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ORIGINAL ARTICLES

Multicenter User Evaluation of ACCU-CHEK® Combo, an Integrated System for Continuous Subcutaneous Insulin Infusion

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Abstract

Background:

The aim of this study was to evaluate a newly developed system for insulin delivery incorporating a multifunctional blood glucose meter and a remotely controlled insulin pump (ACCU-CHEK® Combo system) in established pump users with type 1 diabetes. The technology was assessed both from device performance and subject usability perspectives.

Method:

A multicenter, prospective, single group study was carried out in five centers in the Netherlands and four centers in the United Kingdom for more than 6 months. The study was divided into two phases: Phase 1 (4 weeks) for device validation purposes and phase 2 (22 weeks) to observe the impact of the system on metabolic control, patient satisfaction [using the Diabetes Treatment Satisfaction Questionnaire (DTSQ)] and device safety.

Results:

Eighty subjects completed the planned study period. There were no unexpected device errors. Treatment satisfaction was high at baseline and further increased to study end (DTSQ change version: sum score, 10.6 ± 7.2; scale score range, -18 to +18, $p < 0.0001$). Hemoglobin A1c improved continuously over time, from 7.9% (±0.9%) to 7.7% (±0.8%) at month 3 ($p < 0.001$) and 7.6% (±0.8%) at month 6 ($p < 0.0001$). The frequency of severe hypoglycemia was 0.08 per patient years. There was no case of ketoacidosis.

Conclusions:

The new system was evaluated by experienced continuous subcutaneous insulin infusion users as safe in daily practice and associated with favorable treatment satisfaction and a modest improvement in glycemic control.

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Abbreviations: (BG) blood glucose, (CSII) continuous subcutaneous insulin infusion, (DTSQ) diabetes treatment satisfaction questionnaire, (DTSQc) DTSQ change version, (DTSQs) DTSQ status version, (g) gram, (HbA1c) hemoglobin A1c, (IU) international unit, (SD) standard deviation, (SMBG) self-monitoring of blood glucose, (T1DM) type 1 diabetes

Keywords: bolus advice, continuous subcutaneous insulin infusion, DTSQ, HbA1c, safety, smart insulin pump, treatment satisfaction

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Introduction

The application of a technological approach to the management of type 1 diabetes (T1DM) has produced demonstrable benefits for people living with this condition. The benefits have included improvements in overall blood glucose (BG) control, reduction in the risk of severe hypoglycemia, lower insulin requirements and a positive impact on quality of life.[1,2] In general, the introduction of diabetes-related technologies, such as continuous subcutaneous insulin infusion (CSII), has contributed to greater clinician and subject acceptance of a more intensive approach to T1DM care in adults and children.

However, as with the development of technologies in other areas, manufacturers of devices for insulin delivery continually add features aimed at both improving diabetes management as well as providing a commercial advantage. Most of the technological additions to insulin delivery systems (so-called smart features) have been introduced based on the assumption of benefit without evidence from formal randomized controlled trials.

There has been increased awareness by industry and regulatory authorities as well as clinicians of the need to understand health outcomes from the perspective of subjects.[3] This is particularly relevant for individuals with a chronic disease such as T1DM. For example, for individuals using CSII insulin pump therapy, it is increasingly important to understand the impact of such devices from the user's perspective of "living with a machine" in addition to assessing the performance of a device *per se*.[4]

The aim of this study was to evaluate, from the perspective of subjects with T1DM, a newly developed system for insulin delivery incorporating a multi functional BG meter and a remotely controlled insulin pump. The technology was assessed both from device performance and subject usability perspectives.

Methods

Study Design

A multicenter, prospective, single group study was conducted to evaluate the newly developed ACCU-CHEK® Combo system (Roche Diabetes Care AG, Burgdorf, Switzerland) in subjects using CSII pumps on a daily basis. This system consists of a multifunctional blood glucose meter (ACCU-CHEK Aviva Combo or ACCU-CHEK Performa Combo) and a remotely controlled insulin pump (ACCU-CHEK Spirit Combo). No additional study-specific educational materials were provided to the subjects on how to use the individual features of the ACCU-CHEK Combo system. The study was performed in accordance with the Declaration of Helsinki and International Organization for Standardization (ISO 14155) and was approved by local ethics committees. All patients provided informed consent.

