Fighting the Hydra: Optimizing treatment for type 2 diabetes
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Citation for published version (APA):

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Factors that drive insulin dosing decisions by diabetes care providers: a vignette study in The Netherlands


Diabetic Medicine, In Press
Abstract

Aims
Little is known about the strategies that are followed by care providers when implementing insulin therapy in people with type 2 diabetes. We aimed to test how certain patient factors would influence the decision of Dutch care providers regarding insulin dose adjustments, as we expected that some of these decisions would diverge from recent evidence and consensus statements.

Methods
To test our hypotheses, we developed narrative vignettes describing clinical scenarios of patients on basal insulin therapy. For each vignette, respondents were asked to indicate whether they would advise to change the insulin dose. Five hundred and twenty paper questionnaires were distributed among physicians and nurses in primary and secondary care in the Netherlands. Multivariate linear and logistic regression analyses were performed to identify factors associated with dosing decisions.

Results
One hundred and ninety (37%) questionnaires were returned. In case of a severe instead of a mild hypoglycaemic event care providers were nearly five times more likely to decrease the dose (odds ratio [OR] 4.77; 95% confidence interval [CI] 1.65 to 13.75). Care providers were six times more likely to increase the dose when the patient’s current dose was low (30 units) instead of high (90 units) (OR 6.38 (95% CI 3.04 to 13.37)). The measured plasma glucose value during a hypoglycaemic event and a known history of cardiovascular disease did not influence their dosing decisions.

Conclusion
Evidence regarding optimal insulin titration is not always translated into clinical practice. When formulating guidelines, misconceptions should be identified and addressed.
Introduction

To reduce the risk of microvascular complications, glycaemic management of people with type 2 diabetes mellitus (DM) has become a cornerstone of diabetes care [1]. Given the progressive nature of type 2 DM, many patients will eventually require insulin treatment to maintain adequate glycaemic control. Clinical trials show that the addition of basal insulin to existing oral glucose-lowering therapy leads to adequate glycaemic control in the majority of people with type 2 DM [2;3]. The so-called ‘treat-to-target’ principle, systematically titrating insulin according to predefined plasma glucose criteria, has proven to be indispensable for successful insulin therapy [4]. However, when turning evidence into daily practice, many patients do not have their insulin doses titrated sufficiently and fail to reach treatment targets [1;5]. This is unfortunate, because insulin titration according to the treat-to-target principle is easy, effective and safe [6;7].

A few explanations might contribute to this gap between optimal treatment and current practice.

First, many different algorithms have been developed to titrate basal insulin and this may be confusing for care providers [4]. Of note, consensus statements of well-known diabetes societies differ in their recommended target HbA1c value, being either 48 or 53 mmol/mol (6.5% or 7.0%) [8;9]. Second, in current practice very high insulin doses can be problematic to deal with due to an attenuated dose response with higher insulin volumes [10;11]. Third, the data from the ACCORD study suggested an increased mortality in people with type 2 DM on an intensive glucose-lowering regime, which might be related to the degree of reduction in HbA1c [12]. Consequently, clinicians could now be more hesitant to lower glucose levels promptly. Similarly, patients and health care professionals could justly be reluctant to increase the dose when confronted with side effects such as hypoglycaemia and weight gain [13].

All these (perceived) barriers can make the clinician and patient hesitant to increase the insulin dose.

We hypothesized that these patient factors would influence the decision of Dutch care providers regarding insulin dose adjustments, and that some of these decisions would diverge from recent evidence and consensus statements.

There are many techniques to study the decision-making behaviour of healthcare professionals. One technique that allows to study the decision-making behaviour of many care providers for the same series of cases are clinical vignettes. These are brief, written case histories of fictitious patients based on a realistic clinical situation, and
accompanied by one or more questions that explore what a physician would do if presented with the actual patient. Peabody et al. have shown that vignettes can be used to reliably measure the quality of health care (i.e. the quality of medical decisions) in an outpatient setting. In their study, vignettes provided consistently better measurements of the quality of clinical care than did medical record abstraction, when compared to standardized patients (gold standard) [14]. Vignettes have been successfully employed to study physician decision-making behaviour in areas as diverse as intensive care, cardiology, vascular medicine and paediatrics [15-18].

A better understanding of the decision-making behaviour of diabetes care providers can inform strategies to improve quality of diabetes care. Therefore, the objective of this study was to explore how patient factors influence the decisions of diabetes care providers to adjust the basal insulin dose of people with type 2 DM. We used clinical vignettes in our exploration.

