are made according to guidelines in the book "*Evaluation of analytical instruments. A guide particularly designed for evaluations of instruments in primary health care*" (Christensen, Monsen et al. 1997) [1]. The evaluation of a self-monitoring blood glucose device follows the guidelines in the book, but the evaluation in primary health care is replaced by a user-evaluation conducted among diabetics, based on the model by the NOKLUS-project "*Diabetes-Self-measurements*" [2].

The evaluation comprises the following studies:

- An examination of analytical quality under standardised and optimal conditions done by two biomedical laboratory scientists
- An examination of analytical quality amongst approximately 80 diabetics
- An examination of agreement between Accu-Chek Aviva and a designated comparison method
- A comparison of analytical quality among diabetics with and without training programme
- A comparison of analytical quality among diabetics before and after three weeks of practise
- An examination of variation between three lots of test strips
- An examination to see if hematocrit interferes with the measurements
- An evaluation of user-friendliness of Accu-Chek Aviva
- An evaluation of the user-manual of Accu-Chek Aviva

The blood sampling of the diabetics and the measurements on Accu-Chek Aviva under standardised and optimal conditions, were done by Ingunn Barli and Tone C. Hovelsen, biomedical laboratory scientists, SKUP/NOKLUS central Norway, Levanger Hospital. Two biomedical laboratory scientists, Wenche Eilifsen Hauge and Kjersti Østrem, were given the responsibility for the practical work with the comparison method at the Laboratory at HDH. The statistical calculations and the report writing are done by Camilla Eide Jacobsen, SKUP/NOKLUS Centre.

3. Analytical quality specifications

There are different criteria for setting quality specifications for analytical methods. Ideally the quality goals should be set according to the medical demands the method has to meet. For glucose it is natural that the quality specification is set according to whether the analysis is used for diagnostic purpose or for monitoring diabetes. Accu-Chek Aviva is designed for monitoring blood glucose, and the quality goals must be set according to this.

Precision
For glucose meters designed for monitoring blood glucose one should point out the need of a method with good precision [3]. According to the American Diabetes Association (ADA) the imprecision of new glucose devices must be less than 5 % [4]. Other authors also recommend an imprecision of 5 % or less [5].

Accuracy
According to ADA the total error for meters designed for self monitoring and point of care testing of glucose should not exceed 10 % in the range 1,67 – 22,2 mmol/L. The quality goal from ADA must be seen as an optimal goal for the analytical quality of these meters.

The quality goal for the total error of Accu-Chek Aviva is found in ISO 15197, in vitro diagnostic test systems – Requirements for blood-glucose monitoring systems for self-testing in managing diabetes mellitus [6]. The ISO-guide is an international protocol for evaluating meters designed for glucose monitoring systems.

ISO 15197 gives the following minimum acceptable accuracy requirement:

Ninety-five percent (95 %) of the individual glucose results shall fall within ± 0,83 mmol/L of the results of the comparison method at glucose concentrations < 4,2 mmol/L and within ± 20 % at glucose concentrations ≥ 4,2 mmol/L.

This is a quality goal for measurements by trained laboratory staff. Ideally, the same quality requirement should apply for measurements by the diabetics. Previous investigations under the direction of the NOKLUS-project ”Diabetes-Self-measurements” [5,7], and results from evaluations under the direction of SKUP, have showed that few of the self-monitoring glucose meters that were tested met the ISO-requirements. The results by the diabetics therefore have to be discussed towards a *modified* goal suggested by NOKLUS, with a total error of 25 %. This modified goal has wide, and not ideal, limits. The modified requirements for diabetics will be tightened up over time as the meters improve due to technological development.

Quality demands, adjusted to the diabetics self-measurements:

Ninety-five percent (95 %) of the individual glucose results shall fall within ± 1,0 mmol/L of the results of the comparison method at glucose concentrations < 4,2 mmol/L and within ± 25 % at glucose concentrations ≥ 4,2 mmol/L.

4. Materials and methods

4.1. Statistical terms and expressions

4.1.1. Precision

The common used terms within-series imprecision and between-series imprecision are often misinterpreted. Especially the terms between-series and between-day imprecision are often not precisely defined. In this report, the terms are replaced by the precisely defined terms *repeatability and reproducibility*. Repeatability is the agreement between the results of consecutive measurements of the same component carried out under identical measuring conditions (within the measuring series). Reproducibility is the agreement between the results of discontinuous measurements of the same component carried out under changing measuring conditions over time. The reproducibility includes the repeatability. The two terms are measured as imprecision and are expressed by means of the standard deviation (SD) or coefficient of variation (CV). Precision is descriptive in general terms (good, poor), whereas imprecision is an estimate, reported in the same unit as the analytical result (SD) or in % (CV). The imprecision will be summarised in tables.

4.1.2. Accuracy

Accuracy is the closeness of agreement between the result of one measurement and the true value. Inaccuracy is a measure of a single measurements deviation from a true value, and implies a combination of random and systematic error (analytical imprecision and bias). Inaccuracy, as defined by a single measurement, is not sufficient to distinguish between random and systematic errors in the measuring system. Inaccuracy can be expressed as total error. The inaccuracy will be illustrated by difference plots with quality goals for the total error shown as deviation limits in percent.

4.1.3. Trueness

Trueness is the agreement between an average value obtained from a large number of measuring results and a true value. Trueness is measured as bias (systematic errors). Trueness is descriptive in general terms (good, poor), whereas bias is the estimate, reported in the same unit as the analytical result or in %. The bias at different glucose concentration levels will be summarised in tables.

4.2. Accu-Chek Aviva

Accu-Chek Aviva is a blood glucose monitoring system based on electrochemical technology. The system consist of a meter and dry reagent test strips designed for capillary blood glucose testing by people with diabetes or by health care professionals. The system is calibrated to report glucose plasma values. The system requires calibration by the user (snap-in code chip). The user has to make sure that the code number displayed by the meter when the meter is activated matches the code number printed on the test strip box. The system has over 198 automatic checks to detect and prevent unreliable results. The test strip chemistry uses a pyrroloquinoline quinone-glucose dehydrogenase (PQQ-GDH). PQQ serves as a cofactor and this enzyme system offers the advantages to reduced sensitivity to oxygen compared to glucose oxidase based systems.

The test strips are packaged in a plastic bottle with flip-top closure and desiccant. The system requires a blood volume of 0,6 µL and provides a result in 5 seconds. The meter has the capability of storing 500 results in the memory and detects when a glucose measurement is performed with an Accu-Chek Aviva control solution. Accu-Chek Aviva is cleared for multiple site testing. The meter can be used on less sensitive testing sites like the forearm, upper arm, palm, calf or thigh. Roche recommends to consult Healthcare Professional if use of multiple sampling sites. The Accu-Chek Multiclix lancet device uses a pre-loaded six-lancet drum. The Accu-Chek Compass software is soon available to download the meter`s information to a computer through the meter data port. Technical data from the manufacturer is shown in table 1.

Tabell 1. Technical data for Accu-Chek Aviva

TECHNICAL DATA FOR ACCU-CHEK AVIVA	
Ambient temperature	6 – 44 °C
Sample volume	0,6 µL
Measuring time	Approximately 5 seconds
Measuring range	0.6 – 33,3 mmol / L
Hematokrit	20 – 70 %
Memory	500 tests
Power supply	1x3V Lithium battery supply (CR 2032)
Operating time	Approximately 1000 tests
Dimensions	W= 94 mm, H= 53 mm, D= 22 mm
Weight	60 g (included the battery)

4.2.1. Product information, Accu-Chek Aviva

Accu-Chek Aviva blood glucose meter system
Manufactured by: Roche Diagnostics GmbH

Suppliers of Accu-Chek Aviva in Scandinavian countries:

Sweden:	Norway:	Denmark:
Roche Diagnostics	Roche Diagnostics Norge AS	Roche a/s, Diagnostics
Box 147	Brynsengfaret 6B	Industriholmen 59
161 26 Bromma	PB 6610 Etterstad	2650 Hvidovre
	N-0607 Oslo	
Sweden	Norway	Denmark
Phone:	Phone: 23 37 33 00	Phone: 36 39 99 54
www.accu-chek.se	www.accu-chek.no	www.accu-chek.com

During this user-evaluation 81 Accu-Chek Aviva blood glucose meters were used.
Serial no. 52700031066 (called meter A) and serial no. 52700075276 (called meter B) were used by the biomedical laboratory scientists under the standardised and optimal conditions.
Attachment 1 gives serial numbers for the 79 meters used by the diabetics.