Study Conduct

The study conduct incorporated two observation phases: phase 1, comprising a run-in phase of up to 10 days followed by a 4-week observation period for device validation purposes; and phase 2, lasting 22 weeks to observe effects on metabolic control and subject satisfaction with treatment [using the Diabetes Treatment Satisfaction Questionnaire (DTSQ)] and the devices.

Subjects

The goal was to recruit 95 subjects already established on CSII, taking into account an estimated 15% dropout rate. Main inclusion criteria were the use of CSII therapy for at least 6 months prior to enrollment, age of 18 years or older and hemoglobin A1c (HbA1c) of ≤10%; major exclusion criteria were severe hypoglycemia 4 weeks before screening, being pregnant, lactating or planning pregnancy and using oral or inhaled steroids.

Criteria for Evaluation

Primary objective was to evaluate the frequency of unexpected device errors encountered during the use of the ACCU-CHEK Combo system. Unexpected device errors are all device-related events that have a novel fault description which has not been yet described in the product risk analysis and may result in an adverse event or an event that has a higher frequency of occurrence than the one estimated in the product risk analysis.

Secondary objectives were the documentation of the frequency of system errors and use of system functionalities, collection of clinical data on bolus calculator use, evaluation of treatment satisfaction comparing the DTSQ status (DTSQs) and change (DTSQc) versions and collection of routine clinic data on metabolic status (HbA1c values).

Questionnaires

Treatment satisfaction was assessed using the DTSQs and DTSQc. The DTSQs is a modified DTSQ, which consists of eight items.[5,6] The DTSQs assesses treatment satisfaction during the few weeks before assessment completion. Each item is scored from 0 to 6, with a higher score indicating greater satisfaction. The treatment satisfaction score can range from 0 (very dissatisfied) to 36 (very satisfied). The two additional items measuring perceived frequency of hyperglycemia and hypoglycemia are scored from 0 (none of the time) to 6 (most of the time). The DTSQs can be limited by a ceiling effect when treatment satisfaction is high at baseline.[7]

The DTSQc uses the same eight questions as the DTSQs but has different response options. The DTSQc asks respondents to assess changes in treatment satisfaction with their current treatment compared with their previous treatment and thus overcomes any ceiling effect that may occur with the DTSQs.[8] Each of the six items of the DTSQc is scored from -3 (much less satisfied now) to +3 (much more satisfied now). The DTSQc treatment satisfaction change score can thus range from -18 to +18. The items measuring perceived frequency of hyperglycemia and hypoglycemia are scored from -3 (much less of the time now) to +3 (much more of the time now), such that a higher score indicates more hyperglycemia or hypoglycemia. The DTSQs and DTSQc were completed at baseline and at the end of the study, respectively.

To assess specific features of the evaluated device, a user acceptance questionnaire was completed at study end. It assessed ease of use, level of discretion, user satisfaction and various aspects of bolus advice use. Response options were a seven-point scale (completely disagree to completely agree).

Device Information and Status

The new ACCU-CHEK Combo system consists of an insulin infusion pump and a smart BG meter integrating advanced features including bolus advice, data management, data analysis, reminder functions and remote control of the pump. The insulin pump contains an additional occlusion detection algorithm designed to detect occlusions during basal delivery at an early stage before adversely impacting on BG control.

The novel bolus advice features meal rise, offset time, and acting time as parameters to design an individualized model for correction of postprandial hyperglycemia. High BG values after meals will be corrected to a calculated target value valid for that time point. Meal rise defines the maximum accepted increase in BG above the preprandial BG target value. Offset time defines the duration that the maximum meal rise will be accepted before declining in a linear fashion towards the preprandial target value as long as insulin is expected to be active. This latter parameter is termed acting time and is influenced by the type of rapid-acting insulin (regular or analog) and by the subject's individual insulin sensitivity (i.e., the average bolus dose). An additional parameter is termed snack size, which becomes relevant for individuals recording carbohydrate content of snacks in addition to their main meals.