**Materials and methods**

**Construction of vignettes**

Traditionally, titration guidelines state that decisions on insulin dose adjustments should be based on fasting plasma glucose (FPG), HbA1c, hypoglycaemic events and the patient’s age [4;19]. We postulated that other patient factors would influence this decision, taking into regard recent evidence and consensus statements, common sense and perceptions encountered in clinical practice that are not based on scientific evidence. This set of nine factors is shown in Table 1. We dichotomized the factors to set up nine hypotheses that are described in Table 4. To test our hypotheses, we developed a questionnaire containing nine narrative vignettes describing patients on basal insulin. Vignettes described clinical profiles varying in those characteristics that are requisite for dose adjustments according to consensus statements and treat-to-target algorithms: FPG, HbA1c, hypoglycaemic events and the patient’s age [4;19]. To provide a realistic presentation of a clinical scenario, vignettes also contained information on insulin type, insulin dose and the patient’s gender. We tested our hypotheses by using two versions of the questionnaire (and therefore also two versions of all nine vignettes). Each vignette described one additional characteristic that differed between the two versions of an otherwise identical vignette. Each respondent received one version of a questionnaire that contained a fixed combination of vignettes. An example of a vignette, with their two versions, is shown in Box 1. Other examples can be found in the supplemental Box 1.
### Table 1  Factors that influence the behaviour of care providers when adjusting insulin dose

#### Factors stemming from evidence and consensus statements

<table>
<thead>
<tr>
<th>Factor</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>– Severity of hypoglycaemic event</td>
<td>Consensus statements state that target blood glucose level should be increased immediately after a severe hypoglycaemic episode (i.e. an event requiring third party assistance) [16;21]</td>
</tr>
<tr>
<td>– The plasma glucose value measured during a hypoglycaemic event</td>
<td>Most treat-to-target algorithms only advise to lower the insulin dose if hypoglycaemic symptoms are accompanied by a measured plasma glucose ≤3.9 mmol/L [2;7]</td>
</tr>
<tr>
<td>– Evidence of cardiovascular disease</td>
<td>Results of the ACCORD study and consensus statements recommend that somewhat higher targets should be considered for patients with evidence of cardiovascular disease [10;16;21]</td>
</tr>
</tbody>
</table>

#### Factors stemming from common sense of care providers

<table>
<thead>
<tr>
<th>Factor</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>– Social isolation of the patient that experienced a hypoglycaemic event</td>
<td>Certain risk factors (such as poor vision and social isolation) may put patients at a higher risk of injuries following a hypoglycaemic event</td>
</tr>
</tbody>
</table>

#### Factors stemming from perceptions in clinical practice not based on scientific evidence

<table>
<thead>
<tr>
<th>Factor</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>– Time of occurrence of hypoglycaemic event</td>
<td>Studies suggest that nocturnal hypoglycaemia induces hypoglycaemia unawareness in patients with type 1 diabetes [26]. To our knowledge no similar association has been demonstrated for patients with type 2 diabetes on basal insulin therapy. Nevertheless, pharmaceutical companies claim that nocturnal hypoglycaemia in patients with type 2 diabetes is the main impediment to attaining good glycaemic control [27]</td>
</tr>
<tr>
<td>– Current insulin dose</td>
<td>The maximum dose with most insulin pens is 60 to 80 units. Therefore, care providers might stop increasing insulin dose if the maximum dose has been reached</td>
</tr>
</tbody>
</table>

#### Target values and type of measurement

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>– FPG</td>
<td>The ADA consensus recommends that FPG should be maintained at 7.2 mmol/L [8;16]. Most treat-to-target algorithms and the Dutch guideline for general practitioners advocate a FPG of 5.5 mmol/L [4;28]. Is the insulin dose adjustment different when confronted with an FPG of 5.5-7.2 mmol/L compared to a FPG ≤5.5 mmol/L?</td>
</tr>
<tr>
<td>– Plasma glucose during hypoglycaemia</td>
<td>The ADA consensus has defined any glucose concentration of ≤3.9 mmol/L as hypoglycaemia [4;29]. The EMA recommends a value of 3.0 mmol/L to define hypoglycaemia [30]. If a hypoglycaemic event has occurred, is the insulin dose adjustment different when confronted with a PG of ≤3.0 mmol/L compared to a PG of 3.0-3.9 mmol/L?</td>
</tr>
<tr>
<td>– Type of measurement (FPG or HbA1c)</td>
<td>The ADA consensus recommends an HbA1c target ≤53 mmol/mol (7%) and a FPG target ≤7.2 mmol/L [8;16]. Is the insulin dose adjustment different if only the HbA1c target (HbA1c ≤53 mmol/mol (7%)) but not the FPG has been achieved compared to the situation if only the FPG target (FPG ≤7.2 mmol/L) but not the HbA1c target has been achieved?</td>
</tr>
</tbody>
</table>

