Hypoglycaemia in diabetes

Schopman, J.E.

Publication date
2013

Citation for published version (APA):

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: https://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
Chapter 8

Factors that drive insulin dosing decisions made by diabetes care providers: A vignette study in the Netherlands

Airin C R Simon
Josefine E Schopman
Joost B L Hoekstra
Ameen Abu-Hanna
Victor E A Gerdes
Niels Peek
Frits Holleman

Submitted
FACTORS THAT DRIVE INSULIN DOSING DECISIONS

ABSTRACT

Background
Little is known about which strategies are followed by care providers in practice when implementing insulin therapy in patients with type 2 diabetes.

Objective
We hypothesized that certain 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.

Design
To test our hypotheses, we developed two versions of a questionnaire containing narrative vignettes describing patients on basal insulin therapy.

Setting
520 paper questionnaires were distributed among physicians and nurses in primary and secondary care in the Netherlands.

Measurements
For each vignette, respondents were asked to indicate whether they would advise to change the insulin dose. 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 insulin 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 insulin dose when the patient’s current insulin dose was low (30 IU) instead of high (90 IU). Measured plasma glucose (PG) values during a hypoglycaemic event and a known history of cardiovascular disease did not influence insulin dosing decisions.

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

To reduce the risk of microvascular complications, glycaemic management of patients with type 2 diabetes (DM2) has become a cornerstone of diabetes care. Given the progressive nature of DM2, 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 patients with type 2 diabetes. 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. However, when turning evidence into daily practice, many patients do not have their insulin doses titrated sufficiently and fail to reach treatment targets. This is unfortunate, because insulin titration according to the treat-to-target principle is easy, effective and safe.

A few explanations might contribute to this gap between optimal treatment and current practice. Many different algorithms have been developed to titrate basal insulin and this may be confusing for care providers. Also, consensus statements of well-known diabetes societies differ in their recommended target haemoglobin A1c value, being either 48 or 53 mmol/mol. Furthermore, the data from the ACCORD study suggested an increased mortality in patients with DM2 on an intensive glucose-lowering regime, which might be related to the degree of reduction in haemoglobin A1c. Consequently, clinicians could now be more hesitant to lower glucose levels promptly. Furthermore, side effects such as hypoglycaemia and weight gain and patients’ fear of painful injections could also affect the behaviour of patients and health care professionals.

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 their patients with DM2. We used vignettes of representative clinical scenarios in our exploration.

METHODS

Construction of vignettes
Traditionally, titration guidelines state that decisions on insulin dose adjustments should be based on fasting plasma glucose (FPG), haemoglobin A1c, hypoglycaemic events and patient’s age. 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 2. To test our hypotheses, we developed a questionnaire containing nine narrative vignettes describing patients on basal insulin. Vignettes described clinical profiles varying in those patient characteristics that are requisite for insulin dose adjustments according to consensus statements and treat-to-target algorithms: fasting plasma glucose (FPG), haemoglobin A1c, hypoglycaemic events and patient’s age. To provide a realistic presentation of a clinical scenario, all vignettes also contained information on insulin type, insulin dose and patient’s gender. To test our hypotheses, there were 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. Respondents were asked to select an adjustment of the insulin dose on an ordinal scale (more than six units increase [+6 IU]; six units increase [+4 IU]; four units increase [+2 IU]; two units increase [0 IU]; two units decrease [-2 IU]; four units decrease [-4 IU]; six units decrease [-6 IU]; and more than six units decrease [<-6 IU]) which followed each vignette. They were also asked to fill out an open text field to substantiate their choice for an adjustment of the insulin dose or to note their preference for another measure. An example of two vignettes, with their two versions, is shown in Box 1. Each questionnaire also collected data on the respondent’s gender, profession, age, years of experience, 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 (GP), 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 congress 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 (including internists-diabetologists) randomly selected from the Dutch register of health care.

Procedure
The questionnaires were processed by two researchers (AS and JS) independently. When
Box 1 - 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 haemoglobin A₁c is 62 mmol/mol (7.8%) and he uses 90 IU of insulin. His fasting plasma glucose is approximately 144 mg/dL (8 mmol/L). His last visit was a while back and he asks you whether to adjust his insulin dosing.