The ACCU-CHEK Spirit Combo conformed to the requirements of the European Union (CE mark); the ACCU-CHEK Aviva Combo was covered by a European Union manufacturer declaration.

Statistical Methods

The full analysis set population was defined as the subjects participating in a training visit. No missing replacement or last observation carried forward strategies were applied to missing variables. The primary variable (frequency of unexpected device errors) was tested using the exact binomial test. Furthermore, the 95% Clopper Pearson confidence interval of frequency was calculated. Descriptive statistics were used for the analysis of the secondary variables. For continuous data, the mean, median, standard deviation (SD), interquartile range and minimum and maximum values were determined. Categorical data were reported by means of frequency tables. Treatment satisfaction (DTSQs/DTSQc) was evaluated using the Wilcoxon signed rank test. The tests were used in an exploratory way; no multiple testing procedure was applied.

Results

Disposition and Demographics

A total of 90 subjects were enrolled, and 86 subjects were given access to the ACCU-CHEK Combo system in five centers from the Netherlands (n = 54) and four centers from the UK (n = 32). Eighty subjects completed the planned study period; there were 5 informed consent withdrawals and 1 noncompliant subject. The study was conducted from December 2008 to October 2009. All subjects were on CSII treatment for at least 6 months prior to enrollment.

At baseline the subjects were aged (±SD) 47.9 (±12.4) years; 85% had T1DM and 15% had type 2 diabetes, and the average duration (±SD) of diabetes was 23.9 (±12.1) years (**Table 1**).

Study Objectives

Primary outcome: No unexpected device errors occurred during the course of the study.

Treatment Satisfaction

The treatment satisfaction was relatively high at baseline, with an average (±SD) DTSQs score of 31.4 (±3.7). The DTSQc was used to assess the impact on treatment satisfaction at the end of the study. This is assumed to better reflect potential changes in a population with baseline high treatment satisfaction levels. By the end of the study, treatment satisfaction had increased for all assessed items (**Figure 1, Table 2**), reaching statistical significance for the total score and the six subitems ($p < 0.0001$). No changes were observed with regard to the subjects' perceived frequency (mean ± SD) of hyperglycemia (-0.3 ± 1.6) or hypoglycemia (-0.2 ± 1.4).

With regard to the user acceptance questionnaire, 69 (81%) of 85 subjects who completed the study end questionnaire agreed that the system under evaluation made it easier than before to manage their diabetes. Seventy-six (89%) agreed that daily use of the bolus advisor was easy and 74 (87%) agreed that the bolus advisor helped them with the accuracy of bolus dose calculation.

Glycemic Control

Average (± SD) baseline HbA1c values of 7.9 ± 0.9% decreased continuously over time to 7.7 ± 0.8% at month 3 and 7.6 ± 0.8% at month 6. The reductions were statistically significant for month 3 ($p < 0.001$) and month 6 ($p < 0.0001$) compared to baseline (**Figure 2**). Downloaded meter data were available from 86 subjects. The overall frequency of BG values <3.9 mmol/liter (<70 mg/dl) was 3.0 ± 2.3 per week, with no obvious trend over time.

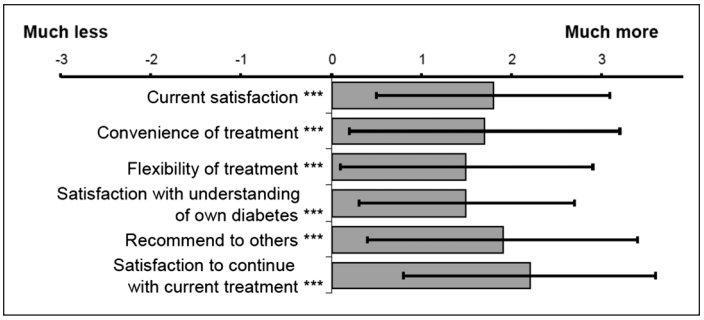

Figure 1. Treatment satisfaction development (mean ± SD DTSQc scores at study end). The asterisks indicate $p < 0.0001$ (Wilcoxon signed rank test).

