Original research

Depressive symptoms prior to and following insulin initiation in patients with type 2 diabetes mellitus: Prevalence, risk factors and effect on physician resource utilisation

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Abstract

Aims: To study the frequency and intensity of depressive symptoms and associations with physician resource utilisation following insulin initiation in patients with type 2 diabetes mellitus.

Methods: SOLVE was a 24-week observational study. In this sub-analysis of data from Poland, depressive symptoms were evaluated using the Patient Health Questionnaire (PHQ)-9.

Results: PHQ-9 was completed by 942 of 1169 patients (80.6%) at baseline, and 751 (64.2%) at both baseline and final (24-week) visit. PHQ-9 scores indicated depressive symptoms in 45.6% (n = 430) at baseline, and 27.2% (n = 223) at final visit. Mean PHQ-9 change was -2.38 [95% CI -2.73, -2.02], p < 0.001. Depressive symptoms at baseline (OR 6.32, p < 0.001), microvascular disease (OR 2.45, p = 0.016), number of physician contacts (OR 1.16, p = 0.009), and change in HbA1c (OR 0.60, p = 0.025) were independently associated with moderate/severe depressive symptoms at final visit. Patients with more severe depressive symptoms spent more time training to self-inject (p = 0.0016), self-adjust (p = 0.0023) and manage other aspects of insulin delivery (p = 0.0001). Patients with persistent depressive symptoms had more telephone contacts and dose changes at final visit than those without (both p < 0.05).

Abbreviations: ACCORD, Action to Control Cardiovascular Risk in Diabetes; CI, confidence interval; FBG, fasting blood glucose; HbA1c, glycosylated haemoglobin A1c; HADS-D, Hospital Anxiety and Depression Scale; OR, odds ratio; OADs, oral antidiabetic drugs; PHQ-9, Patient Health Questionnaire 9; SOLVE, Study of Once Daily LeVEmir; T2DM, type 2 diabetes mellitus.

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Conclusions: Depressive symptoms are common with type 2 diabetes and associated with increased healthcare utilisation, reinforcing the need for holistic interdisciplinary management approaches.

1. Introduction

Patient involvement in diabetes disease management is critical to reaching agreed treatment goals; however, comorbid psychological conditions, such as depressive symptoms and diabetes distress, are common [1,2]. Depressive symptoms and major depressive disorder are estimated to be twice as prevalent in patients with diabetes compared with patients without diabetes [3]. Left unrecognised and untreated, even low levels of depressive symptoms can negatively affect self-care behaviour, which may ultimately impact glycaemic control [4] and contribute to poor health related quality of life and well-being [5]. These associations may be particularly important in patients with complex or insulin-based treatment regimens [6]. The presence of depressive symptoms has also been reported as a barrier to insulin initiation [7].

Increased recognition and follow-up of comorbid depressive symptoms in patients with diabetes is important to mitigate negative health outcomes associated with poor self-care behaviour, such as missed medical appointments [4]. Patients with diabetes and comorbid depressive symptoms have more frequent physician office visits, hospital admissions, and prescriptions, all of which contribute to an increase in healthcare costs of up to 65% [8]. Depressed patients are also more likely to switch, augment, and/or discontinue oral antidiabetic drugs (OADs) than non-depressed patients [9]. Thus, treatment aimed at improving patient well-being and self-care may also improve healthcare utilisation.

The purpose of this sub-analysis of a large observational study of insulin initiation in a cohort of patients with type 2 diabetes mellitus (T2DM) was to report on the prevalence of depressive symptoms prior to and following insulin initiation. Furthermore, we identified demographic and clinical factors associated with the severity and persistence of depressive symptoms and investigated the effect of depressive symptoms on physician resource utilisation.

2. Methods

SOLVE (Study of Once Daily LeVeMir) is an observational study of basal insulin initiation in people with T2DM treated with one or more OADs. The study was conducted in 10 countries and patient selection and study methodology has been previously described in detail [10,11]. The study was pre-registered with clinicaltrials.gov (NCT00825643 and NCT00740519) and was approved by local ethics committees in each participating country. In Poland, participating patients were managed exclusively by specialists in accordance with national guidelines, which recommend specialist care for all T2DM patients receiving treatment with insulin.

