Fighting the Hydra: Optimizing treatment for type 2 diabetes
Simon, A.C.R.

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Clinical effectiveness of an e-health system to support patients in adjusting insulin dose at home: a randomized controlled trial

Airin C R Simon, Frits Holleman, Bas Goorden, Ameen Abu-Hanna, Joost B L Hoekstra, Niels Peek

Submitted for publication
Abstract

Background
New approaches for care delivery are necessary to achieve and maintain the target level of HbA1C among patients with type 2 diabetes. A promising patient-oriented strategy is to let insulin titration successfully be undertaken by patients themselves. We previously developed and validated a web-based e-health system to guide patients in insulin self-titration. The main objective of the present study is to determine whether this system is effective in improving glycaemic control in patients with diabetes mellitus type 2 using basal insulin compared to usual care.

Methods
We performed a multi-centre randomized controlled trial. Patients were randomized to either the intervention group (web-based insulin titration with usual care) or the control group (usual care only). Patients were recruited from December 2012 until January 2014. We set the minimum follow-up duration to 12 weeks. The primary outcome was change in HbA1c. Secondary outcomes included laboratory FPG and treatment satisfaction as measured with the Diabetes Treatment Satisfaction Questionnaire status questionnaire (DTSQs). We used linear mixed effects models to analyse the primary and secondary endpoints that were determined at baseline and each subsequent 12 weeks of follow-up. Furthermore, the effect of the intervention was evaluated in subgroups defined by duration of insulin use (insulin starters versus long-term insulin users) and type of diabetes care (primary versus secondary care).

Results
Of 123 patients screened, 73 were randomized, 38 were allocated to the intervention group and 35 were allocated to the control group. We did not reach the target number of 160 patients. The intervention group showed a greater HbA1c decrease than the control group but this was not statistically significant in the overall study population (mean difference (MD): -3.1, 95% CI: -8.1 to 1.7). However, in patients from primary care, the intervention group showed a significant HbA1c decrease (MD: -4.9, 95% CI: -9.8 to -0.4). In patients that used insulin for more than six weeks before inclusion, there was a trend towards a greater HbA1c decrease in the intervention group than control group (MD: -4.5, 95% CI: -9.6 to 0.6). Treatment satisfaction was higher in the intervention group than in the control group (MD: 5.3; 95% CI: 1.2 to 9.5).
Conclusion
This study suffered from a low number of included patients and did not establish better glycaemic control through web-based insulin titration in the overall patient group. Subgroup analyses showed that web-based insulin titration was effective in improving glycaemic control in patients from primary care and suggested a similar effect in patients that have been using insulin for a longer period as opposed to insulin starters. In this selected group of trial participants that were willing and able to use PANDIT, treatment satisfaction was higher among PANDIT users than among non-users.
Introduction

Many patients with type 2 diabetes mellitus (T2DM) eventually need insulin therapy to achieve the glycated haemoglobin (HbA1c) targets [1,2]. A once daily basal insulin regimen is then the recommended choice because it is more convenient and equally effective as other treatments [3,4]. Clinical trials showed that the addition of basal insulin to existing oral glucose-lowering therapy leads to adequate glycaemic control in the majority of patients with T2DM when applying the so-called ‘treat-to-target’ principle [5,6], i.e. systematically titrating basal insulin according to predefined fasting plasma glucose (FPG) criteria [7]. Unfortunately, most patients with T2DM do not reach the HbA1c target in daily practice [8-10].

New approaches that improve quality of diabetes care are therefore necessary to achieve and maintain target levels of HbA1c. Tricco et al. found that, in general, quality improvement interventions targeting patients showed greater improvements in HbA1c than interventions aimed at clinicians [11]. With the rapid increase in internet access in households, the last decade has witnessed novel opportunities to disseminate such interventions and involve patients in their own care. There is evidence that e-health systems for chronically ill patients improve their knowledge and social support, and can help them to change their behaviour and improve clinical outcomes [12]. For patients with T2DM specifically, e-health systems with computerized decision support (CDS) functionalities can be used to assist T2DM patients in performing insulin titration at home. So far, the majority of CDS evaluative studies investigated the clinical effect of assisting clinicians in making treatment decisions for their T2DM patients [13-15], while the effectiveness of CDS systems targeting patients with T2DM is understudied [15,16]. To our knowledge, there are two randomized controlled trials that have specifically investigated the effectiveness of a CDS system that provides insulin dosing advice to patients with T2DM. Both studies found a greater reduction in HbA1c from baseline to end point in the intervention group than in usual care. In the study of Lim et al., this effect seemed primarily the result of lifestyle change advice, rather than insulin dose adjustment advice [17]. Therefore, the clinical effectiveness specific to the automatic insulin dosing advice remained obscure. Kim et al. specifically focused on patients starting on insulin glargine [18]. International guidelines state that either intermediate acting insulin NPH or long acting insulin glargine or insulin detemir may be used when starting basal insulin therapy [3]. Furthermore, we postulate that patients already using insulin might also benefit from automatic insulin dosing advice. We want to elaborate further on these two previous studies, and test
the effectiveness of a CDS system that provides insulin dosing advice to all patients on any basal insulin.