Accu-Chek Aviva blood glucose test strips:

Lot-no. 300011	Expiry 30-06-2006
Lot-no. 300006	Expiry 31-05-2006
Lot-no. 300007	Expiry 31-05-2006

Accu-Chek Aviva Control 2:

Lot-no. 1433800	Expiry 06-2006

Accu-Chek Multiclix six-lancet drum

4.3. Designated comparison method

Definition
A designated comparison method is a fully specified method, which, in the absence of a reference method, serves at the common basis for the comparison of a field method.

Verifying of trueness
The results from SMBG-devices must be compared with a recognized comparison method. The comparison method should be a plasma method, hexokinase by preference. The method has to show traceability equivalent to that of an internationally accepted reference solution, such as the standards supplied by the National Institute of Standards & Technology, NIST. The NIST-standard SRM 965a with four levels of glucose concentrations was used in this evaluation. In addition, freshly frozen, human serum controls from NOKLUS with glucose concentrations at two levels were analysed. The NOKLUS-controls have target values determined with an isotope-dilution gas chromatography/mass spectrometry method at a Reference laboratory in Belgium; Laboratory for Analytical Chemistry, University of Gent, Belgium [8]. The results are summarized in chapter 6.1.2.

The designated comparison method in this evaluation
In this evaluation, the routine method for quantitative determination of glucose in human serum, plasma (lithium heparin) and urine at the Laboratory at Haraldsplass Diaconal Hospital was used as the designated comparison method. The method will be called *the comparison method* in this report. The comparison method is a photometric enzymatic method based on the method by Slein, utilising hexokinase and glucose-6-phosphate dehydrogenase enzymes. The method is implemented on the Advia 1650 Chemistry System from Bayer, with reagents and calibrators from Bayer. The Advia 1650 Chemistry System Glucose Hexokinase II method is a two-component reagent. Sample is added to Reagent 1, which contains buffer, ATP and NAD. Absorbance readings of the sample in Reagent 1 are used to correct for interfering substances in the sample. Reagent 2 is added, which initiates the conversion of glucose and the development of an absorbance at 340 nm. The difference between the absorbance in Reagent 1 and Reagent 2 is proportional to the glucose concentration. The measuring principle in the Advia 1650 is as follows: Glucose is phosphorylated by ATP in the presence of hexokinase. The glucose-6-phosphate that forms is oxidised in the presence of glucose-6-phosphate dehydrogenate causing the reduction of NAD to NADH. The absorbance of NADH is measured as an endpoint reaction at 340 nm.

Internal quality assurance of the Advia 1650 comparison method during the evaluation period
The Autonorm Human Liquid Control Solutions at two levels from Sero AS were part of all the measuring series for this evaluation. The controls were measured as the first and the last samples in all the series. The results are summarised in table 4.

4.3.1. Product information, comparison method

Designated comparison method Advia 1650
Manufactured by: Bayer AS
Serial no. CA 175524-196

Reagents
Bayer Glucose Hexokinase method II (B01-4597-01)
Lot-no. 0581X

Calibrator
Chemistry Cal Bayer
Lot-no. 179747 Expiry 2005-10 Reference value = 13,5 mmol/L

Internal control
Seronorm Autonorm Human Liquid 1 and 2, Sero AS
Liquid 1: Value = 5,2 ± 0,36 mmol/L Lot-no. NO3588 Expiry 2006-01
Liquid 2: Value = 15,0 ± 1,05 mmol/L Lot-no. MI4298 Expiry 2006-07

NOKLUS control
(ID-GCMS method; reference value from Laboratory for Analytical Chemistry, University of Gent, Belgium)
Level 1: Value = 3,20 ± 0,010 mmol/L
Level 2: Value = 7,78 ± 0,026 mmol/L

NIST standards
Standard Reference Material® 965a, National Institute of Standards & Technology
Level 1: Value = 1,918 ± 0,020 mmol/L
Level 2: Value = 4,357 ± 0,048 mmol/L
Level 3: Value = 6,777 ± 0,073 mmol/L
Level 4: Value = 16,24 ± 0,19 mmol/L

Tubes used for sampling for the designated comparison method
Microvette CB 300 LH (litium-heparin) manufactured by Sarstedt AS
Lot-no. 4074301 Expiry 2007-11

Blood sampling device
Accu-Chek SoftClix Pro: Lot-no. WIP 011
Accu-Chek SoftClix Pro lancets: Lot-no. WIP 45 G 3 Expiry 2008-12-31

Centrifuge used for samples for the designated comparison method:
Eppendorf Centrifuge 5415D, manufactured by Eppendorf AG Hamburg
Serial no. 0057100

4.4. Evaluation procedure

4.4.1. Model for the evaluation

The practical work with the evaluation was carried out during 8 weeks from May to June 2005 (from week number 18 to week number 25) at Levanger Hospital in central Norway. The practical work was done by Ingunn Barli and Tone C. Hovelsen. They are biomedical laboratory scientists.

The evaluation consisted of two parallel evaluations. One part of the evaluation was done by two biomedical laboratory scientists under standardised and optimal conditions. This part of the evaluation is done by laboratory educated personnel, completely according to the protocol and user manual after having received thoroughly training. All possibilities for disturbance of, and interference with, the measurements will be tried kept at a minimum. The evaluation under standardised and optimal conditions documents the quality of the system under best possible conditions. The other part of the evaluation was done by diabetics. In order to determine the analytical quality of Accu-Chek Aviva by the users, 79 diabetics tested their blood glucose using Accu-Chek Aviva. The diabetics were divided into two groups (random distribution). **40 diabetics** were called in and received personal training in how to use the blood glucose meter, here called the "training group". **39 diabetics** received the blood glucose meter and instructions by post, here called the "postgroup". The reason for dividing the diabetics into a "training group and a "postgroup" is that this reflects the actual market situation regarding training when diabetics acquire blood glucose meters [2]. The model for the evaluation is shown in figure 1.

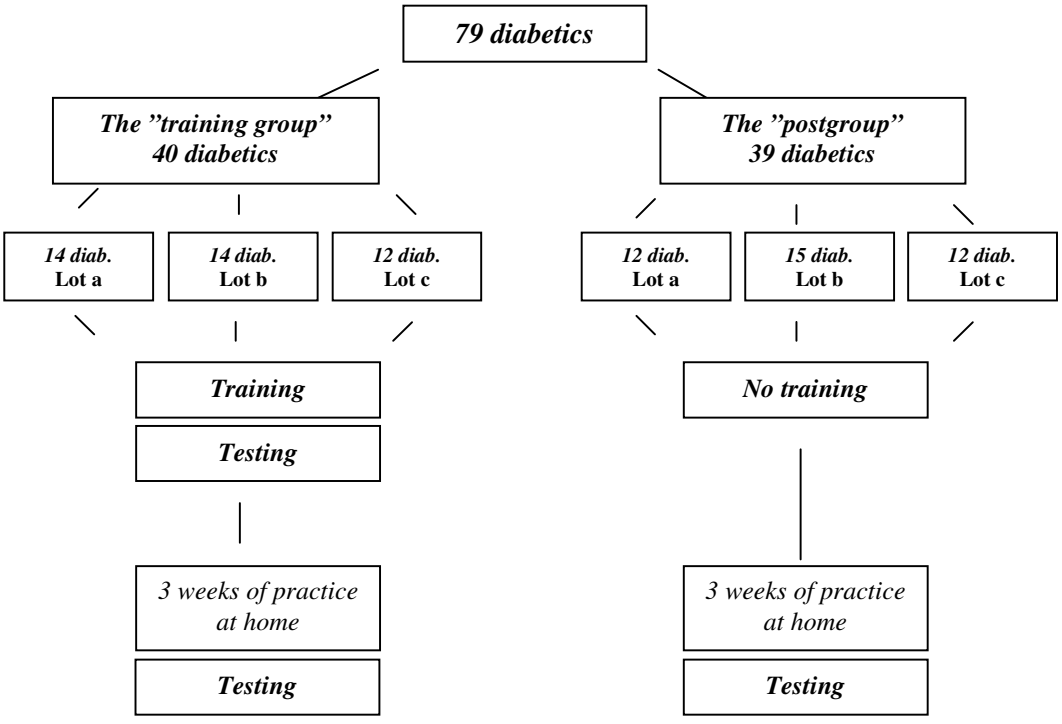


Figure 1. Model for the evaluation

All the diabetics could not participate in the user evaluation during the same weeks. The biomedical laboratory scientists had capacity to receive approximately 25-30 diabetics a week. Therefore the start-up was spread out over 3 weeks, and the final consultation consequently spread out correspondingly.