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 haemoglobin A₁c is 62 mmol/mol (7.8%) and he uses 30 IU of insulin. His fasting plasma glucose is approximately 144 mg/dL (8 mmol/L). His last visit was a while back and he asks you whether to adjust his insulin dosing.

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 IU. His fasting glucose values are between 126 mg/dL (7 mmol/L) and 144 mg/dL (8 mmol/L), and his haemoglobin A₁c is 57 mmol/mol (7.4%). He has not experienced any hypoglycaemic events.

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 IU. 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.

the respondent did not select an adjustment of the insulin dose on an ordinal scale 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 open text field, the missing value was coded as “0” (no adjustment of insulin dose). If the open 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”).
Table 1 - Factors that influence the behaviour of care providers when adjusting insulin dose.

Factors stemming from evidence and consensus statements

- **Severity of hypoglycaemic event**
  - 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) 13, 19

- **The plasma glucose value measured during a hypoglycaemic event**
  - Most treat-to-target algorithms only advise to lower the insulin dose if hypoglycaemic symptoms are accompanied by a measured plasma glucose ≤70 mg/dL [≤3.9 mmol] 2, 9

- **Evidence of cardiovascular disease**
  - Results of the ACCORD study and consensus statements recommend that somewhat higher targets should be considered for patients with evidence of cardiovascular disease 12, 13, 19

Factors stemming from common sense of care providers

- **Social isolation of the patient that experienced a hypoglycaemic event**
  - Certain risk factors (such as poor vision and social isolation) may put patients at a higher risk of injuries following a hypoglycaemic event

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

- **Time of occurrence of hypoglycaemic event**
  - Studies suggest that nocturnal hypoglycaemia induces hypoglycaemia unawareness among patients with type 1 diabetes 27. 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 among patients with type 2 diabetes is the main impediment to attaining good glycaemic control 21, 22

- **Current insulin dose**
  - 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

Variability in recommended targets

- **FPG values ≤130 mg/dL [FPG ≤7.2 mmol/L]**
  - The ADA consensus recommends that FPG should be maintained at 130 mg/dL [7.2 mmol/L] 10, 13. Most treat to target algorithms and the Dutch guideline for general practitioners advocate a FPG of 99 mg/dL [5.5 mmol/L] 5, 28. Is the insulin dose adjustment different when confronted with an FPG of 99-130 mg/dL compared to a FPG ≤99 mg/dL?

- **Plasma glucose values ≤70 mg/dL [≤3.9 mmol/L]**
  - The ADA consensus has defined any glucose concentration of ≤70 mg/dL [≤3.9 mmol/L] as hypoglycaemia 5, 26, 30. The EMA recommends a value of ≤54 mg/dL [≤3.0 mmol/L] to define hypoglycaemia 31. If a hypoglycaemic event has occurred, is the insulin dose adjustment different when confronted with a PG of ≤54 mg/dL compared to a PG of 54-70 mg/dL?

- **Type of measurement (FPG or HbA1c)**
  - The ADA consensus recommends an HbA1c target ≤53 mmol/mol and a FPG target ≤130 mmol/L 10-13. Is the insulin dose adjustment different if only the HbA1c target (HbA1c ≤53 mmol/mol) but not the FPG has been achieved compared to the situation if only the FPG target (FPG ≤130 mg/dL) but not the HbA1c target has been achieved?

---

PG: plasma glucose, FPG: fasting plasma glucose, HbA1c: haemoglobin A1c; EMA: European Medicines Agency; ADA: American Diabetes Association
Statistical analysis
Data were analysed using SPSS version 18.0 for windows.

The first analysis concerned the set of hypotheses as described in Table 2. The primary outcome was the odds that a care provider would adjust the basal insulin dose based on the characteristic that differed between the two versions of the vignette. We performed 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 insulin 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 insulin dose, this was coded as no increase. The secondary outcome was the mean adjustment of insulin dose based on the characteristic that differed between the two versions of the vignette. To calculate this, we performed a multivariate linear regression analysis on adjustment in insulin dose.