PG, plasma glucose; FPG, fasting plasma glucose; EMA, European Medicines Agency; ADA, American Diabetes Association.
**Box 1** Example of a vignette

Vignette 1 version a

A 60-year old obese male patient with a body mass index of 37 kg/m2 uses insulin glargine since 1 year. His hemoglobin A1c is 62 mmol/mol (7.8%) and he uses 90 IU of insulin. His fasting plasma glucose is approximately 8 mmol/L (144 mg/dL). His last visit was a while back and he asks you whether to adjust his insulin dosing.

What would you advise the patient with regard to his insulin dose?

- Increase by more than 6 units
- Increase by 6 units
- Increase by 4 units
- Increase by 2 units
- No adjustment
- Decrease by 2 units
- Decrease by 4 units
- Decrease by 6 units
- Decrease by more than 6 units

Please substantiate your choice

Vignette 1 version b

A 60-year old obese male patient with a body mass index of 37 kg/m2 uses insulin glargine since 1 year. His hemoglobin A1c is 62 mmol/mol (7.8%) and he uses 30 IU of insulin. His fasting plasma glucose is approximately 8 mmol/L (144 mg/dL). His last visit was a while back and he asks you whether to adjust his insulin dosing.

What would you advise the patient with regard to his insulin dose?

- Increase by more than 6 units
- Increase by 6 units
- Increase by 4 units
- Increase by 2 units
- No adjustment
- Decrease by 2 units
- Decrease by 4 units
- Decrease by 6 units
- Decrease by more than 6 units

Please substantiate your choice

Respondents were asked to select an adjustment of the insulin dose on an ordinal scale which followed each vignette. They were also asked to substantiate their choice or to note their preference for another measure. Each questionnaire collected data...
on the respondent’s gender, profession, age, years of experience, number of patients seen per week and city of residence.

Selection of diabetes care professionals
Three hundred and seventy paper questionnaires were distributed on a Dutch diabetes conference for general practitioners, specialized diabetes nurses and nurse practitioners in primary care by active recruitment. All of these have an active role in insulin dose titration in the Netherlands. This conference was visited by 2023 care providers of which 89% were female; most visitors worked as a nurse practitioner in general practice (60%), 21% worked as a specialized diabetes nurse in secondary care and 15% were general practitioners. Furthermore, the questionnaires were sent by mail to a randomly selected sample of 100 internists-diabetologists that had visited a Dutch diabetes research meeting. In addition, questionnaires were sent by mail to 50 internists randomly selected from the Dutch register of health care.

Procedure
The questionnaires were processed by two researchers (AS and JS) independently. When the respondent did not select an adjustment of the insulin dose this was coded as “missing”. However, if both diabetes researchers concluded that the care provider preferred to take other measures (lifestyle/education/reassurance), as indicated by the entry in the free text field, the missing value was coded as “0” (no adjustment of insulin dose). If the free text field contained a comment, two reviewers independently categorized the comment according to a codebook that was developed bottom-up by reading and re-reading samples of text fields (e.g. as “substantiation of the dose adjustment” or as a “request for more information”).

Statistical methods
Data were analysed using SPSS version 18.0 for Windows. The first analysis concerned the set of hypotheses as described in Table 4. The primary outcome was the odds ratio of adjusting the insulin dose (‘yes’ or ‘no’) when comparing the two versions of each (additional) patient characteristic. We performed a multivariate logistic regression analysis including care provider characteristics as covariates, and we transformed the ordinal scale to indicate adjustment of the insulin dose into a binary variable that served as the outcome. For the first five vignettes, each of which included a hypoglycaemic event, the answer was coded as ‘yes’ or ‘no’ decrease of insulin dose. If the care provider decided to increase the dose, this was coded as no decrease. For
the next four vignettes, which did not include hypoglycaemic events, the answer was coded as ‘yes’ or ‘no’ increase of insulin dose. If the care provider decided to decrease the dose, this was coded as no increase. The secondary outcome was the mean difference in dosing advice when comparing the two versions of each (additional) patient characteristic. To calculate this, we performed a multivariate linear regression analysis on adjustment of insulin dose.

The second analysis concerned the characteristics that are requisite for dose adjustments according to titration guidelines and are present in all vignettes. The outcome was the mean difference in dosing advice when comparing the variations in these characteristics among the nine vignettes in one questionnaire. We performed multivariate linear regression analyses including the patient characteristics and care provider characteristics, using adjustment of insulin dose as response variable.