We previously developed and validated a web-based CDS system to guide patients with T2DM on basal insulin in their self-titration [19]. The objective of the present study was to determine whether this system is effective in improving glycaemic control in T2DM patients using basal insulin, when compared to usual care.

**Methods**

**Study design and patients**

We performed a multi-centre randomized controlled trial. Patients were randomized to either the intervention group (web-based insulin titration with usual care) or the control group (usual care only). The study population consisted of patients with diabetes mellitus type 2, aged 18-80 using basal insulin therapy once a day. Patients should have access to the Internet and having a mobile phone. Furthermore they had to be able to read and understand the Dutch language (see Table 1 for the in- and exclusion criteria). As the target population of diabetic patients using basal insulin only are principally treated by general practitioners, patients were primarily recruited from general practices. Patients were also recruited from the outpatient clinics of five hospitals. These general practices and hospitals were located in and around Amsterdam. General practices and hospitals were actively recruited by the research team by invitation per letter and telephone and passively recruited by posting advertisements in two diabetes magazines for healthcare professionals.

This study was approved by the Institutional Review Board of the Academic Medical Centre, Amsterdam, the Netherlands. The study is registered on ClinicalTrials.gov (NCT01715090).
In- and exclusion criteria used during screening, which took place before randomization

**Inclusion criteria**
- Male or female between 18 and 80 years
- Type 2 diabetes mellitus (diagnosed clinically) for ≥6 months
- Use of once daily basal insulin therapy
- BMI <40 kg/m²
- Ability to read and understand the Dutch language
- Having access to the Internet and having a mobile phone
- Ability and willingness to adhere to the protocol including daily performance of self-monitored plasma glucose profiles according to the protocol
- Ability and willingness to use a web-based insulin self-titration system
- Confirmed written consent

**Exclusion criteria**
- Type 1 diabetes
- Recurrent severe hypoglycaemia (more than 1 severe hypoglycaemic episode during the last 12 months) or hypoglycaemic unawareness as judged by the Investigator
- Active proliferative diabetic retinopathy, as defined by the application of photocoagulation or surgery, in the 6 months before study entry or any other unstable (rapidly progressing) retinopathy that may require photocoagulation or surgery during the study (an optic fundus examination should have been performed within 2 years prior to study entry)
- Any clinically significant disease or disorder, except for conditions associated with type 2 diabetes, which in the Investigator’s opinion could interfere with the results of the trial
- Mental condition rendering the patient unable to understand the nature, scope and possible consequences of the study

**System description**

Our research group developed a web-based glucose system containing a diary to guide patients in self-titration, called PANDIT (Patient Assisting Net-based Diabetes Insulin Titration). This diary is shown in Figure 1. Patients needed to consult the PANDIT system once every three days, to enter their latest FPG values, their current insulin dose and whether they experienced symptomatic hypoglycaemic events. PANDIT will immediately provide an insulin dosing advice for the patient, taking into account the body weight and age of the patient. When the patient does not access the system in time, PANDIT will send a text message to the mobile phone of the patient. Patients can also choose to consult the system with another visit frequency, e.g. once every seven days, and/or receive a reminder text message by e-mail. Care providers also had access to PANDIT through a dedicated user interface allowing them to access their patients’ diaries.

The insulin dosing advice from PANDIT are based on a treat-to-target algorithm that systematically increases the insulin dose by two to four units to obtain FPG values between 4 and 7 mmol/L [19]. In case of a hypoglycaemic event, i.e. a glucose value below 3.9 mmol/L, the insulin dose will be decreased. PANDIT also incorporates...
an algorithm that decides when it is necessary for the care provider to review the patient data and to stop the automatic dosing advice, i.e. if a patient has experienced two or more hypoglycaemic events in one month or if a patient uses variable insulin doses (varying more than 4 units). After reviewing the data, the care provider has the possibility to take over the provision of insulin dosing advice through the system. As soon as the patient is sufficiently stabilized according to the care provider, the care provider can decide to “unblock” the automatic dosing advice, and let PANDIT generate new insulin dosing advice again. The care provider has the possibility to adjust the upper limit of the target FPG range of 7 mmol/L to prevent future hypoglycaemic events.