The second analysis concerned the characteristics that drive decisions to adjust the insulin dose according to titration guidelines. The outcome was mean adjustment of insulin dose based on each patient characteristic that differed between the nine vignettes in one questionnaire. We performed multivariate linear regression analyses including the fixed set of patient characteristics and care provider characteristics, using adjustment in insulin dose as response variable.

Associations between explanatory variables and insulin dose decisions were expressed as odds ratios (and 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 insulin dose adjustment: in the first analysis missing values were coded as ‘0’ (no adjustment in insulin dose) after judgement by the diabetes researcher and in the second analysis the missing values were coded as missing.

RESULTS
Of all 520 distributed questionnaires, 190 (37%) were returned. The demographic characteristics of respondents are shown in Table 3. Most respondents were female and the greatest percentage of respondents worked as a nurse practitioner in primary care. Of all 1710 individual vignettes 1604 (94%) were completed. In 1532 (90%) of all 1710 individual vignettes
Table 2 - Hypotheses regarding the behaviour of the care providers in insulin treatment, odds ratios of adjusting insulin dose and mean difference 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>Mean difference in dose adjustment, IU (95%)</th>
<th>N (%) of resp. that decreased 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>-1.27 (-1.97 to -0.65)</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>-0.12 (-0.84 to -0.60)</td>
<td>37% vs 35%</td>
</tr>
<tr>
<td>III. if measured PG value during event indicated a real hypoglycaemic event (PG ≤70 mg/dL) rather than a pseudohypoglycaemic event (PG &gt;70 mg/dL)</td>
<td>0.49 (0.20 to 1.23)</td>
<td>0.22 (-0.67 to 1.10)</td>
<td>28% vs 37%</td>
</tr>
<tr>
<td>IV. if measured PG value ≤54 mg/dL rather than 54-70 mg/dL</td>
<td>1.76 (0.73 to 4.29)</td>
<td>-0.73 (-1.58 to -0.12)</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>-0.12 (-0.75 to 0.51)</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>Odds ratio to increase dose</th>
<th>Mean difference in dose adjustment</th>
<th>N (%) of resp. that increased the dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>VI. if FPG values are 99-130 mg/dL rather ≤99 mg/dL</td>
<td>7.88 (2.96 to 20.99)</td>
<td>0.87 (0.49 to 1.26)</td>
<td>34% vs 6%</td>
</tr>
<tr>
<td>VII. if only HbA1c target has been achieved (HbA1c ≤53 mmol/mol and FPG &gt;130 mg/dL) rather than only FPG target (FPG ≤130 mg/dL and HbA1c &gt;53 mmol/mol)</td>
<td>0.57 (0.29 to 1.08)</td>
<td>-0.43 (-0.92 to 0.05)</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>-0.01 (-0.60 to 0.58)</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>1.37 (0.57 to 2.17)</td>
<td>78% vs 35%</td>
</tr>
</tbody>
</table>

PG: plasma glucose, FPG: fasting plasma glucose, HbA1c: haemoglobin A1c; IU: international units

(completed and not completed) free text fields were filled out. Of all 190 care providers 189 (99%) filled out at least one free text field. In 1009 (59%) of the 1710 vignettes the free text field contained substantiation for the adjustment of the insulin dose and in 252 (15%) more information on patient characteristics was requested. In 33 (2%) of the 1710 vignettes concerning a hypoglycaemic event the respondent decided to increase the insulin dose. In 22 (1%) of the 1710 vignettes not concerning a hypoglycaemic event the respondent decided to decrease the insulin dose.
Table 3 - Demographic characteristics of respondents (N = 190)

<table>
<thead>
<tr>
<th>Characteristic</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 our-digit postal area, and was categorised in 1) urban (>2500 households), 2) mid (500-2500 households) and 3) rural (<500 households)