4.4.2. Recruiting of the diabetics

The Accu-Chek Aviva glucose meter was tested in use by 79 diabetics. The evaluation started with 85 diabetics of whom 6 did not have the opportunity to participate after all or didn't show up. The diabetics were recruited through advertisement in the daily press and by mail inquiry sent to members of the local branch of the Norwegian Diabetes Association. The group of diabetics was representative for diabetics who carry out self-monitoring of blood glucose (SMBG). None of the diabetics used Accu-Chek Aviva as their own device. The group included diabetics from across a range of self-monitoring frequencies, i.e. diabetics who performed self-monitoring often (one or more times a day) and those who performed self-monitoring less frequently (once a week). Patient characteristics of the group are shown in table 2.

Table 2. Characteristics of diabetic patients included in the evaluation (n=79).

		Diabetic patients
Total		
Sex	Men	48
	Women	31
Age (years), median and range		57,5 (21 – 72)
Diabetes	Type 1	29
	Type 2	50
Treatment	Insulin	37
	Tablets	30
	Diet	11
	Unspecified	1
Frequency of SMBG	1- 3 per month	1
	1 -3 per week	10
	4 – 6 per week	4
	7 – 10 per week	24
	> 10 per week	34
	Unspecified	6

Some of the diabetic patients used more than one SMBG-device at home, but only one device is registered here.

The SMBG-devices that the diabetics use regularly were:
Accu-Chek (3), Accu-Chek Compact (27), Accu-Chek Sensor (14), Accutrend (2), Ascensia Contour (6), Ascensia Breeze (1), Ascensia Elite (2), OneTouch Ultra (8), InDuo (1), Precision Xtra (7), FreeStyle (4), Soft Sense (1), doesn't do SMBG (1) and unspecified (2).

4.4.3. The training group at the first consultation

The 40 diabetics selected to participate in a training programme were called in two and two at the time. They received the Accu-Chek Aviva device along with an information letter (see attachment 2), test strips, lancet pen, lancets and user manual. The responsibility for the training programme was undertaken by SKUP. Ingunn Barli and Tone C. Hovlsen were in charge of the training of the diabetics, after having been trained themselves by a representative from Roche.

Training programme
The training programme covered a simple demonstration of how to use Accu-Chek Aviva with an explanation of the display and error messages, insertion of the test strips, blood sampling and drawing of blood into the test strip, as well as precautions for storage and the shelf-life of test strips, etc. The training programme was standardised to make sure that all the diabetics received the same instruction.

Blood sampling
After have been trained, the 40 diabetics made duplicate blood glucose tests on Accu-Chek Aviva. These results were registered for the evaluation. Afterwards they brought the Accu-Chek Aviva blood glucose meter home to use the meter over a three-week period. After this period, they attended a final consultation and made two new duplicate blood glucose tests, which were registered.

4.4.4. The postgroup

39 diabetics received the Accu-Chek Aviva device by post, along with test strips, lancet pen, lancets, user manual and an information letter with explanations regarding what to do with the Accu-Chek Aviva device during the period at home. No training was given. They used the meter over a three-week period at home. After this period, they attended a final consultation to have two duplicate blood glucose tests done. The results of these tests were registered.

4.4.5. Use of Accu-Chek Aviva by the diabetics at home

The diabetics used Accu-Chek Aviva at home for three weeks. The length of this practice period ought not to exceed three weeks by more than a few days. Most users read the user manual at once when they receive the meter. As the diabetics should evaluate the user manual at the final consultation, it would be unfortunate if the practice period at home was too long. During the practice period the diabetics used Accu-Chek Aviva in addition to their own glucose meter and they continued to carry out self-measurements with their own meter as normal.

The first and the second week
The diabetics familiarised themselves with the new device during the first two weeks. Each diabetic used approximately 25 test strips to measure his/her blood glucose with Accu-Chek Aviva. They could choose when to do the measurements themselves. Fasting was not necessary. If more convenient to them, they could perform the measurement at the same time as they measured their blood glucose with their own meter.

The third week
During the third week the diabetics performed five measurements in duplicate on Accu-Chek Aviva on different days. The results were recorded on a provided form. They pricked a finger and made two consecutive measurements with blood from the same prick. If necessary they pricked another finger for the second measurement. They were free to choose when to perform the measurements, and it was not necessary to be fasting. They could choose whether to use the lancets provided for the evaluation, or the lancets they use ordinarily.

Internal quality control
The diabetics are not familiar with control solutions for self-measurements. Therefore they were not instructed to use control solution on Accu-Chek Aviva in the evaluation. To document correct functioning on the Accu-Chek Aviva meters used by the diabetics during the test period, the biomedical laboratory scientist in charge of the practical work controlled the meters when the diabetics were called for the consultations.

4.4.6. The final consultation

Blood sampling
After the three week practice period at home, the 79 diabetics were called for, one by one, to a consultation. Each diabetic brought their assigned Accu-Chek Aviva meter and the remaining test strips to this consultation. They made duplicate blood glucose tests on Accu-Chek Aviva. These results were registered for the evaluation. Finally, a venous sample for hematocrit was taken.

The questionnaires
After all the blood samples were collected and the measurements on Accu-Chek Aviva were done, the diabetics filled out two questionnaires. The first questionnaire was about the user-friendliness of the Accu-Chek Aviva device, the second about the user-manual. The questionnaires (in Norwegian) are attached to the report. After the evaluation, the diabetics could choose whether to keep Accu-Chek Aviva or return it to the project.

4.4.7. Evaluation under standardised and optimal conditions

The two biomedical laboratory scientists used two Accu-Chek Aviva blood glucose meters for the evaluation (meter "A" and meter "B"). Meter "A" was used for one lot of test strips for all measurements on all the diabetics. Meter "B" was used for the same three lots as distributed among the diabetics. In this way, the variation between the three lots, or more precisely, the agreement of the three lots to the comparison method, can be assessed. The number of samples for each lot of test strips measured under standardised and optimal conditions is shown in table 3.

Table 3. The number of samples (n) for each lot of test strips measured under standard and optimal conditions.

Accu-Chek Aviva		Lot 300011 (n)	Lot 300006 (n)	Lot 300007 (n)
Meter A	1st consultation	40 x 2		
	2nd consultation	79 x 2		
Meter B	1st consultation	39 x 2	1 x 2	
	2nd consultation		66 x 2	13 x 2
Total		158 x 2	67 x 2	13 x 2

Comment: The three lots of test strips (meter B) are not likely distributed between the two consultations. This is due to a misunderstanding between SKUP and the biomedical laboratory scientists that did the practical work.

Blood sampling
Meter "A" and meter "B" were checked by means of the manufacturer's control solution every day they were used.

The blood sampling and analysis were done in the following order:

1. The biomedical laboratory scientist took a sample for the comparison method
2. The diabetic took duplicate samples for their assigned meter
3. The biomedical laboratory scientist took samples and analysed on meter "A", "B", "A" and "B"
4. The biomedical laboratory scientist took a new sample for the comparison method
5. The biomedical scientist measured internal quality control at the diabetic`s meter

The duration of the sampling should not exceed 10 minutes.

The order of the meters "A" and "B" was changed between each diabetic, but the blood samples for the comparison method were always taken first and last in accordance with ISO 15197.
The biomedical laboratory scientist registered whether the diabetic had set the right or wrong calibration code in the blood glucose meter, used correct cleaning, drying, and skin puncture procedure, applied the blood sample correctly to the test strip, and otherwise followed manufacturer's instructions for performing a glucose meter test. At the final consultation, i.e. after the period with use of Accu-Chek Aviva at home, a venous sample for hematocrit determination was taken. Hematocrit may influence blood glucose readings, especially in meters designed for self-monitoring. This also applies to Accu-Chek Aviva, which recommend hematocrit from 20 – 70 %.