The PANDIT system was developed specifically for this study using Gaston, a state-of-the-art framework for building CDS systems [20]. PANDIT runs on a secure server and is password protected, with a personal account for each patient. The system architecture meets the requirements of NEN7510, the Dutch standard for information security in health care [21]. The safety of the insulin dosing advice and the usability of the PANDIT system was previously confirmed in a pilot study [19].

Figure 1 Patient diary of the PANDIT system
Recruitment
Patients were recruited from December 2012 until January 2014. We set the minimum follow-up duration to 12 weeks with optional extensions of 12 weeks until the end of the study period, which was April 2014. We applied two recruitment strategies. Eligible patients were recruited by care providers from participating general practices and hospitals. Furthermore, we placed study recruitment advertisements in regional and national newspapers in the Netherlands. If a patient contacted our research team and was eligible, the general practice or hospital of his or her treating physician was invited to participate.

Randomisation
We randomly assigned patients to the two study arms in sequentially numbered opaque sealed envelopes. To ensure good balance of patient characteristics in each group, randomisation was stratified according to duration of use of insulin (insulin starters, i.e. duration of insulin use was equal or shorter than six weeks at baseline, or long-term insulin users, i.e. duration of insulin use was longer than 6 weeks at baseline) and type of care (primary or secondary care). Researchers, caregivers and patients were not blinded to whether they were randomized to the intervention or control group.

Allocation
Patients were seen by a researcher at baseline to perform screening and randomization to either the intervention group (PANDIT with usual care) or the control group (usual care). Furthermore, after enrolment, patients were seen each subsequent 12 weeks until the end of follow-up to collect study data. Contacts with the research staff were offered to the patient as a site visit or a phone call contact. In addition to these mandatory study visits, patients in both study arms could contact their own care provider for counselling at any time, which fall under usual care. Patients allocated to the intervention group received, in addition to usual care, a personal account to access the PANDIT system and five minute instructions by the researcher on how they should use the system. Patients allocated to the control group received usual care from their general practice or hospital. Furthermore, they received a paper diary to record hypoglycaemic events. Care providers in the control group were informed about the titration target used in the intervention group. In both study groups, diabetes treatment other than insulin could be (dis)continued at the care providers.
discretion during the study. Patients were free to withdraw at any time without giving a reason.

Outcome measures
The primary outcome was change in HbA1c. Secondary outcomes were laboratory FPG, treatment satisfaction as measured with the Diabetes Treatment Satisfaction Questionnaire status questionnaire (DTSQs) [22] and the Diabetes Treatment Satisfaction Questionnaire change questionnaire (DTSQc) [23], occurrence of hypoglycaemia and serious adverse events. Insulin doses and body weight were also recorded during the study. Furthermore, at each study visit, patients were questioned about adverse events. The occurrence of hypoglycaemic events was self-recorded in PANDIT (intervention group) or in the paper diary (control group). Furthermore, the occurrence of hypoglycaemic events was also self-reported at each study contact, i.e. patients in both groups were asked about the occurrence of hypoglycaemic events.

Sample size
We aimed to detect a clinically significant HbA1c difference of 0.5% between both groups after 26 weeks of follow-up. Using the standard sample size calculation formulas for binary endpoints, a sample size of 64 patients per group was needed to detect this difference with a power of 80% and 5% risk of type I errors. Accounting for a drop-out rate of 20%, we aimed to recruit 80 patients per group.

Statistical analysis
We used linear mixed effects models to analyse the primary and secondary endpoints that were determined at baseline and each subsequent 12 weeks of follow-up. These models appropriately account for the correlation between measurements from the same patient over time. For each endpoint we used mixed models that consisted of three fixed effects: time (days since first visit), intervention (yes/no), and the interaction between time and intervention, where the latter effect was of primary interest to answer our research question. Analyses were conducted on an intention-to-treat basis, including all patients in the groups to which they were randomized. Furthermore, the effect of the intervention was evaluated in subgroups defined by duration of insulin use (insulin starters versus long-term insulin users) and type of diabetes care (primary versus secondary care). The Wilcoxon rank-sum test was used to compare study duration between both study arms. All statistical analyses
were performed using the R statistical environment, version 3.1.0 (R Foundation for Statistical Computing, 2014). A two-sided type I error rate of 5% was used throughout.