Table 4 displays the mean insulin dose adjustment for the care provider characteristics and vignette characteristics that differed between the nine vignettes in one questionnaire. In general, physicians selected higher dose changes than nurse practitioners. Internists-diabetologists selected the highest dose changes, followed by other internists and by general practitioners. There were no differences between nurse practitioners in primary care and diabetes nurses in secondary care. Furthermore, older care providers (>51 years) generally chose dose adjustments that were lower than younger care providers (≤50 years) [mean difference in dose adjustment: 0.40 (0.63 to 1.67), p <0.001], while there was no influence of number of years of professional experience, number of diabetes patients seen per week, or grade of urbanization. Concerning the vignette characteristics, an increment of 1 mmol/L FPG and an increment of 1% HbA1c resulted in a dose increment of respectively 1.28 IU (1.04 to 1.53) and 1.25 IU (0.80 to 1.70). The occurrence of a hypoglycaemic event and a high current insulin dose (> 90 IU) lead to an insulin dosing advice that was respectively 1.19 IU (1.64 to 0.74) and 1.20 IU (-1.77 to -0.62) lower. Each increase in patient age of ten years was associated with a dose decrement of 0.31 IU (-0.45 to -0.16).
## Table 4 - Mean insulin dose adjustment associated with care provider characteristics and vignette characteristics (N=1710).

<table>
<thead>
<tr>
<th>Care provider characteristics</th>
<th>Mean difference in dose adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Male vs. female</strong></td>
<td>0.05 (-0.36 to 0.46)</td>
</tr>
<tr>
<td><strong>Profession</strong></td>
<td></td>
</tr>
<tr>
<td>Specialised diabetes nurse</td>
<td>0.07 (-0.27 to 0.41)</td>
</tr>
<tr>
<td>General practitioner</td>
<td>0.72 (0.28 to 1.17)</td>
</tr>
<tr>
<td>Internist-diabetologist</td>
<td>0.83 (0.32 to 1.33)</td>
</tr>
<tr>
<td>Internist-other</td>
<td>0.72 (0.22 to 1.23)</td>
</tr>
<tr>
<td>Nurse practitioner in primary care</td>
<td>reference category</td>
</tr>
<tr>
<td><strong>Older age (&gt;50 years)</strong></td>
<td>-0.40 (-0.63 to -1.67)</td>
</tr>
<tr>
<td><strong>More years of experience (&gt;10 years)</strong></td>
<td>0.10 (-0.18 to 0.38)</td>
</tr>
<tr>
<td><strong>More diabetes patients (&gt;20 seen per week)</strong></td>
<td>0.03 (-0.22 to 0.28)</td>
</tr>
<tr>
<td><strong>Urban area</strong></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vignette characteristics</th>
<th>Mean difference in dose adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoglycaemic event vs. no event</td>
<td>-1.19 (-1.64 to -0.74)</td>
</tr>
<tr>
<td>FPG (per 1 mmol/L)</td>
<td>1.28 (1.04 to 1.53)</td>
</tr>
<tr>
<td>HbA1c (per 1 mmol/mol)</td>
<td>1.25 (0.80 to 1.70)</td>
</tr>
<tr>
<td>Age patient (per 10 years)</td>
<td>-0.31 (-0.45 to -0.16)</td>
</tr>
<tr>
<td>Insulin dose 90 vs. &lt;60 IU</td>
<td>-1.20 (-1.77 to -0.62)</td>
</tr>
</tbody>
</table>

FPG: fasting plasma glucose, HbA1c: haemoglobin A1c; IU: international units

To limit the number of parameters in the multivariate model physician characteristic were dichotomized and patient characteristics were considered continuous variables.

To define the correlation between physician characteristic and the selected adjustment in insulin dose, the ordinal scale to indicate adjustment of the insulin dose was considered a continuous variable of absolute numbers.

To define the correlation between patient characteristic and the selected adjustment in insulin dose, the ordinal scale to indicate adjustment of the insulin dose was considered a continuous variable of real numbers.

Table 2 presents the odds ratios and mean differences in insulin dose for a care provider adjusting the basal insulin dose with vs. without the characteristic that differed between the two versions of a vignette. This analysis indicated that of all nine characteristics three 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 IU lower compared to the advice given to patients with mild hypoglycaemic events. Most care providers indicated in the open text field to decrease 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 in the open text field 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 99 mg/dL [5.5 mmol/L] and 130 mg/dL [7.2 mmol/L] instead of below 99 mg/dL, and the corresponding dosing advice was 0.87 IU higher, on average. The decision to increase the insulin dose in case of an FPG between 99 mg/dL and 130 mg/dL was mostly substantiated in the open text field with the argument that the FPG target value was not achieved. Third, in case of a low current dose of insulin (30 IU) 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 IU). The mean difference in advice was 1.37 IU. 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.