Associations between explanatory variables and insulin dose decisions were expressed as odds ratios (and 95% confidence interval (95% CI)) associated with change (i.e. increase or decrease) and average size of adjustments, expressed as insulin units. A sensitivity analysis was performed for all missing values of dose adjustment: in the first analysis missing values were coded as ‘0’ (no adjustment of insulin dose) after judgement by the diabetes researcher and in the second analysis the missing values were coded as missing.

**Ethics statement**

The Medical Ethics Board of the Academic Medical Center Amsterdam gave exemption for ethical approval for the study.

**Results**

Of all 520 distributed questionnaires, 190 (37%) were returned. The demographic characteristics of respondents are shown in Table 2. Of all 1710 individual vignettes 1604 (94%) were completed. In 1532 (90%) vignettes free text fields were filled out. In 252 (15%) vignettes respondents requested more information on patient characteristics. In 19 (2%) out of 950 vignettes concerning a hypoglycaemic event the respondent decided to increase the insulin dose. In 11 (1%) of the 760 vignettes not concerning a hypoglycaemic event the respondent decided to decrease the insulin dose.
Table 2  Demographic characteristics of respondents (n=190)

<table>
<thead>
<tr>
<th></th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>54 (28.4)</td>
</tr>
<tr>
<td>Profession</td>
<td></td>
</tr>
<tr>
<td>Nurse practitioner in primary care</td>
<td>90 (47.4)</td>
</tr>
<tr>
<td>Diabetes nurse in secondary care</td>
<td>31 (16.3)</td>
</tr>
<tr>
<td>General practitioner</td>
<td>20 (10.5)</td>
</tr>
<tr>
<td>Internist-endocrinologist</td>
<td>28 (14.7)</td>
</tr>
<tr>
<td>Internist-other</td>
<td>21 (11.1)</td>
</tr>
<tr>
<td>Age of care provider</td>
<td></td>
</tr>
<tr>
<td>&lt;40 years</td>
<td>22 (11.6)</td>
</tr>
<tr>
<td>41-50 years</td>
<td>76 (40.0)</td>
</tr>
<tr>
<td>51-60 years</td>
<td>78 (41.1)</td>
</tr>
<tr>
<td>61-70 years</td>
<td>13 (6.8)</td>
</tr>
<tr>
<td>Years of professional experience</td>
<td></td>
</tr>
<tr>
<td>1-5 years</td>
<td>41 (21.6)</td>
</tr>
<tr>
<td>6-10 years</td>
<td>62 (32.6)</td>
</tr>
<tr>
<td>11-20 years</td>
<td>44 (23.2)</td>
</tr>
<tr>
<td>&gt;20 years</td>
<td>42 (22.1)</td>
</tr>
<tr>
<td>Number of diabetes patients seen per week</td>
<td></td>
</tr>
<tr>
<td>0-5</td>
<td>24 (12.6)</td>
</tr>
<tr>
<td>6-10</td>
<td>28 (14.7)</td>
</tr>
<tr>
<td>11-20</td>
<td>61 (32.1)</td>
</tr>
<tr>
<td>&gt;20</td>
<td>67 (35.3)</td>
</tr>
<tr>
<td>Urbanization grade*</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>59 (31.1)</td>
</tr>
<tr>
<td>2</td>
<td>64 (33.7)</td>
</tr>
<tr>
<td>3</td>
<td>53 (27.9)</td>
</tr>
</tbody>
</table>

*Urbanisation was based on the number of households per four-digit postal area, and was categorised in 1) urban (>2500 households per square km), 2) mid (500-2500 households per square km) and 3) rural (<500 households per square km)

Table 3 displays the mean difference in dosing advice when comparing variations in provider characteristics and when comparing variations in characteristics among the nine vignettes. Mean insulin dose adjustment for the care provider characteristics and vignette characteristics that differed between the nine vignettes in each questionnaire. In general, physicians selected higher dose changes than nurse practitioners. The analyses also show that, for example, an increment of 1 mmol/L FPG resulted in a dose increment of respectively 1.28 units (95% CI 1.04 to 1.53). This implies that if the care provider is confronted with a patient with a FPG of, for example, 13 mmol/L, he or she provides an insulin dosing advice that is 5 units higher than if the patient’s FPG was 9 mmol/L.
Table 3  The mean difference in dosing advice when comparing variations in provider characteristics and when comparing variations in characteristics among the nine vignettes (n=1710).