Results

Patient population
Care providers from five hospitals and 126 general practices participated. We have no data on the total number of potentially eligible patients that were invited by their care providers to participate, as not all care providers were willing or able to record these data. According to the care providers, the main reason for patients to not participate was the patients’ perceived inability or fear to deal with computers or their perception that this would increase the mental burden that they already have with the use of insulin.

The flow of patients through the trial is shown in Figure 2. Of 123 patients screened, 73 were randomized, 38 were allocated to the intervention group and 35 were allocated to the control group. We did not reach the target number of 160 patients. A substantial number of patients had to be excluded prior to randomization as they did not meet the inclusion criteria, primarily because they had to switch to a more intensive insulin regime. Other reasons were not having a computer or inability to understand the Dutch language. Also, a substantial number of patients declined to participate or did not respond.

Table 2 shows the baseline demographic and clinical characteristics for both treatment groups. Although HbA1c data were available, baseline demographic data for one patient in the control group could not be retrieved since he repeatedly failed to show up for his baseline study visit. The majority of patients were male, were recruited from primary care and were considered long-term users of insulin at baseline. Study duration was similar in both groups (intervention group: median (IQR) 5.1 (3.4-6.7); control group: median (IQR) 5.1 (3.3-6.3); \( p=0.74 \)).
Figure 2  The flowchart of patients enrolled in the study

Table 2  Baseline demographic and clinical characteristics of the intervention and control group

<table>
<thead>
<tr>
<th>Variables</th>
<th>Intervention group (PANDIT with usual care) (n=35)</th>
<th>n</th>
<th>Control group (usual care) (n=33)</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years (mean (SD))</td>
<td>60.3 (7.2)</td>
<td>35</td>
<td>61 (8.8)</td>
<td>32</td>
</tr>
<tr>
<td>Male sex (n (%))</td>
<td>21 (60%)/ 14 (40%)</td>
<td>35</td>
<td>24 (75%)/ 8 (25%)</td>
<td>33</td>
</tr>
<tr>
<td>Primary care (n (%))</td>
<td>29 (82.9%)/ 6 (17.1%)</td>
<td>35</td>
<td>25 (78.1%)/ 7 (21.9%)</td>
<td>32</td>
</tr>
<tr>
<td>Started with insulin within the last six weeks (n (%))</td>
<td>10 (28.6%)/ 25 (71.4%)</td>
<td>35</td>
<td>7 (21.9%)/ 25 (78.1%)</td>
<td>32</td>
</tr>
<tr>
<td>Ethnic groups (n (%))</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>24 (68.6%)</td>
<td>35</td>
<td>22 (62.9%)</td>
<td>30</td>
</tr>
<tr>
<td>Surinamese/ Hindu</td>
<td>5 (14.3%)</td>
<td></td>
<td>5 (14.3%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>6 (17.1%)</td>
<td></td>
<td>3 (8.6%)</td>
<td></td>
</tr>
<tr>
<td>Duration of diabetes in years (median (IQR))</td>
<td>10 (6-14)</td>
<td>34</td>
<td>9.5 (5.2-14)</td>
<td>32</td>
</tr>
<tr>
<td>Duration of insulin use in years (median (IQR))</td>
<td>0.7 (0.1-2.1)</td>
<td>34</td>
<td>1 (0.1-4.6)</td>
<td>32</td>
</tr>
<tr>
<td>Insulin dose in units (median (IQR))</td>
<td>24 (14-41)</td>
<td>34</td>
<td>24 (17-33)</td>
<td>32</td>
</tr>
</tbody>
</table>
Chapter 10

Table 3 shows the mean difference in HbA1c change between the intervention group and the control group in the overall patient group and in subgroups of patients. In the overall patient group, the intervention group showed a significant decrease in HbA1c after 26 weeks of treatment. The HbA1c decrease in the control group was not statistically significant. The difference in HbA1c change between the two study groups was not statistically significant. In the subgroup of patients from primary care, the intervention group showed a greater HbA1c decrease than the control group. Likewise, in long-term users of insulin there was a trend towards a greater HbA1c decrease in the intervention group than the control group.

Table 3 also shows the mean difference in FPG change between the intervention group and the control group for all patients and in subgroups of patients. There were no significant differences in FPG change between the intervention group and the control group in the overall patient group or in subgroups of patients. However, the intervention group showed a trend towards a greater FPG decrease than the control group in the overall patient group, in primary care patients and in long-term users of insulin.