DISCUSSION

We explored how patient characteristics influence the decisions of diabetes care providers to adjust the basal insulin dose of their patients with type 2 diabetes. Previous studies mainly investigated care providers’ attitudes and beliefs towards the initiation of insulin therapy. The DAWN study showed that many care providers delay insulin therapy until absolutely necessary and identified factors associated with this behaviour. The authors of that study advocate the need of addressing factors associated with this resistance towards insulin therapy. An increasing body of evidence showed that not only timely initiation of insulin therapy but also effective use of insulin, i.e. intensification of insulin dose and/or insulin regimen is a cornerstone of diabetes care.

The current study showed that FPG, HbA1c, the occurrence of (severe) hypoglycaemic events and age of patient influenced the decisions of a care provider when adjusting the basal 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.

On the other hand, this study 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 less intensive glucose lowering regime, although the ACCORD study and consensus
FACTORS THAT DRIVE INSULIN DOSING DECISIONS

statements recommend that somewhat higher targets should be considered for patients with evidence of cardiovascular disease [12, 13, 19]. Furthermore, although most treat-to-target algorithms only advise to lower the insulin dose if hypoglycaemic symptoms are accompanied by a measured plasma glucose ≤70 mg/dL [≤3.9 mmol] [2, 9], 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 caregiver 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 insulin 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 [20]. We did not test this specifically in this study. In our study care providers did not discriminate between a nocturnal or daytime hypoglycaemic event when deciding to adjust the insulin dose, even though nocturnal hypoglycaemia among patients with type 2 diabetes has been claimed by pharmaceutical companies to be the main impediment to attaining good glycaemic control [21, 22].

This study showed that care provider opinions differ on the FPG target, ≤130 mg/dL or ≤99 mg/dL, that should be achieved. This effect probably reflects concurrent implementation of guidelines that advocate a FPG ≤130 mg/dL [10] and treat-to-target algorithms that strive for a FPG ≤99 mg/dL [5].

When comparing different care providers, physicians provide higher insulin dosing advice than nurse practitioners. Internist-diabetologists provide 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.

A major advantage of the vignette method is that it allowed us to study the treatment advice of many diabetes care providers for the same series of cases. Vignette scores have been evaluated to be a valid overall measure of the process of care provided by physicians [13]. In the Netherlands and in many other countries the care for patients with
type 2 diabetes is predominantly delivered by nurse practitioners in primary care and by general practitioners \(^24, 25\). The distribution of respondents in this study therefore most probably corresponds to the division of the workload of care for patients with type 2 diabetes in our country. Finally, we assumed that care providers would not increase the insulin dose in all vignettes concerning a hypoglycaemic event and would not decrease the insulin dose in all vignettes concerning no hypoglycaemic event. This assumption was empirically confirmed in this study. The current study also has certain limitations. Some feel that abstracts from medical records may give a more realistic view of the behaviour of the individual practitioner \(^23, 26\). Furthermore, patient-specific determinants, in particular living status, may have a different impact on care providers in real life. Also inherent to the vignette method is a risk of response bias: respondents answer questions in the way they think the questioner wants them to answer rather than according to their true beliefs. By distributing the vignettes among clinicians visiting diabetes congresses, we might have introduced selection bias by selecting those care providers with a special affinity for diabetes care. Also, due to lack of statistical power we were not able to differentiate between the different types of care providers when testing the effect of each determinant on their decisions.

This study provides insight in the practical implementation of basal insulin therapy by care providers. A substantial number of care providers strive for a stringent FPG target of 99 mg/dL. Pseudohypoglycaemic events and high insulin doses were barriers for intensifying insulin dose, although this is not based on scientific evidence. In contrast, a patient history of myocardial infarction did 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 our Dutch practical guidelines directed at care providers performing insulin dose adjustments should mention cut-off values for hypoglycaemia and give recommendations on coping with high insulin doses. Furthermore, these guidelines should also increase awareness for the risk of intensive treatment in patients with cardiovascular disease.

This is a first explorative study that explored the decisions of Dutch care providers. 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.
REFERENCES