<table>
<thead>
<tr>
<th>Care provider characteristics</th>
<th>Mean difference in dosing advice in IU (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male vs. female</td>
<td>0.05 (-0.36 to 0.46)</td>
<td>0.84</td>
</tr>
<tr>
<td>Profession</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Specialised diabetes nurse</td>
<td>0.07 (-0.27 to 0.41)</td>
<td>0.66</td>
</tr>
<tr>
<td>General practitioner</td>
<td>0.72 (0.28 to 1.17)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Internist-diabetologist</td>
<td>0.83 (0.32 to 1.33)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Internist-other</td>
<td>0.72 (0.22 to 1.23)</td>
<td>0.004</td>
</tr>
<tr>
<td>Nurse practitioner in primary care</td>
<td>reference category</td>
<td></td>
</tr>
<tr>
<td>Older age (&gt;50 years)</td>
<td>-0.40 (-0.63 to -1.67)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>More years of experience (&gt;10 years)</td>
<td>0.10 (-0.18 to -0.38)</td>
<td>0.50</td>
</tr>
<tr>
<td>More diabetes patients (&gt;20 seen per week)</td>
<td>0.03 (-0.22 to 0.28)</td>
<td>0.79</td>
</tr>
<tr>
<td>Urban area</td>
<td>0.03 (-0.21 to -0.27)</td>
<td>0.80</td>
</tr>
</tbody>
</table>

Table 4 presents the odds ratios of adjusting the insulin dose (yes/no) and mean differences in dosing advice when comparing the two versions of each (additional) patient characteristics. This analysis indicated that three out of nine characteristics significantly influenced the decision behaviour of care providers. First, in case of severe hypoglycaemic events care providers were nearly five times more likely to decrease the insulin dose compared to mild hypoglycaemic events. On average, patients that experienced a severe hypoglycaemic event received a dosing advice that was 1.27 units lower compared to the advice given to patients with mild hypoglycaemic events. Most care providers indicated in the free text field that they decreased the
insulin dose in case of a severe hypoglycaemic event to reduce the risk of having a second hypoglycaemic event. The most frequently stated substantiation regarding the continuation of the current insulin dose in case of a mild hypoglycaemic event was that a first hypoglycaemic event does not predict future hypoglycaemic events. Second, care providers were almost eight times more likely to increase the insulin dose if the patient’s FPG was between 5.5 mmol/L and 7.2 mmol/L instead of below 5.5 mmol/L, and the corresponding dosing advice was 0.87 units higher, on average. The decision to increase the insulin dose in case of an FPG between 5.5 mmol/L and 7.2 mmol/L was mostly substantiated with the argument that the FPG target value was not achieved. Third, in case of a low current dose of insulin (30 units) care providers were more than six times more likely to increase the insulin dose compared to the case when a patient already used a high dose of insulin (90 units). The mean difference in advice was 1.37 units. The high HbA1c was the most frequently stated argument to increase the insulin dose in case of a low current insulin dose. In case of a high current insulin dose, care providers substantiated to continue the insulin dose based on expected insulin resistance.

The sensitivity analysis to explore the handling of missing values showed that the results did not meaningfully change.
### Table 4

Hypotheses regarding the behaviour of the care providers in insulin treatment, odds ratios of adjusting insulin dose (yes or no) and mean differences in dosing advice (n=190). For each of the nine hypotheses, there were two versions of an otherwise identical vignette where the relevant characteristic differed.