Treatment satisfaction was higher in the intervention group than in the control group as measured with the DTSQs questionnaire. Treatment satisfaction change as measured with DTSQc at end of follow-up was also higher in the intervention than in the control group (12.8 and 5.8, \( p < 0.001 \)).

<table>
<thead>
<tr>
<th>Variables</th>
<th>Intervention group (PANDIT with usual care) (n=35)</th>
<th>Control group (usual care) (n=33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of basal insulin (n (%))</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NPH</td>
<td>10 (29.4%)</td>
<td>5 (14.7%)</td>
</tr>
<tr>
<td>Glargine</td>
<td>22 (64.7%)</td>
<td>22 (64.7%)</td>
</tr>
<tr>
<td>Detemir</td>
<td>2 (5.9%)</td>
<td>5 (14.7%)</td>
</tr>
<tr>
<td>HbA1c in mmol/mol (mean (SD))</td>
<td>67 (12.5)</td>
<td>64.2 (11.8)</td>
</tr>
<tr>
<td>FPG in mmol/L (mean (SD))</td>
<td>9.4 (3.3)</td>
<td>8.5 (2.8)</td>
</tr>
<tr>
<td>BMI in kg/m2 (mean (SD))</td>
<td>29.8 (5.7)</td>
<td>29.4 (4.8)</td>
</tr>
</tbody>
</table>

SD, standard deviation; IQR, interquartile range; NPH, Neutral Protamine Hagedorn; FPG, fasting plasma glucose; BMI, Body Mass Index.

Effectiveness

Table 3 shows the mean difference in HbA1c change between the intervention group and the control group in the overall patient group and in subgroups of patients. In the overall patient group, the intervention group showed a significant decrease in HbA1c after 26 weeks of treatment. The HbA1c decrease in the control group was not statistically significant. The difference in HbA1c change between the two study groups was not statistically significant. In the subgroup of patients from primary care, the intervention group showed a greater HbA1c decrease than the control group. Likewise, in long-term users of insulin there was a trend towards a greater HbA1c decrease in the intervention group than the control group.

Table 3 also shows the mean difference in FPG change between the intervention group and the control group for all patients and in subgroups of patients. There were no significant differences in FPG change between the intervention group and the control group in the overall patient group or in subgroups of patients. However, the intervention group showed a trend towards a greater FPG decrease than the control group in the overall patient group, in primary care patients and in long-term users of insulin.

Treatment satisfaction was higher in the intervention group than in the control group as measured with the DTSQs questionnaire. Treatment satisfaction change as measured with DTSQc at end of follow-up was also higher in the intervention than in the control group (12.8 and 5.8, \( p < 0.001 \)).
Table 3  The mean change in outcome per half year and the mean difference in outcome between the intervention group and the control group for all patients and in subgroups of patients