Handling of the samples for the comparison method
The samples for the comparison method were capillary taken using a Microvette Li-heparin tube from Sarstedt. The samples were centrifuged immediately for three minutes at 13000 g, and plasma was separated into sample vials for Advia 1650. The reference samples were frozen directly as the plasma was separated and the plasma was stored at minus 80°C. The samples were gathered and sent frozen in a quantity of about 80 samples at a time. The samples were transported under cold storage (minus 18°C to minus 24°C) to NOKLUS Center in Bergen where they were kept at minus 80°C until the analysis took place.

Analysing the samples for the comparison method
The samples were analysed with Advia 1650. Recommended minimum volume for analysis of glucose on Advia 1650 in this evaluation was 120 µL plasma. The samples were thawed at NOKLUS Centre just before they were analysed. The first and the second sample for the comparison method, taken at the start and at the end of each blood sampling, reflect the stability of the glucose concentration during the sampling time. When the paired measurements give agreeable glucose concentrations at the comparison method, the mean of the two results is looked upon as the estimate of the true value of the sample. Basically, the difference between the first and the second comparative reading must not be more than 4 % or 0.22 mmol/L (per ISO 15197 Section 7.3.2.). If the difference between any paired results exceeded these limits, the sample was re-analysed. If the result from the re-run confirmed the difference, the difference was looked upon as a real difference in the glucose concentration in the two samples. Deviations > 10 % were regarded as not acceptable and such results were excluded. As a consequence of this, the matching Accu-Chek Aviva results were excluded for accuracy and trueness calculations. Differences between 4 and 10% are discussed and included in the calculations (see chapter 6.1.3.). If the deviation between the two results was not confirmed by the re-run, the result from the re-run was used as the accepted result.

The questionnaires
The biomedical laboratory scientist evaluated the user-friendliness of Accu-Chek Aviva and the user-manual. The biomedical laboratory scientist provided a description in the form of key words and looked for any defects and deficiencies or whether there was anything in the system that did not function optimally.

4.4.8. Evaluation of analytical quality

The following sets of data give the basis for the evaluation of the analytical quality:

1. Results from 40 diabetics in the “training group” who had participated in the training programme, but not practised using the blood glucose meter at home.
2. Results from the same diabetics after they had practised using Accu-Chek Aviva at home for three weeks
3. Results from 39 diabetics in the “postgroup” who had not participated in the training programme, but who had practised using Accu-Chek Aviva at home for three weeks
4. Results from 119 measurements under standardised and optimal conditions
5. Results from 119 measurements from the comparison method.

The results from the group with and without training were compared (group 2 and 3) and the results from the group with and without practise at home (group 1 and 2) were also compared. All

the diabetic measurements were evaluated against the results achieved under standardised and optimal conditions. User-friendliness and user-manual were evaluated by means of questionnaires. The three lots of test strips were distributed evenly between the diabetics in the group with and without training (random distribution in each group). Each lot was used by approximately 13 diabetics in each group (see figure 1).

5. Statistical calculations

5.1. Number of samples

79 diabetics completed the evaluation. 40 diabetics from the "training group" met at the first consultation, and the same 40 diabetics met at the final consultation together with the 39 diabetics from the "postgroup". Blood samples were taken at each consultation. This means that the total number is 119 x 2 (duplicates) x 4 (meter A, meter B, diabetic's meter, comparison method) = 952 samples.

5.2. Statistical outliers

All results are checked for outliers according to Burnett [9], with repeated truncations. The model takes into consideration the number of observations together with the statistical significance level for the test. The significance level is often set to 5 %, so also in this evaluation. Where the results are classified according to different glucose concentration levels, the outlier-testing is done at each level separately. Statistical outliers are excluded from all calculations. Possible outliers will be commented on under each table.

5.3. Missing or excluded results

Besides the outliers, some results are missing or excluded for other reasons. They are summarized and explained here:

- ID number 436 (1st consultation), 418 (2nd consultation) and 524 (2nd consultation) had a difference > 10 % between the paired results on the comparison method. The difference was confirmed by a re-run. As a consequence of this, the results from ID 436, 418 and 524 are excluded when Accu-Chek Aviva is compared with the comparison method (accuracy and trueness). These results are included in the calculations regarding the imprecision at Accu-Chek Aviva because each set of duplicate measurements on Accu-Chek Aviva is completed in less then a minute.
- ID number 548 had only one result on the comparison method. ID number 436 had only one result on Accu-Chek Aviva. In the calculation of trueness these single results will represent an estimation of the samples and are not excluded.
- ID number 560 had only one result on the comparison method and this result differ a lot from the result obtained with Accu-Chek Aviva (negative bias). ID 560 is excluded from the calculations regarding trueness and accuracy because this single result on the comparison method most probably was wrong.

5.4. Calculations of imprecision based on duplicate results

Two capillary samples were taken of each diabetic patient to meter "A", meter "B", the diabetic`s meters and at the comparison method at each consultation. The imprecision was calculated by use of paired measurements, based on the following formula:

$SD = \sqrt{\frac{\sum d^2}{2n}}$, d = difference between two paired measurements, n = number of differences

The assumption for using this formula is that there must be no systematic difference between the 1st and the 2nd measurement. Table 4 shows that there is no difference in glucose concentration between the paired measurements on Accu-Chek Aviva in this evaluation.

Table 4. No systematic difference between the 1st and 2nd measurements. T-test for paired values.

		Glucose level mmol/L	Mean 1st measurement mmol/L	Mean 2nd measurement mmol/L	Mean difference 2nd – 1st measurement mmol/L	95 % CI for the mean difference, mmol/L	n
Accu-Chek Aviva	Meter A						
		< 7	5,2	5,3	0,07	-0,10 – 0,24	13
		7 – 10	8,4	8,5	0,06	-0,07 – 0,20	37
		> 10	12,3	12,3	0,00	-0,26 – 0,26	26

5.5. Calculation of trueness

To measure the trueness of the measurements on Accu-Chek Aviva, the average bias at three glucose concentration levels is calculated based on the results obtained under standardised and optimal measuring conditions. A paired t-test is used with the mean values of the duplicate results at the comparison method and the mean result at Accu-Chek Aviva meter A.

5.6. Calculation of accuracy

To evaluate the accuracy of the results at Accu-Chek Aviva, the agreement between Accu-Chek Aviva and the comparison method is illustrated in difference plots. In the plots the x-axis represents the mean value of the duplicate results at the comparison method. The y-axis shows the difference between the first measurement at Accu-Chek Aviva and the mean value of the duplicate results at the comparison method.

6. Results and discussion

6.1. Precision and trueness of the designated comparison method

6.1.1. The precision of the comparison method

The repeatability of the comparison method is shown in table 6 and table 7. The results are obtained with the SRM 965a standards supplied by the National Institute of Standards & Technology, NIST and freshly frozen, human serum controls from NOKLUS. The repeatability is calculated as a combined CV %.

The reproducibility of the comparison method is shown in table 5. The results are obtained with the internal control solution at two levels of glucose concentrations (Seronorm Autonorm Human Liquid Control Solution). The controls were analysed in duplicate in each series of samples, giving a total number of more than 100 results. In table 5 only the first result in each series is included. All the results are shown in attachment 3.

Table 5. The comparison method – Reproducibility (results with internal control solutions Autonorm 1 and 2).

Control Solution	Target value glucose (mmol/L)	Mean value glucose (mmol/L)	n	Outliers	CV % (95 % CI)
Autonorm 1	5,2 ± 0,36	5,2	52	0	0,6 (0,5-0,7)
Autonorm 2	15,0 ± 1,05	15,1	52	0	0,6 (0,5-0,8)

Discussion

The precision of the comparison method is good. The repeatability is less than 0,5 CV% and the between series imprecision is less than 1 CV %.

6.1.2. The trueness of the comparison method

In order to demonstrate the trueness of the comparison method, the SRM 965a standards supplied by the National Institute of Standards & Technology, NIST, were analysed at several occasions during the evaluation period. SRM 965a consists of ampoules with human serum with certified concentrations and uncertainties for glucose at four concentrations. The SRM 965a materials cover a glucose concentration range from 1,9 to 16,2 mmol/L.

The agreement between the comparison method and the NIST-standards is shown in table 6.