<table>
<thead>
<tr>
<th>Following a hypoglycaemic event, care providers are more likely to reduce insulin dose:</th>
<th>OR (95% CI) to decrease dose</th>
<th>p-value</th>
<th>Mean difference in dosing advice in IU (95% CI)</th>
<th>p-value</th>
<th>n (%) of respondents that decreased the dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. if the hypoglycaemic episode was considered severe (i.e. requiring third party assistance to recover) rather than mild</td>
<td>4.77 (1.65 to 13.75)</td>
<td>0.004</td>
<td>-1.27 (-1.97 to -0.65)</td>
<td>&lt;0.001</td>
<td>37% vs 17%</td>
</tr>
<tr>
<td>II. if the patient was living alone rather than living together</td>
<td>1.36 (0.56 to 3.31)</td>
<td>0.49</td>
<td>-0.12 (-0.84 to -0.60)</td>
<td>0.74</td>
<td>37% vs 35%</td>
</tr>
<tr>
<td>III. if measured PG value during event indicated a real hypoglycaemic event (PG ≤3.9 mmol/L) rather than a pseudohypoglycaemic event (PG &gt;3.9 mmol/L)</td>
<td>0.49 (0.20 to 1.23)</td>
<td>0.13</td>
<td>0.22 (-0.67 to 1.10)</td>
<td>0.63</td>
<td>28% vs 37%</td>
</tr>
<tr>
<td>IV. if measured PG value ≤3.0 mmol/L rather than 3.0-3.9 mmol/L</td>
<td>1.76 (0.73 to 4.29)</td>
<td>0.21</td>
<td>-0.73 (-1.58 to -0.12)</td>
<td>0.09</td>
<td>37% vs 28%</td>
</tr>
<tr>
<td>V. if the event occurred during the night time</td>
<td>0.74 (0.39 to 1.42)</td>
<td>0.37</td>
<td>-0.12 (-0.75 to 0.51)</td>
<td>0.72</td>
<td>48% vs 51%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Care providers are more likely to increase basal insulin dose</th>
<th>OR (95% CI) to increase dose</th>
<th>p-value</th>
<th>Mean difference in dosing adviceyes in IU (95% CI)</th>
<th>p-value</th>
<th>n (%) of respondents that increased the dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>VI. if FPG values are 5.5-7.2 mmol/L rather than ≤5.5 mmol/L</td>
<td>7.88 (2.96 to 21.99)</td>
<td>&lt;0.001</td>
<td>0.87 (0.49 to 1.26)</td>
<td>&lt;0.001</td>
<td>34% vs 6%</td>
</tr>
<tr>
<td>VII. if only HbA1c target has been achieved (HbA1c ≤53 mmol/mol (7%) and FPG &gt;7.2 mmol/L) rather than only FPG target (FPG ≤7.2 mmol/L and HbA1c &gt;53 mmol/mol (7%)).</td>
<td>0.57 (0.29 to 1.08)</td>
<td>0.08</td>
<td>-0.43 (-0.92 to 0.05)</td>
<td>0.08</td>
<td>42% vs 49%</td>
</tr>
<tr>
<td>VIII. if the patient has no medical history of myocardial infarction</td>
<td>1.17 (0.56 to 2.43)</td>
<td>0.67</td>
<td>-0.01 (-0.60 to 0.58)</td>
<td>0.96</td>
<td>73% vs 72%</td>
</tr>
<tr>
<td>IX. if the patient has a low current insulin dose (30 IU) rather than a high current insulin dose (90 IU)</td>
<td>6.38 (3.04 to 13.37)</td>
<td>&lt;0.001</td>
<td>1.37 (0.57 to 2.17)</td>
<td>&lt;0.001</td>
<td>78% vs 35%</td>
</tr>
</tbody>
</table>

OR, Odds ratio; PG, plasma glucose; FPG, fasting plasma glucose; HbA1c, HbA1c; IU, international unit.
Discussion

We explored how patient characteristics influenced the decisions of diabetes care providers to adjust the basal insulin dose of people with type 2 DM. Previous studies mainly investigated care providers’ attitudes and beliefs towards the initiation of insulin therapy [20;21]. An increasing body of evidence showed that not only timely initiation of insulin therapy but also effective use of insulin, i.e. the intensification of insulin dose and/or insulin regimen is a cornerstone of diabetes care [22;23].

The current study showed that FPG, HbA1c, the occurrence of (severe) hypoglycaemic events and the age of the patient influenced the decision of a care provider when adjusting the insulin dose. These findings reflect proper implementation of consensus statements and treat-to-target algorithms stating that FPG and HbA1c are the major focus of therapy and that the choice for a treatment target should be individualized according to the occurrence of hypoglycaemic events and life expectancy [4;8;19].

This study also showed that some recommended criteria are not fully considered by care providers when choosing treatment targets for patients. We found that previous evidence of cardiovascular disease did not trigger the care provider to strive for a less intensive glucose-lowering regime, although the ACCORD study and consensus statements recommend that somewhat higher targets should be considered for people with evidence of cardiovascular disease [12;19;24]. Furthermore, although most treat-to-target algorithms only advise to lower the insulin dose if hypoglycaemic symptoms are accompanied by a measured plasma glucose ≤3.9 mmol/L [2;7], this study showed that this decision was taken irrespectively of the glucose value measured. This could be the result of fear of hypoglycaemic symptoms or of a lack of knowledge on threshold values that define hypoglycaemia.

This study confirmed our hypothesis that a high insulin dose influenced the decision of the care provider when aiming at good glycaemic control; a high insulin dose was perceived as a barrier to further increase the dose. However, there is no evidence that one should be more reluctant to increase the dose if a patient already uses a high insulin dose, as insulin can be dosed without an upper limit. The most plausible rationale for this observed behaviour is that a high insulin dose often reflects insulin resistance for which other strategies such as diet and lifestyle adjustment could be advocated [25]. We did not test this specifically in this study.