<table>
<thead>
<tr>
<th>Outcome characteristic</th>
<th>Total group (n=68)</th>
<th>Intervention group (PANDIT with usual care) (n=35)</th>
<th>Control group (usual care) (n=33)</th>
<th>Mean difference (95% CI) between intervention and control group</th>
<th>p value</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Mean change (95% CI in group)</td>
<td>Baseline</td>
<td>Mean change (95% CI in group)</td>
<td></td>
</tr>
<tr>
<td>HbA1c (mmol/mol)^a</td>
<td>65.3 (62.4 to 68.3)</td>
<td>-3.1 (-5.4 to -0.6)</td>
<td>66.7 (60.9 to 72.6)</td>
<td>-4.5 (-8.2 to -1.4)</td>
<td>-3.1 (-8.1 to 1.7)</td>
</tr>
<tr>
<td>FPG (mmol/L)^a</td>
<td>8.9 (8.2 to 9.6)</td>
<td>0.0 (-0.8 to 1.0)</td>
<td>9.2 (7.8 to 10.6)</td>
<td>-0.6 (-2.3 to 1.0)</td>
<td>8.5 (7.5 to 9.5)</td>
</tr>
<tr>
<td>Insulin dose (units)^b</td>
<td>29.0 (23.6 to 34.4)</td>
<td>8.9 (6.3 to 11.5)</td>
<td>30.7 (19.9 to 41.5)</td>
<td>10.8 (5.5 to 16.2)</td>
<td>27.2 (19.4 to 35.0)</td>
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<tr>
<td>Body weight (kg)^b</td>
<td>88.5 (83.8 to 93.1)</td>
<td>0.2 (-0.7 to 1.0)</td>
<td>88.6 (79.2 to 97.9)</td>
<td>0.5 (-1.3 to 2.3)</td>
<td>88.4 (81.6 to 95.1)</td>
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<td>DTSQs^b</td>
<td>27.9 (26.4 to 29.3)</td>
<td>1.3 (-0.8 to 3.3)</td>
<td>26.9 (23.7 to 29.8)</td>
<td>3.4 (-0.6 to 7.6)</td>
<td>29.2 (27.1 to 32.4)</td>
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<table>
<thead>
<tr>
<th>Outcome characteristic</th>
<th>Insulin starters (n=17)</th>
<th>Intervention group (PANDIT with usual care) (n=10)</th>
<th>Control group (usual care) (n=7)</th>
<th>Mean difference (95% CI) between intervention and control group</th>
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<tr>
<td></td>
<td>Baseline</td>
<td>Mean change (95% CI in group)</td>
<td>Baseline</td>
<td>Mean change (95% CI in group)</td>
<td></td>
</tr>
<tr>
<td>HbA1c (mmol/mol)</td>
<td>68.2 (62.5 to 74.0)</td>
<td>-6.0 (-11.3 to -1.1)</td>
<td>68.6 (57.0 to 80.2)</td>
<td>-5.6 (-16.8 to 4.4)</td>
<td>67.7 (58.8 to 76.6)</td>
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<td>FPG (mmol/L)</td>
<td>9.5 (7.5 to 11.6)</td>
<td>-1.4 (-2.8 to -0.2)</td>
<td>9.7 (5.5 to 13.8)</td>
<td>-1.3 (-3.9 to 1.4)</td>
<td>9.5 (6.3 to 12.7)</td>
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<tr>
<td>Insulin dose (units)</td>
<td>15.3 (9.3 to 21.4)</td>
<td>10.5 (5.8 to 15.2)</td>
<td>14.1 (1.7 to 26.3)</td>
<td>11.3 (1.4 to 21.2)</td>
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<table>
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<th>Outcome characteristic</th>
<th>Long-term users of insulin (n=51)</th>
<th>Intervention group (PANDIT with usual care) (n=25)</th>
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<tr>
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<td>Baseline</td>
<td>Mean change (95% CI in group)</td>
<td>Baseline</td>
<td>Mean change (95% CI in group)</td>
<td></td>
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<tr>
<td>HbA1c (mmol/mol)</td>
<td>64.3 (60.9 to 67.7)</td>
<td>-1.7 (-4.3 to 1.1)</td>
<td>66.0 (59.2 to 72.7)</td>
<td>-4.0 (-9.1 to 1.1)</td>
<td>62.8 (58.0 to 67.5)</td>
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<tr>
<td>FPG (mmol/L)</td>
<td>8.6 (7.9 to 9.4)</td>
<td>0.9 (-0.3 to 2.0)</td>
<td>8.9 (7.5 to 10.4)</td>
<td>-0.1 (-2.3 to 2.0)</td>
<td>8.3 (7.3 to 9.4)</td>
</tr>
<tr>
<td>Insulin dose (units)</td>
<td>33.7 (27.2 to 40.3)</td>
<td>8.0 (4.8 to 11.1)</td>
<td>37.5 (24.6 to 50.4)</td>
<td>10.5 (4.3 to 16.7)</td>
<td>30.1 (21.0 to 39.2)</td>
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### Outcome characteristic