Table 1.
Subject Baseline Characteristics

	N	Mean ± SD
Male/female (*n*)	37/49 (*N* = 86)	—
Age (years)	86	47.9 ± 12.4
Weight (kg)	86	78.6 ± 17.3
Body mass index (kg/m^2)	86	26.1 ± 5.2
HbA1c (%)	80	7.9 ± 0.9
Diabetes Type (%)		
Type 1 Type 2	73 (84.9%) 13 (15.1%)	—
Duration since diagnosis (years)	86	23.9 ± 12.1
Insulin Dose (IU/day)		
Total Insulin Total Basal Total Bolus	85 86 85	48.5 ± 27.2 28.3 ± 20.5 20.1 ± 11.9
Average No. of SMBG per day	73	4.6 ± 1.9

Table 2.
Treatment Satisfaction Development (DTSQc Scores at Study End)

	N	Mean	SD	*p* Value[a]
DTSQ sum score	82	10.6	7.2	< 0.0001
Questions				
Current satisfaction	82	1.8	1.3	< 0.0001
Convenience of treatment	82	1.7	1.5	< 0.0001
Flexibility of treatment	82	1.5	1.4	< 0.0001
Satisfaction with understanding of own diabetes	82	1.5	1.2	< 0.0001
Recommend to others	82	1.9	1.5	< 0.0001
Satisfaction to continue with current treatment	82	2.2	1.4	< 0.0001
Perception of Glycemic Control				
Perceived frequency of hyperglycemia	82	-0.3	1.6	0.1207
Perceived frequency of hypoglycemia	81	-0.2	1.4	0.2349

[a] Wilcoxon signed rank test, testing of unchanged satisfaction

Device Use

The majority of subjects used default settings for meal rise, acting time, and offset time and did not adjust them during the study. At baseline, a total of 31 subjects (36%) selected the default meal rise setting of 2.8 mmol/liter (50 mg/dl), and 42 subjects (49%) used 3.0 mmol/liter (54 mg/dl). Seventy-two (84%) selected the default acting time of 240 minutes, and 13 (15%) used a shorter setting (ranging from 90 to 180 minutes). Seventy-four subjects (86%) selected the default offset time of 60 minutes (ranging from 45 to 120 minutes). Seventeen subjects (20%) selected a snack size of 0 grams (g) carbohydrates, and 69 of them chose between 1 and 24 g, with a preference for 15 and 10 g (40 and 19%). Sixty-four subjects (74%) maintained their initial settings throughout the study. There was no obvious trend regarding the parameters adjusted by the other subjects.

The frequency of self-monitoring of blood glucose (SMBG) as evaluated for months 1, 3 and 6 increased by about one additional SMBG to 5.2 ± 1.7 (mean ± SD) per day during the first month compared to baseline (4.5 ± 2.0) and then decreased again to values comparable with those at baseline (month 3: 4.6 ± 1.8; month 6: 4.5 ± 2.0).

The number of bolus doses per 24 hours specified at baseline was 3.6 ± 1.1 (case report form data). From the downloads, the average number of boluses was slightly higher, with at least five boluses per day in months 1, 3 and 6. There are two main approaches to delivering a bolus: accepting bolus advice or directly using the bolus button on the pump. The percentage of bolus advice use decreased from 58% in month 1 to 48% at month 6, whereas the number of subjects using the buttons directly on the pump to deliver a bolus increased over the same time, from 34 to 50%, respectively. A third alternative, to program a bolus using the meter remote but without utilizing the bolus adviser feature, was used rarely. On average, three carbohydrate entries were recorded per day (**Table 3**), suggesting that in this group of experienced CSII users (81% formerly used an ACCU-CHEK or Disetronic pupmp), insulin was dosed for smaller snacks on the pump directly. In months 1, 3 and 6 the calculated bolus dose was used more than 80% of the time without subjects making any adjustment. Total daily insulin dose and distribution between basal and bolus insulin, calculated from device data corresponding to 7 days before study visit, were similar over time (data not shown). Mean values before study end were 50.2 ± 25.9 international units (IU) per day, with 54.6% of the dose used as basal insulin. This compares to baseline values of 48.5 ± 27 IU/day, with 58.4% given as basal insulin (case report form data).