This study also showed that care provider opinions differ on the FPG target, ≤7.2 mmol/L or ≤5.5 mmol/L, that should be achieved. This effect probably reflects
concurrent implementation of guidelines that advocate a FPG ≤7.2 mmol/L [8] and treat-to-target algorithms that strive for a FPG ≤5.5 mmol/L [4].

When comparing different care providers, physicians provided a higher insulin dosing advice than nurse practitioners. Internist-diabetologists provided the highest insulin dosing advice of all care providers. This might be explained by the use of more stringent treatment targets by physicians. It also resembles findings from the DAWN study, where nurses and general practitioners were more reluctant than specialist physicians to initiate insulin therapy. Another explanation might be that nurse practitioners anticipate the higher frequency of consultations in their decision-making.

Vignettes simulate a patient’s case that contains realistic clinical detail, and are used in this study to find out what the care provider would do if confronted with a situation similar to the one described in the vignette. The care provider is instructed to answer each question as they would ordinarily do in everyday professional practice, not necessarily with what they know to be the ideal evidence-based recommendation [14]. A limitation of this study is that it suffers from a low response rate of 40%. This is a common problem, in particular for physician surveys when compared to non-physician surveys [26]. Yet, if in the worst case scenario we assume that non-respondents take different decisions than the respondents, we can still conclude that there is a substantial number of care providers that strive for a stringent FPG target of 5.5 mmol/L, that consider a high insulin dose as a barrier for intensifying the insulin dose, and that decrease the insulin dose if a pseudohypoglycaemic event has occurred. Yet, if all non-respondents strive for lower glucose targets if a patient has a history of cardiovascular disease, the finding of our study that previous evidence of cardiovascular disease did not trigger the care provider to strive for less intensive glucose lowering regime would be invalidated. However, it is unlikely that all non-responders act differently that those who did respond. Another limitation of the study is that we neither randomized the order of the vignettes within a questionnaire nor randomized the two vignette versions among the two versions of the questionnaire. This fixed combination of vignettes in a questionnaire might have biased the respondents answer to each single vignette, because the answer to the first vignettes could contaminate the response to the subsequent vignettes.

In the Netherlands and in many other countries the care for people with type 2 DM is predominantly delivered by nurse practitioners in primary care and by general practitioners [27;28]. The distribution of respondents in this study therefore
most probably corresponds to the division of the workload of care for people with type 2 DM in the Netherlands.

This study provides insight in the practical implementation of basal insulin therapy by care providers. This study showed that a substantial number of care providers strive for a stringent FPG target value of 5.5 mmol/L. Furthermore, it showed that pseudohypoglycaemic events and high insulin doses are barriers for intensifying insulin dose. Also, this study presumes that a patient history of myocardial infarction does not restrain care providers from increasing the dose as might be expected following the results of the ACCORD study. Following these results, we recommend that the Dutch practical guidelines directed at care providers performing dose adjustments should mention threshold values for hypoglycaemia and give recommendations on coping with high insulin doses. Furthermore, those guidelines should also increase awareness for the risk of intensive treatment in people with cardiovascular disease.

To our knowledge, this is the first study that explored the decisions of care providers with regard to insulin titration. Evidence regarding optimal insulin titration is not always translated into clinical practice. When formulating and implementing guidelines, misconceptions should be specifically identified and addressed. Larger scaled studies are needed to determine whether the results of this study are applicable to care providers in other countries.
BOX S1  Examples of vignettes

Vignette 2 version a

A 65-year old male patient visits the outpatient clinic after some time. *One year ago he had endured two myocardial infarctions. The first episode was treated with percutaneous coronary intervention. After the second episode the patient had undergone bypass surgery.* He asks you advice on his insulin dose. His current basal insulin dose is 52 units. His fasting glucose values are between 7 mmol/L (126 mg/dL) and 8 mmol/L (144 mg/dL), and his haemoglobin A1c is 57 mmol/mol (7.4%). He has not experienced any hypoglycaemic events.

What would you advise the patient with regard to his insulin dose?

- □ Increase by more than 6 units
- □ Increase by 6 units
- □ Increase by 4 units
- □ Increase by 2 units
- □ No adjustment
- □ Decrease by 2 units
- □ Decrease by 4 units
- □ Decrease by 6 units
- □ Decrease by more than 6 units

Please substantiate your choice

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Vignette 2 version b

A 65-year old male patient visits the outpatient clinic after some time. *He has no clinically significant disease or complications of his diabetes.* He asks you advice on his insulin dose. His current basal insulin dose is 52 units. His fasting glucose values are between 7 mmol/L (126 mg/dL) and 8 mmol/L (144 mg/dL), and his haemoglobin A1c is 57 mmol/mol (7.4%). He has not experienced any hypoglycaemic events.