<table>
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<th>Primary care (n=55)</th>
<th>Intervention group (PANDIT with usual care) (n=29)</th>
<th>Control group (usual care) (n=26)</th>
<th>Mean difference (95% CI) between intervention and control group</th>
<th>p value</th>
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<tr>
<td><strong>Baseline</strong></td>
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<tr>
<td>HbA1c (mmol/mol)</td>
<td>64.4 (61.1 to 67.7)</td>
<td>65.9 (59.3 to 72.5)</td>
<td>62.7 (57.9 to 67.5)</td>
<td>-4.9 (-9.8 to -0.4)</td>
<td>0.04</td>
</tr>
<tr>
<td>FPG (mmol/L)</td>
<td>8.7 (8.1 to 9.4)</td>
<td>8.8 (7.5 to 10.2)</td>
<td>8.7 (7.7 to 9.7)</td>
<td>-1.5 (-3.2 to 0.2)</td>
<td>0.08</td>
</tr>
<tr>
<td>Insulin dose (units)</td>
<td>28.6 (23.2 to 33.9)</td>
<td>28.7 (17.9 to 39.4)</td>
<td>28.5 (20.7 to 36.3)</td>
<td>2.3 (-3.5 to 8.1)</td>
<td>0.43</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Secondary care (n=13)</th>
<th>Intervention group (PANDIT with usual care) (n=6)</th>
<th>Control group (usual care) (n=7)</th>
<th>Mean difference (95% CI) between intervention and control group</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
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</tr>
<tr>
<td>HbA1c (mmol/mol)</td>
<td>69.5 (63.6 to 75.5)</td>
<td>70.7 (58.7 to 82.7)</td>
<td>68.6 (60.4 to 76.8)</td>
<td>4.8 (-9.2 to 18.0)</td>
<td>0.44</td>
</tr>
<tr>
<td>FPG (mmol/L)</td>
<td>9.5 (7.2 to 11.8)</td>
<td>11.1 (6.9 to 15.4)</td>
<td>8.0 (5.1 to 10.9)</td>
<td>-0.5 (-3.3 to 2.2)</td>
<td>0.71</td>
</tr>
<tr>
<td>Insulin dose (units)</td>
<td>30.9 (12.1 to 49.6)</td>
<td>41.2 (7.1 to 75.2)</td>
<td>21.6 (-2.5 to 45.7)</td>
<td>14.8 (3.2 to 26.2)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

* Patient-level random intercepts with random time slopes
* Patient-level random intercepts with fixed time slopes

CI, confidence interval; FPG, fasting plasma glucose; DTSQ, diabetes treatment satisfaction questionnaire
Adverse events
No patients in the control group had recorded any hypoglycaemic event in the paper diary. On the other hand, 19 patients (58%) recorded hypoglycaemic events in PANDIT. With regard to the self-reported hypoglycaemic events at each study contact, 7 patients (21%) in the intervention group reported to have experienced at least one hypoglycaemia during the study, compared to 10 patients (38%) in the control group ($p=0.18$). In each study group, 4 patients stated to have experienced more than one hypoglycaemic event.

Three patients experienced a severe adverse event during study follow-up; in the intervention group one patient had a myocardial infarction and another patient had a transient ischemic attack. One patient in the control group was hospitalized due to recurrent kidney stones.

Other outcomes
The intervention group had a significantly higher mean insulin dose increment than the control group in the overall patient group. This was also the case in long-term users of insulin and in patients from secondary care. There was no difference in change of body weight between the intervention and the control group in the overall patient group. The median number of contacts with the caregiver, either by telephone or a visit at the practice/hospital, during the study was 1.0 (0.5-6.0) in the intervention group compared to 2.5 (1.0-7.0) in the control group ($p=0.15$).

Discussion
The present study did not detect a statistically significant difference in glycaemic control between patients using a web-based system for self-titrating their insulin dose and receiving usual care and patients receiving usual care alone. This is likely due to a lack of statistical power because we were unable to recruit a sufficient number of patients for the study for reasons discussed below. Insulin dose increments were higher in the intervention group and there was a trend towards a greater improvement in FPG values. Furthermore, we did find that PANDIT was effective in lowering HbA1c in patients from primary care. This was accompanied by a trend towards a greater FPG decrease, but we found no difference in insulin dose increments between intervention and control group. Similarly, our data also suggest that long-term users of insulin benefited from PANDIT, given a trend towards a greater HbA1c and FPG decrease and significantly higher insulin dose increments in the intervention group.
Finally, this study showed that the use of PANDIT improved treatment satisfaction among selected patients that were able and willing to use a web-based insulin self-titration system.

A major limitation of this study was that we were unable to enrol enough patients for adequate statistical power to detect improvements in patient outcomes. In our study, eligible patients were recruited by care providers from participating general practices and hospitals. Due this two stepped recruitment process we were faced with technology resistance by both health care professionals and patients that are both often sceptical and show little support for e-health [24]. We included a great number of general practices, however, only few general practices actively recruited patients. Therefore, we expect that we lost the bulk of potential eligible patients during local recruitment at general practices.