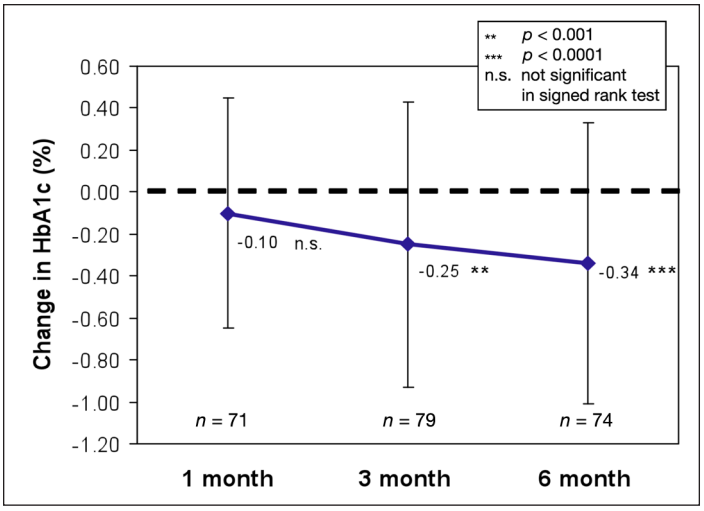

Figure 2. HbA1c changes compared to baseline (mean ± SD).

Table 3.
Number of Carbohydrate Entries and Amounts

Carb Entries (*n*/day)	*N* (subjects)	Mean	SD
Month 1	83	3.3	1.3
Month 3	75	2.8	1.2
Month 6	75	2.6	1.3
Carb Amount (g/day)	Number of Days[a]	Mean	SD
Month 1	2078	140.3	76.9
Month 3	2000	125.6	71.0
Month 6	1835	121.0	76.9

[a] 30 days until visit of month x; only days with entry counted.

Device Function

Occlusion alarms which were triggered either by force thresholds or the new algorithm occurred, with an incidence of 15.3 per patient year, similar to its precursor ACCU-CHEK Spirit (n = 16).[9] About 54% of the alarms here were triggered by the new algorithm. Sixteen subjects reported transient and minor problems with Bluetooth communication during the study.

Safety Findings

There was not a single case of ketoacidosis. Three events of severe hypoglycemia (third party help) occurred, corresponding to an incidence of 0.08 events per patient year. Eight cases of hyperglycemia were reported as device-related (3 occlusions, 3 infusion set dislodgements, 1 meter failure with alarm and 1 pump failure with alarm).

Discussion

There has been a significant growth in the use of CSII and other technologies for the management of T1DM, although there remains important geographical variation in access to these technologies.[10] It is generally accepted that CSII offers distinct and measurable advantages for adults and children with T1DM.[11,12] However, despite the dearth of robust data from large prospective randomized controlled clinical trials, there is a general consensus that part of the reason for the enhanced popularity of this form of insulin delivery has been the incorporation of novel features. These have included electronic food diaries, multifunctional BG meters, remote monitoring systems, in combination with continuous glucose monitoring systems and bolus calculators.[13–15]

In this study, we have shown that during a 26-week period of assessment, the use of a multifunctional BG meter and a remotely controlled insulin pump was not associated with unexpected device errors and that the users reported positive experiences in terms of treatment satisfaction. In addition, overall glycemic control, as assessed by change in HbA1c levels, also improved in the absence of a major change in total daily insulin dose or a sustained change in frequency of SMBG. It is also noteworthy that the study was performed in subjects with a long duration of T1DM and experience with CSII. In these subjects the enhanced treatment satisfaction appeared to arise from domains beyond the devices impact on perceived frequency of hyperglycemia and hypoglycemia.