What would you advise the patient with regard to his insulin dose?

- □ Increase by more than 6 units
- □ Increase by 6 units
- □ Increase by 4 units
- □ Increase by 2 units
- □ No adjustment
- □ Decrease by 2 units
- □ Decrease by 4 units
- □ Decrease by 6 units
- □ Decrease by more than 6 units

Please substantiate your choice

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Vignette 3 version a

A 75-year old vital woman visits the outpatient clinic with her daughter. She regularly goes on vacation and works as a volunteer at Amnesty International. She has been diagnosed with micro albuminuria for a long time. Since one year she uses NPH insulin once daily, and her current insulin dose is 36 units. A few weeks ago she had a nightmare and awoke sweating. She instantly measured her blood sugar, which was 3.0 mmol/L (54 mg/dL). Her haemoglobin A1c is 54 mmol/mol (7.1%) and her fasting values are varying between 6 mmol/L (108 mg/dL) and 7 mmol/L (126 mg/dL). She was a little bit shocked and ask for advice on her insulin dose.

What would you advise the patient with regard to his insulin dose?

☐ Increase by more than 6 units
☐ Increase by 6 units
☐ Increase by 4 units
☐ Increase by 2 units
☐ No adjustment
☐ Decrease by 2 units
☐ Decrease by 4 units
☐ Decrease by 6 units
☐ Decrease by more than 6 units

Please substantiate your choice

Vignette 3 version b

A 75-year old vital woman visits the outpatient clinic with her daughter. She regularly goes on vacation and works as a volunteer at Amnesty International. She has been diagnosed with micro albuminuria for a long time. Since one year she uses NPH insulin once daily, and her current insulin dose is 36 units. A few weeks ago she felt palpitations and had trembling hands at the office of Amnesty International. She instantly measured her blood sugar, which was 3.0 mmol/L (54 mg/dL). Her haemoglobin A1c is 54 mmol/mol (7.1%) and her fasting values are varying between 6 mmol/L (108 mg/dL) and 7 mmol/L (126 mg/dL). She was a little bit shocked and ask for advice on her insulin dose.

What would you advise the patient with regard to his insulin dose?

☐ Increase by more than 6 units
☐ Increase by 6 units
☐ Increase by 4 units
☐ Increase by 2 units
☐ No adjustment
☐ Decrease by 2 units
☐ Decrease by 4 units
☐ Decrease by 6 units
☐ Decrease by more than 6 units

Please substantiate your choice
Vignette 4 version a

A 64-year-old man visits your practice. He lives with his wife, with whom he has been married for 40 years. He is the director of a large telecommunications company. Several months ago he had been diagnosed with diabetes and he uses once daily insulin glargine since last month. His current insulin dose is 25 units and his haemoglobin A1c is 51 mmol/mol (6.8%). His fasting glucose levels are on average around 6.5 mmol/L (117 mg/dL). He is very satisfied with the treatment. However, last weekend, his daughter found him lying on the floor and he looked confused. His daughter thought that this could be a hypo and put some glucose gel in his cheek. After a few minutes, he recuperated and did not realize what had happened until his daughter told him the story.

What would you advise the patient with regard to his insulin dose?

☐ Increase by more than 6 units
☐ Increase by 6 units
☐ Increase by 4 units
☐ Increase by 2 units
☐ No adjustment
☐ Decrease by 2 units
☐ Decrease by 4 units
☐ Decrease by 6 units
☐ Decrease by more than 6 units

Please substantiate your choice


Vignette 4 version b

A 64-year-old man visits your practice. He lives with his wife, with whom he has been married for 40 years. He is the director of a large telecommunications company. Several months ago he had been diagnosed with diabetes and he uses once daily insulin glargine since last month. His current insulin dose is 25 units and his haemoglobin A1c is 51 mmol/mol (6.8%). His fasting glucose levels are on average around 6.5 mmol/L (117 mg/dL). He is very satisfied with the treatment. However, last weekend, he suddenly felt lightheaded and began to sweat. He did not measure his blood sugar value and drank a glass of juice, after which he immediately recuperated.

What would you advise the patient with regard to his insulin dose?

☐ Increase by more than 6 units
☐ Increase by 6 units
☐ Increase by 4 units
☐ Increase by 2 units
☐ No adjustment
☐ Decrease by 2 units
☐ Decrease by 4 units
☐ Decrease by 6 units
☐ Decrease by more than 6 units

Please substantiate your choice


Reference List