There exist a wide spectrum of e-health interventions for patients with T2DM, including both clinical and home based systems focusing on diet, exercise, and use of medication. A recent systematic review and meta-analysis suggests that, overall, such systems may induce a small but statistically significant HbA1c reduction of 2.3 mmol/mol [16]. However, there was substantial heterogeneity in measured effects, suggesting the underlying interventions are too diverse too be placed under a common denominator. As mentioned in the introduction, two previous studies have specifically investigated the clinical effectiveness of systems that provide insulin dosing advice through decision support technologies [17;18]. These two previous studies differ from our study regarding their objective and study design. Nevertheless, the detected HbA1c decrease of 4-5 mmol/mol caused by the intervention are in line with what we found in the subgroup of patients from primary care. A meta-analysis of clinical decision support systems targeting care providers already presumed that type of care (primary or secondary care) is an important source of heterogeneity found among and within study populations [15]. Our study confirmed this for type of care but also found an effect for duration of use of insulin. In contrast to many other e-health trials, our intervention group did not suffer from a high drop-out rate [25]. Unfortunately, we can only speculate on which factors positively influenced attrition such as a high perceived usefulness, the simplicity of the concept/diary, the integration of the system in usual care and the access to technical support when needed.

In addition to the lack of statistical power, our study was subjected to other limitations. The randomization on a patient level could have created contamination of treatment effects, i.e. greater HbA1c improvement in the intervention group
might have resulted in more aggressive titration in usual care by care providers to attain similar benefits. Also, we expect that the local recruitment at general practices was a highly selective process, but we were unable to record information on the characteristics of all eligible and invited patients. Nevertheless, the randomized design allowed for control of selection bias. Furthermore, our study underscores the difficulty of reporting on hypoglycaemic events. We were only able to compare the proportion of patients affected by self-reported hypoglycaemic events between study groups, as established at each study visit. The zero recorded hypoglycaemic events in the paper diary in the control group does not reflect reality. And we found a discrepancy between the incidence of self-reported (at each study visit) and self-recorded (in PANDIT) hypoglycaemia in the intervention group, emphasizing that self-reported hypoglycaemic events are also an unreliable source of information. Finally, if inclusion of patients were not an issue, we would opt for an additional randomization arm of patients using an electronic diary without CDS. This would provide insight into which part(s) of the system, either the electronic diary or the insulin dosing advice, contributed to improvements in glycaemic control.

Our study showed that PANDIT was effective in improving glycaemic control in patients from primary care, but this was not through higher insulin dose increments. One possible explanation is that use of PANDIT raised awareness of high blood glucose values among patients with a disease which also can be greatly influenced by lifestyle. Results of this study also suggest that long-term insulin users benefited from PANDIT; it is likely that the high insulin dose increments by PANDIT during the study period have resulted in glycaemic improvement compared to insulin doses that were barely increased in usual care only. On the contrary, in the group of insulin starters, insulin doses in usual care only were also substantially increased and therefore PANDIT had no additional benefit. Against our expectations, the higher insulin dose increments by PANDIT in secondary care did not seem to coincide with a decrease in HbA1c in the intervention group when compared to the control group. This could be due to lack of statistical power. Another possible explanation is that patients with diabetes referred to secondary care have more complex diabetes and/or co-morbid diseases for which the simple treat-to-target strategy is not sufficient.

The results of this study suggest that e-health to support insulin titration system at home should be implemented in primary care and primarily targeted at patients that have been using basal insulin for a longer period. However, due to our relatively small sample size, these findings still need to be confirmed in a large-scaled trial. This study confirmed that type of care and duration of insulin use is a significant source
of heterogeneity in study outcomes. Future studies investigating e-health systems in general should either avoid the inclusion of large and heterogeneous populations which makes finding an effect unlikely or perform subgroup analysis to detect subgroup of patients that would benefit from this type of care. So far, much research has focused on the effectiveness of e-health systems. However, to really benefit from those new e-health applications in the pipeline, research should also focus on the question how to increase the uptake of e-health technologies.

**Conclusion**

This study suffered from a low number of included patients and did not establish better glycaemic control through web-based insulin titration in the overall patient group. Subgroup analyses showed that web-based insulin titration was effective in improving glycaemic control in patients from primary care and suggested a similar effect in patients that have been using insulin for a longer period as opposed to insulin starters. In this selected group of trial participants that were willing and able to use PANDIT, treatment satisfaction was higher among PANDIT users than among non-users. We recommend that e-health to support patients in self-adjusting insulin dose should be implemented in primary care and should primarily be targeting those that have been using insulin for more than six weeks.
Reference List


23. Bradley C, Plowright R, Stewart J, Valentine J, Witthaus E. The Diabetes Treatment Satisfaction Questionnaire change version (DTSQc) evaluated in insulin glargine trials shows greater responsiveness to improvements than the original DTSQ. Health Qual Life Outcomes 2007; 5:57.