Table 6. The comparison method – Standard Reference Material (SRM 965a) measured on the comparison method during the evaluation period.

SRM 965a	Date	Target value (mmol/L)	Mean value glucose (mmol/L)	n	Combined CV % (95 % CI)	% deviation from target value
Level 1	14.06.05	1,918 (1,898 - 1,938)	1,98	5	0,6 (0,4-1,1)	+3,3
	04.07.05		1,97	6		+2,8
	Total		**1,98**	**11**		**+3,0**
Level 2	14.06.05	4,357 (4,309 - 4,405)	4,43	5	0,5 (0,4-0,9)	+1,7
	06.07.05		4,46	6		+2,4
	Total		**4,45**	**11**		**+2,1**
Level 3	15.06.05	6,777 (6,704 - 6,850)	6,94	5	0,3 (0,2-0,5)	+2,3
	06.07.05		6,97	6		+2,8
	Total		**6,95**	**11**		**+2,6**
Level 4	15.06.05	16,24 (16,05 - 16,43)	16,44	5	0,4 (0,3-0,7)	+1,2
	11.07.05		16,48	6		+1,5
	Total		**16,46**	**11**		**+1,4**

Table 6 reveals that glucose results at Advia 1650 are approximately 2 % higher than the target values from NIST. Even though the obtained results are only just outside the given uncertainty limits for the Reference Material, it was decided that all results from Advia should be adjusted according to the findings presented in the table above. The adjustment was done by means of the following regression equation ($R^2 = 1,0$):

$$\mathbf{y = 0,9892x - 0,0555}$$

From now on in this report, whenever any result from Advia is presented, the result has already been adjusted according to this equation.

To verify the trueness of the comparison method, freshly frozen, human serum controls from NOKLUS with glucose concentrations at two levels were analysed. The NOKLUS-controls have target values determined with an isotope-dilution gas chromatography/mass spectrometry method at a Reference laboratory in Belgium; Laboratory for Analytical Chemistry, University of Gent, Belgium [8]. The agreement with target values from the reference laboratory in Belgium is shown in table 7.

Table 7. The comparison method – Control samples from NOKLUS's External Quality Assessment program, measured on the comparison method during the test period.

Control solution	Date	Target value from Reference lab. in Belgium (mmol/L)	Mean value glucose (mmol/L)	n	Outliers	Combined CV% (95% CI)	% deviation from target value
NOKLUS 1	10.06.05	3,20	3,15	7		0,4 (0,3-0,6)	-1,5
	16.06.05		3,15	6			-1,4
	28.06.05		3,15	6			-1,6
	Total		**3,15**	**19**	**0**		**-1,5**
NOKLUS 2	10.06.05	7,78	7,78	7		0,3 (0,2-0,4)	-0,3
	17.06.05		7,72	6			-0,8
	29.06.05		7,72	6			-0,8
	Total		**7,73**	**19**	**0**		**-0,6**

Discussion
The trueness of the comparison method is very satisfactory.

6.1.3 Stability of the glucose concentration during sampling

The first and the second sample for the comparison method, taken at the start and at the end of each blood sampling, reflect the stability of the glucose concentration during the sampling time (see chapter 4.4.7). In this evaluation, deviations > 10 % were regarded as not acceptable and such results were excluded without further discussion. This applies for ID number 436 (1st consultation), 418 (2nd consultation) and 524 (2nd consultation). For further explanation, see chapter 5.3. One sample with a low glucose concentration (below 4,2 mmol/L) had a difference just over the limit at 0,22 mmol/L, but is still included in the calculations. 13 of 119 paired results at the comparison method gave deviations between 4 and 10 %. For 9 of these 13 samples the deviation was less than 6 %. Three of the four differences between 6 and 10 % concern normal glucose concentrations, where a deviation expressed in percent more easily exceeds the limitations. After a general evaluation of all the results, the paired measurements with differences between 4 and 10 % are included in the calculations in this evaluation. The summing up in table 13 has been done with and without these 14 results. The percentage number of results that falls within the different quality limits is not dependent on keeping or excluding these results. In both cases, the final results in the evaluation fulfil the quality goals set by ISO.

6.2. Precision, trueness and accuracy of Accu-Chek Aviva

6.2.1. Precision of Accu-Chek Aviva

All of the Accu-Chek Aviva meters in the user evaluation were checked by the biomedical laboratory scientists with the manufacturer's control solution. All of the results were inside the limits of the control.

All the results from the calculations of the precision are discussed at the end of this chapter.

Repeatability under standardised and optimal measuring conditions
The repeatability obtained under standardised and optimal conditions with capillary blood samples is shown in table 8. The table gives the results from the biomedical laboratory scientists' measurements at the first and the final consultation together. Raw data is shown in attachment 4.

Table 8. Accu-Chek Aviva – Repeatability (results with patient samples) measured under standard and optimal conditions, n = 118 (meter A), n = 118 (meter B)

Accu-Chek Aviva	Glucose level (mmol/L)	Mean value glucose (mmol/L)	n	Outliers	CV % (95 % CI)
Meter A	< 7	5,3	25	0	4,0 (3,1 – 5,5)
Meter B	< 7	5,4	27	0	3,9 (3,0 – 5,3)
Meter A	7 – 10	8,5	54	0	3,0 (2,5 – 3,7)
Meter B	7 – 10	8,5	53	0	3,3 (2,8 – 4,1)
Meter A	> 10	12,5	39	0	3,3 (2,7 – 4,2)
Meter B	> 10	12,6	38	0	3,2 (2,6 – 4,1)

ID number 436 had only one result on Accu-Chek Aviva. This result is excluded from the calculation regarding repeatability at meter A og meter B.

Repeatability obtained by the diabetic patients
The repeatability obtained by the diabetic patients with capillary blood samples is shown in table 9. The table gives the results from the measurements at the first and second consultation for the "training" group, the consultation for the "postgroup", together with the results they obtained at home. The results obtained at home of course have a higher degree of uncertainty since it is impossible to control what has actually been done. The reporting of these home-values also reveals that some of the diabetic patients did not quite understand "the recipe" on how to perform and report the five duplicate measurements they were supposed to carry out according to the written instruction they had recieved.

Raw data from the diabetic patients' measurements at NOKLUS is shown in attachment 5.
Raw data from the diabetic patients' measurements at home is shown in attachment 6.

Table 9. Accu-Chek Aviva – Repeatability (results with patient samples) measured by the "training group" and the "postrgoup"

Accu-Chek Aviva	Consultation	Glucose level (mmol/L)	Mean value glucose (mmol/L)	n	Outliers	CV % (95 % CI)
NOKLUS	1st trained	< 7	5,9	14	0	4,6 (3,3-7,4)
	2nd trained	< 7	5,0	7	0	4,5 (2,9-9,9)
	postgroup	< 7	5,4	8	0	4,2 (2,8-8,5)
Home		< 7	5,5	133	4	5,2 (4,6-5,9)
NOKLUS	1st trained	7 – 10	8,7	12	0	3,0 (2,1-5,1)
	2nd trained	7 – 10	8,5	20	0	5,0 (3,8-7,3)
	postgroup	7 – 10	8,8	18	0	3,6 (2,7-5,4)
Home		7 – 10	8,4	151	1	4,3 (3,9-4,9)
NOKLUS	1st trained	> 10	12,9	14	0	4,7 (3,4-7,6)
	2nd trained	> 10	12,8	13	0	4,7 (3,4-7,7)
	postgroup	> 10	12,9	12	0	5,1 (3,6-8,6)
Home		> 10	12,8	90	1	4,1 (3,6-4,8)

* The "postgroup": ID 561 is excluded because of missing duplicate result.
** "Home": 10 measurements are missing and six outliers are excluded.

Reproducibility with Internal Quality Control

The results for reproducibility are obtained with the Accu-Chek Aviva Control. The measurements are carried out on meter A and B during the whole evaluation period and at all the meters in use by the diabetic patients. All the control measurements are done by two biomedical laboratory scientists. The control measurements on the diabetics' meters were done with the test strips that were distributed to each diabetic patient. The control solution was kept at NOKLUS during the evaluation period.

The reproducibility of Accu-Chek Aviva at meter A and B is shown in table 10.
The reproducibility at all the meters of the diabetic patients is shown in table 11.
Raw data is shown in attachment 7.