During CSII, insulin delivery may be disrupted by a number of factors such as disconnection of the catheter, pump failure, and crystallization of the insulin, with the potential for unexpected glucose excursions above an individual's target range.[16–18] Evidence suggests that the latter may be influenced by the type of insulin used as well as the duration of use of a single catheter.[19] Here, an additional feature of the CSII system under review was the use of a novel feature for the early detection of occlusions. We found an occlusion detection rate (19, data on file), that was similar to previous experience with the ACCU-CHECK Spirit device but more than half of the detected occlusions were triggered by the new algorithm. It remains to be determined whether earlier detection will lead to meaningful clinical improvements for subjects.

Using a qualitative approach, we have also reported that for individuals with T1DM and using CSII, "living with a machine" leads, ironically, to greater humanization of their care.[4] Subjects using pumps report more control over diabetes-related symptoms and insulin doses, a greater sense of personal empowerment in terms of knowledge and self-care and a greater sense of self-acceptance and partnership between themselves and their professional careers. In contrast, anecdotally one of the most common reasons for an individual to not opt for CSII is a reluctance to be continuously attached to a machine. It is likely that this in part relates to the size of the currently available devices, and therefore the wearer has a "badge" highlighting the presence of diabetes. The current system, although of comparable size, is more discreet due to the novel addition of the remote control hand set. Therefore the wearer can make changes to the insulin infusion frequency and rate without having to directly access the infusion device. Devices communicate using Bluetooth technology, and we did not encounter major problems with connectivity. Some subjects reported transient and minor problems with connectivity that were clinically insignificant. Subsequent to the study, design changes to the devices were implemented to enhance connectivity. During this 6-month user evaluation, we observed no cases of ketoacidosis, and the frequency of severe hypoglycemia was lower compared to large studies using an earlier version of insulin pump.[9,20]

It is noteworthy that we did not provide additional study-specific educational materials for the smart features of the ACCU-CHEK Combo system at study onset. Accordingly, none of the subjects used all of the smart pump features. However, subjects used the bolus advice more than 80% of the time without modification, presumably reflecting the confidence in bolus advice. Although the majority of subjects used the default settings for meal rise, acting and offset time, almost 75% did not alter the initial settings. The interpretation of this is not clear but may reflect previous learned experience related to insulin dose adjustment, i.e., the subjects were already comfortable with insulin dose calculation and adjustment. Alternatively, the content and delivery of the education and training associated with using such features may not have adequately covered problems with literacy or numeracy.[21] The majority of subjects did, however, value the new system in terms of managing their diabetes and easy use of the bolus advisor, as evaluated in the user acceptance questionnaire. A recent cross-over trial reported that use of automated bolus calculators can assist in controlling postprandial glycemia without significantly inducing hypoglycemia and that there may be a difference in efficacy between the devices.[22]

This study has several limitations. First, the design did not include an active control group, and individuals were recruited with long-standing T1DM as well as experience in CSII. The impact of this particular CSII for subjects newly starting CSII is not known. We also did not include children and adolescents. As mentioned above, we did not assess learning skills including numeracy and literacy; this may have influenced an individual's ability to use the new features. Although we included a novel algorithm for occlusion detection, we did not formally assess its impact on day-to-day glycemic excursions. The number of entries for snacks and meal-related carbohydrates was lower than expected and indicates that use of the bolus advisor was less frequent than anticipated in this group of experienced pump users. Again this may reflect shortcomings in training, inflexibility in the behavior of subjects experienced with infusion pumps or an unwillingness to accept bolus advice.

Conclusions

In summary, the use of a discrete insulin pump system with added features related to advice on meal and correction insulin dosing and a new algorithm for earlier detection of occlusions was well received by experienced insulin pump users. Overall treatment satisfaction measurably improved and was associated with a modest reduction in HbA1c levels. As T1DM is a life-long condition, the importance of assessing the impact of new technologies from the perspective of users cannot be overemphasized.

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