Table 10. Accu-Chek Aviva – Reproducibility (results with Accu-Chek Aviva Control 2) measured by the biomedical laboratory scientist on meter A and on meter B.

Accu-Chek Aviva	Lot of strips	Target value (mmol/L)	Mean value glucose (mmol/L)	n	Outliers	CV % (95 % CI)
Meter A	300011	14,2 – 19,1	17,64	28	0	1,9 (1,5 – 2,6)
Meter B	300011	14,2 – 19,1	17,63	8	0	2,3 (1,5 – 4,7)
Meter B	300007	14,2 – 19,1	17,77	7	0	1,4 (0,9 – 3,1)

Table 11. Accu-Chek Aviva – Reproducibility (results with Accu-Chek Aviva Control 2) measured by the biomedical laboratory scientist on the diabetic patient's meters, n = 114

Accu-Chek Aviva	Lot of strips	Target value (mmol/L)	Mean value glucose (mmol/L)	n	Outliers	CV % (95 % CI)
1st consultation						
The diabetic patient's meters	300011	14,2–19,1	17,6	14	0	2,4 (1,7 - 3,8)
	300006	14,2-19,1	17,5	12	0	1,9 (1,4 – 3,3)
	300007	14,2-19,1	17,7	11	0	2,3 (1,6 – 4,1)
2nd consultation						
The diabetic patient's meters	300011	14,2-19,1	18,0	26	0	3,1 (2,4 – 4,2)
	300006	14,2-19,1	17,8	29	0	2,7 (2,1 – 3,6)
	300007	14,2-19,1	18,1	22	0	3,4 (2,6 – 4,8)

The internal quality control was forgotten at three of the diabetic patient's meters at first consultation and at two of the diabetic patients' meters at second consultation.

Discussion

The precision at Accu-Chek Aviva is acceptable. The repeatability obtained under standardised and optimal conditions is somewhere between 3,0 and 4,0 % (meter A and meter B).The repeatability obtained at NOKLUS by the diabetic patients in the "training group" and the "postgroup" is nearly as good as the precision achieved by the biomedical laboratory scientists. The CV % is between 4 and 5. The results at home show that the diabetic patients have been practising with the new system according to the instructions, but one should not make a point of the calculated CV values.

The reproducibility at Accu-Chek Aviva meter A and B is good when measured with an internal control solution. The CV is approximately 2 %. At the diabetics' meters the reproducibility are good both at the first consultation and the second consultation The CV was approximately 3 %.

6.2.2. Trueness

The trueness of Accu-Chek Aviva is calculated from the results done by the biomedical laboratory scientists at the final consultation (the "training group" and the "postgroup") and is shown in table 12.

Table 12. Mean difference between Accu-Chek Aviva and the comparison method. Results under standardised and optimal conditions from the final consultation, n = 75.

	< 7 mmol/L		**7 – 10 mmol/L**		**> 10 mmol/L**	
	The comparison method	**Meter A**	**The comparison method**	**Meter A**	**The comparison method**	**Meter A**
Mean glucose, mmol/L	5,2	5,4	8,3	8,5	12,5	12,7
% deviation from the comparison method (95 % CI)	2,9 (-1,1 – (+6,9))		3,1 (1,3 – (+4,9))		1,8 (-0,1 – (+3,6))	
n	14		35		26	
Outliers	1		0		1	
p-value	0,127		0,001		0,056	

ID number 548 had only one result on the comparison method. ID 436 had only one result at Accu-Chek Aviva. In the calculations these results represent the best estimation of the samples and are not excluded. ID 560 had only one result at the comparison method and ID 560 is the outlier detected at glucose level > 10 mmol/L. This single result on the comparison method was most probably wrong.

Discussion

The agreement between Accu-Chek Aviva and the comparison method is good. There is a small, but significant bias between the two methods at one level of glucose concentrations (7-10 mmol/L). Accu-Chek Aviva gives slightly higher values than the comparison method. The glucose results at Accu-Chek Aviva still fulfil the quality goal set by ISO (see chapter 6.2.3).

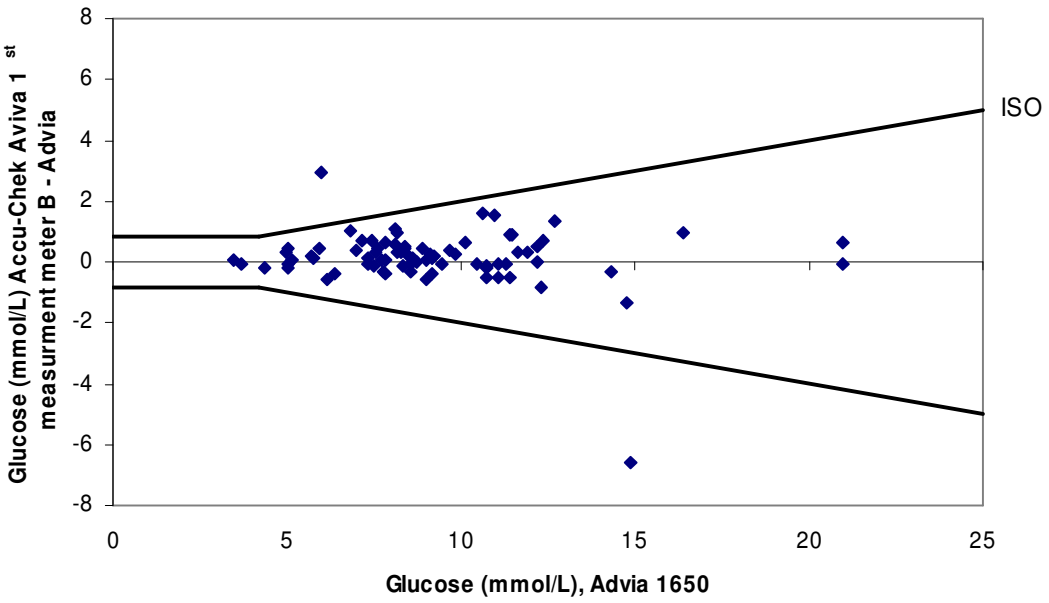
6.2.3. Accuracy

To evaluate the accuracy of the results at Accu-Chek Aviva, the agreement between Accu-Chek Aviva and the comparison method is illustrated in two difference plots. The difference plots give a picture of both random and systematic deviation and reflect the total measuring error at Accu-Chek Aviva. The total error is demonstrated for the first measurements of the paired results, only. At meter A only one lot of test strips were used. At meter B three different lots were used. The same three lots were randomly distributed between the diabetic patients.

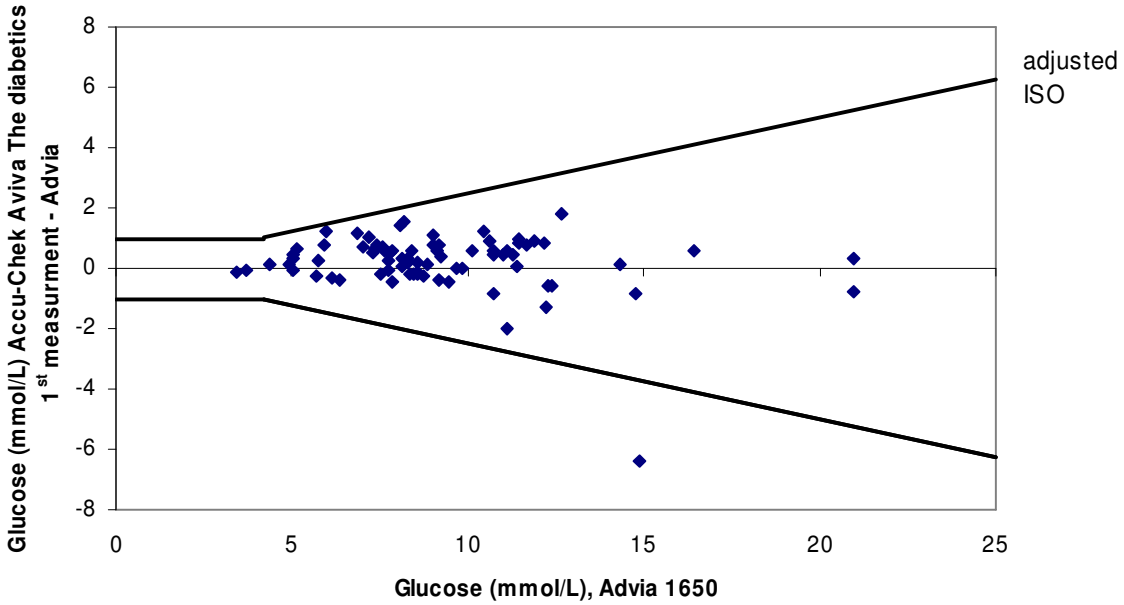
The limits in the plots are based upon the quality goals discussed in a previous chapter of this report. Under standardised and optimal measuring conditions the ISO-goal at 20 % is used. For the diabetic patients' self-measurements the "adjusted ISO-goal" at 25 % is used.

The accuracy, Accu-Chek Aviva meter B, under standardised and optimal measuring conditions, with the first measurement at the final consultation is shown in figure 2.
The accuracy, Accu-Chek Aviva, as measured by the diabetic patients with the first measurement at the second consultation is shown in figure 3. The results from the two difference plots are summarised in table 13 and discussed afterwards. Raw data from the diabetic patients' measurements at the comparison method is shown in attachment 8.

In figure 2 and 3 one point is far below the deviation limit. The coordinates for this point are encumbered with only one result on the comparison method that differ a lot from duplicates on Accu-Chek Aviva (meter B and the diabetic`s meter).



Figur 2. Accuracy. Accu-Chek Aviva meter B (three lots of test strips) under standardised and optimal measuring conditions at the final consultation. The x-axis represents the mean value of the duplicate results at the comparison method. The y-axis shows the difference between the first measurement at Accu-Chek Aviva and the mean value of the duplicate results at the comparison method, n = 77. The outlier with the negative bias is probably due to problems with the comparison method.



Figur 3. Accuracy. The diabetic patients' self-measurements at the final consultation. Three lots of test strips. The x-axis represents the mean value of the duplicate results at the comparison method. The y-axis shows the difference between the first measurement at Accu-Chek Aviva and the mean value of the duplicate results at the comparison method, n = 77. The outlier with the negative bias is probably due to problems with the comparison method.

Table13. Total error of Accu-Chek Aviva results compared to the reference method. Percentage Accu-Chek Aviva results within the limits.

Measurements done by	Consultation	Meter	n	Number of results (%)			Shown in figure
				< ADA (< ±10 %)	**< ISO** < ±20 % (and < ±0,83 mmol/L at consentrations ≤ 4,2)	**< "adjusted ISO"** < ±25 % (and < ±1,0 mmol/L at consentrations ≤ 4,2)	
Biomedical laboratory scientist	1st	A 1st measurement	39	79	95		
		B 1st measurement	39	92	92		
Biomedical laboratory scientist	2nd *	A 1st measurement	76	89	99		
		B 1st measurement	76	89	99		2
Diabetic patients at NOKLUS	1st	1st measurement	39	77	90	95	
	2nd *	1st measurement	76	83	99	100	3

* ID560 is excluded from the calculations because there was only one result from Advia 1650, and because this single result most probably was wrong.

Discussion
Figure 2 shows that 99 % of all the results obtained under standardised and optimal measuring conditions for meter B are within the ISO-limits. The summing up in table 13 shows that all the first measurements at the final consultation fulfil the limits recommended by ISO, but only 89 % are within the limits recommended by ADA. Figure 3 show that the diabetic patients' first self-measurements at the final consultation fulfil the "adjusted ISO-goal". The results also fulfil the ISO-goal, as shown in table 13. The results from the first and final consultation do not fulfil the optimal quality goals from ADA.

Conclusion
The Accu-Chek Aviva device fulfils the quality goals set in the ISO 15197 when used under standardised and optimal conditions. The quality goals are also met by the measurements of the diabetic patients.

6.3. Variation between three lots of test strips

All the measurements on meter A were performed with the same lot. The measurements on meter B were performed with three different lot numbers of test strips, on three different groups of diabetics. The three lots can not be compared with each other because the mean glucose concentrations in the three groups of diabetics are different. To measure the variation between the three lots, all the mean glucose results at Accu-Chek Aviva obtained under standardised and optimal conditions at meter B were compared with the mean of the paired values from the comparison method (paired t-test). The results are shown in table 14.

Table 14. Variation between three lots of test strips. T-test for paired values between three lots at meter B and the comparison method under standardised and optimal conditions at the final consultation, n = 112

	The reference method	**Meter B Lot 300011**	**The reference method**	**Meter B Lot 300006**	**The reference method**	**Meter B Lot 300007**
Mean glucose, mmol/L	8,6	8,7	8,9	9,1	10,7	11,0
% deviation from the reference method (95 % CI)	1,0 (-0,4 – (+3,1))		2,2 (1,0 – (+3,5))		3,0 (0,4 – (+5,5))	
n	36		64		12	
Outliers	2		2		0	
p-value	0,133		0,001		0,02	

ID number 548 had only one result on the comparison method. ID 436 had only one result at Accu-Chek Aviva. In the calculations these results represent the best estimation of the samples and are not excluded. ID 560 had only one result at the comparison method and ID 560 is the outlier detected at Lot 300006. This single result on the comparison method was most probably wrong.

Discussion

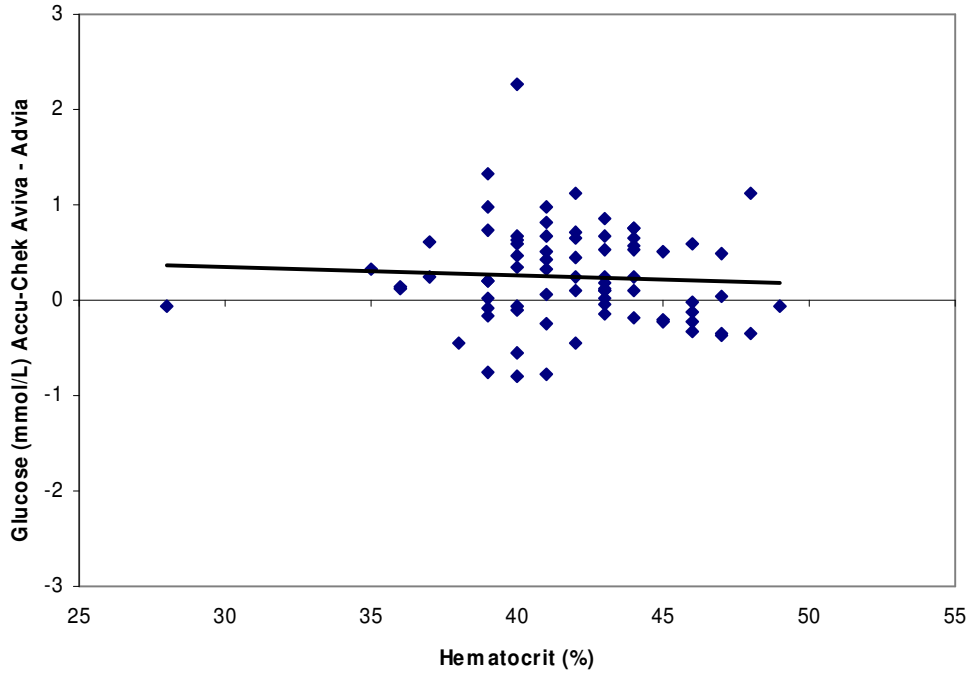
The three lots show good agreement with the comparison method. The results at Accu-Chek Aviva are slightly higher than the comparison method, and for lot 300006 and 300007 the small bias is significant. The results still fulfil the quality goal set in ISO 15197.

7. Effect of hematocrit

The package insert of Accu-Chek Aviva test strips states that normal glucose concentrations are not affected by hematocrit-values between 20 and 70 %. To measure the effect of hematocrit at Accu-Chek Aviva, a venous sample was taken of the diabetic patients (voluntarily) at the final consultation. All the diabetics were willing to have a sample for hematocrit taken. Out off the 79 diabetic patients that met for the final consultation, the sampling to hematocrit was successful in all cases.

The measurements on Accu-Chek Aviva are performed under standardised and optimal measuring conditions. The glucose concentration range in the samples was from 3,4 to 21,2 mmol/L. The hematocrit range was 28 – 49 %.

The effect of hematocrit is shown in figure 4. The x-axis in the plot shows the hematocrit value, and the y-axis shows the difference in glucose concentration in mmol/L between Accu-Chek Aviva and the comparison method (Accu-Chek Aviva – the comparison method). Raw data is shown in attachment 9.



Figur 4. The effect of hematocrit at glucose measurements (in mmol/L) at Accu-Chek Aviva under standardised and optimal conditions. The x-axis shows the hematocrit value in %. The y-axis shows the difference in glucose concentration between Accu-Chek Aviva and the comparison method in mmol/L. n= 76

*Result from one diabetic patient showed big difference between Accu-Chek Aviva and the comparison method (-5,9 mmol/L). This result is excluded from the calculation.

Discussion
The trend-line in figure 4 shows that the glucose measurements on Accu-Chek Aviva are not affected by hematocrit values between 28 – 49 %. Hematocrit outside this range has not been tested.

8. Evaluation of user friendliness

Each diabetic patient filled out a questionnaire about the user-friendliness and a questionnaire about the user-manual of Accu-Chek Aviva when they attended the second consultation (n = 79). Some patients needed assistance in filling out the questionnaires.

Questionnaire about the user-friendliness (in Norwegian), see attachment 10.
Questionnaire about the user-manual (in Norwegian), see attachment 11.

8.1. Questionnaire about user-friendliness concerning Accu-Chek Aviva

The questionnaire about the user-friendliness had nine questions concerning Accu-Chek Aviva and one question concerning Accu-Chek Multiclix lancet pen. In addition, each patient should give the name of the blood glucose meter he/she uses regularly on the same questionnaire. The answers to these questions are summarized in table 15 and 16.

Table 15 summarizes seven questions where the patients were asked to rank the answers on a scale from 1 to 6, where 1 is difficult and 6 is simple. The mean is 5,7 and 5,8 on the questions about calibrating the meter, inserting a strip into the meter and about filling the strip with blood, respectively. This indicates that the patients seemed satisfied with the use of the test strip and that it was easy to calibrate the meter. The patients also seemed satisfied with the use of the meter. The mean is between 5,6 and 6,0 on the questions about reading the figures in the display, recognizing the meters' sound signal and operating the meter, all in all. Regarding Multiclix lancet pen the mean is 5,3 which indicates that the patients were satisfied with the lancet pen too.

Table 15. Accu-Chek Aviva - Questions about the meter and about Multiclix lancet pen.

Questions about Accu-Chek Aviva and about Multiclix lancet pen		mean	range	Not answered (% of total)	Total number
How will you rank the following questions on a scale from 1 to 6, where 1 is difficult and 6 is simple:	1. To calibrate the meter	5,7	2-6	3 %	79
	2. To insert a strip into the meter	5,7	4-6	1 %	79
	3. To fill the strip with blood	5,8	4-6	1 %	79
	4. To read the figures in the display	6,0	5-6	1 %	79
	5. To recognize the meters' sound signal?	5,7	4-6	1 %	79
	6. All in all, to operate the meter	5,6	2-6	1 %	79
	7. To operate Multiclix lancet pen	5,3	2-6	8 %	79

Table 16 summarizes one other question about Accu-Chek Aviva. Nine patients (11 %) answered that they had technical problems with the meter during the testing period. For three of these patients the written comments indicate that the problems were not technical ones. One patient got a new device because of error EEE problem. The rest of the nine patients had undefined error problems connected to the test strips.

Table 16. Accu-Chek Aviva – Questions about the meter.

Questions about Accu-Chek Aviva	Yes	No	Not answered (% of total)	Total number
Did you have any technical problems with the meter during the testing period?	9	69	1 %	79

Positive comments
66 patients reported one or more advantages with Accu-Chek Aviva. The reported advantages are grouped as follows:
1. simple operating of the meter (30)
2. the meter/strip needs little blood sample volume (17)
3. the meter has short measuring time (30)
4. the size of the meter (16)
5. the use of Multiclix lancet pen (7)
6. the memory function (3)

Negative comments
30 patients reported one or more disadvantages with Accu-Chek Aviva.
70% of the reported disadvantages were connected to the test strips:
- The test strips are placed in bottles
- It is difficult to get the strips out of the bottle
- It is more convenient with individually packed test strips or device that can load several test strips at the time

Two of the disadvantages are concerning the carrying case and the Multiclix lancet pen. The carrying case seems too large for some of the patients (17 %). The Multiclix lancet pen seems too large and the lancet drum was difficult to replace (7 %). Finally 5 % emphasized that they wanted automatic calibration.

8.2. Questionnaire about user-manual concerning Accu-Chek Aviva

On the questionnaire about the user manual each patient first was asked whether he/she had used the manual. If not, they were to ignore the rest of the questions in the questionnaire.

Table 17 shows that 81 % of the patients had used the user manual, i.e. 64 of the 79 patients that participated in the study. Approximately 47 % of them had read the entire manual and approximately 63 % had consulted the manual when they needed. The 64 patients that had been reading in the user manual seemed satisfied with the manual. 91 % answered they were satisfied with the description of how to perform a blood glucose measurement with Accu-Chek Aviva. 5 % of them thought the manual had essential shortcomings like description of the Multiclix lancet pen and changing of the six-lancet drum, and how to handle the test strips bottle.

Table 17. Accu-Chek Aviva – Questions about the user manual.

Questions about the user manual	Yes (%)	No (%)	Not answered (%)	Number
Have you been reading in the user manual?	81%	13%	6 %	79
If yes, did you read the entire user manual?	47%	45%	9 %	64
And/or did you only consult the user manual when needed?	63%	20%	17 %	64
1. Are you satisfied with the description of how to perform a blood glucose measurement with this meter?	91%	2%	8 %	64
2. Do you think the user manual has essential shortcomings?	5%	88%	8 %	64
3. All in all, are you satisfied with the user manual?	95%		5 %	64

9. References

1. Christensen, N.G, Monsen G, Sandberg S, *Utprøving av analyseinstrumenter*. 1997: Alma Mater Forlag.
2. Skeie, S., et al., *Instruments for self-monitoring of blood glucose: comparisons of testing quality achieved by patients and a technician.* Clin Chem, 2002. **48**(7): p. 994-1003.
3. Stöckl D, Baadenhuijsen H, Fraser CG, Libeer JC, Petersen PH, Ricos C, "Desirable Routine Analytical Goals for Quantities Assayed in serum". *Eur J Clin Biochem* 1995; **33** (3): 157 – 169.
4. American Diabetes Association. Self-monitoring of blood glucose. Diabetes Care 1996; **19** (suppl 1): 62 – 66.
5. Skeie S, Thue G, Sandberg S, "Patient-derived Quality Specifications for Instruments Used in Self-Monitoring of Blood Glucose". *Clinical Chemistry* 2001; **47** (1): 67 – 73.
6. In vitro diagnostic test systems - Requirements for blood-glucose monitoring systems for self- testing in managing diabetes mellitus, ed. ISO. 2003.
7. Kristensen, G.B., et al., *Standardized evaluation of instruments for self-monitoring of blood glucose by patients and a technologist.* Clin Chem, 2004. **50**(6): p. 1068-71.
8. Thienpont, L.M., et al., *Determination of reference method values by isotope dilution-gas chromatography/mass spectrometry: a five years' experience of two European Reference Laboratories.* Eur J Clin Chem Clin Biochem, 1996. **34**(10): p. 853-60.
9. Burnett RW, "Accurate Estimation of Standard Deviations for Quantitive Methods Used in Clinical Chemistry". *Clinical Chemistry* 1975; **21** (13): 1935 – 1938.

10. Attachments

1. Serial numbers, Accu-Chek Aviva meters
2. Information letter to the diabetic patients (in Norwegian)
3. Raw data, internal quality control, Advia
4. Raw data, Accu-Chek Aviva results under standardised conditions, meter A and meter B
5. Raw data, Accu-Chek Aviva results, the diabetics measurements at NOKLUS
6. Raw data, Accu-Chek Aviva results, the diabetics measurements at home
7. Raw data, internal quality control, Accu-Chek Aviva
8. Raw data, Advia results, diabetic patients
9. Raw data, hematocrit
10. Questionnaire, user-friendliness (in Norwegian)
11. Questionnaire, user manual (in Norwegian)

Attachments with raw data are included only in the report to Roche Diagnostics.