Patients were eligible for inclusion if they had been diagnosed with T2DM, were receiving treatment with one or more OADs, and were being started on treatment with insulin detemir. Children aged <18 years, patients who were pregnant or breast-feeding or who intended to become pregnant and patients deviating in the number of daily injections of insulin detemir from once daily were excluded from the study. Patients were observed at three time points: pre-insulin (baseline), 12 weeks (interim visit), and 24 weeks (final visit). The study was non-interventional and there was no imposed follow-up schedule. Instead, data were collected at the visit closest to the protocol-defined follow-up interval. All treatment decisions including the decision to initiate insulin detemir were at the discretion of the investigator.

The primary endpoint of the study was the incidence of severe adverse drug reactions. Secondary endpoints included severe hypoglycaemia (requiring third party assistance), any minor hypoglycaemia (blood glucose <3.1 mmol/L), minor nocturnal hypoglycaemia, change in glycosylated haemoglobin A₁c (HbA₁c), fasting blood glucose (FBG), weight and body mass index. Physician resource utilisation was assessed by a questionnaire, and reports of office visits and telephone contacts at interim and final visits.

This sub-analysis in Poland included the use of Patient Health Questionnaire (PHQ)-9 at baseline and final visits (online Appendix). PHQ-9 is a nine-item depression scale, which assesses symptoms and functional impairment over the preceding 2 weeks. Each item scores 0–3 according to a Likert scale; these scores are then summed as follows: none (score <5), mild (score 5–9), moderate (score 10–14), moderately severe (score 15–19), and severe (score ≥20) depressive symptoms. As such, PHQ-9 indicates whether or not a patient is likely to have clinical depression and evaluates the impact of depressive symptoms on patients’ social interactions at home and in the work place. PHQ-9 is a validated tool for identifying depressive symptoms and monitoring severity of depression over time [12]; the questionnaire has also been used as a screening tool in patients with chronic illnesses including T2DM [13], and high symptom scores are associated with adverse outcomes [14]. According to the protocol, any patient with suspected major clinical depression (i.e., PHQ-9 scores indicating moderately severe or severe depressive symptoms) at baseline was referred to a psychiatrist for follow-up.

Physician resource utilisation was assessed by recording the time taken to train patients upon insulin initiation and the number of telephone contacts, office visits and dose changes at interim and final visits. Physicians recorded the amount of time spent on training patients to self-inject and dose self-adjust. Any training not related to these aspects was recorded as other training time.
The incidence of hypoglycaemia is expressed as events per patient year. Group comparisons were made using unpaired t-tests for continuous variables and the Chi-Square test for categorical variables unless otherwise specified. The paired t-test was used to compare continuous measurements at baseline and final visit (i.e., change from baseline). Hypoglycaemia data were analysed and compared using the Wilcoxon signed rank test. The Jonckheere–Terpstra test was used to test for trends across categories with an a priori ordering (i.e., none to severe depressive symptoms).

Minor nocturnal hypoglycaemia (events per patient year) was used to evaluate predictors of depressive symptoms at baseline and final visit. The level of significance was defined as α = 0.05. All statistical analyses were performed using Statistical Analysis Software v9.1 or newer (Cary, NC, USA). Imputation was used to handle missing data in the regression models (online Appendix).

### 3. Results

#### 3.1. Patient demographics

In Poland, 1169 patients were included in the SOLVE study after 21 patients had been excluded from the study for the following reasons: no informed consent (n = 16), no insulin treatment (n = 1), or both (n = 4). PHQ-9 was completed by 942 of 1169 patients (80.6%) at baseline (Table 1). The majority of patients completed PHQ-9 at both baseline and final visit (n = 751, 64.2%; online Appendix). Significant differences in demographic were found at baseline between patients completing the PHQ-9 questionnaire (PHQ+) and those who did not (PHQ−) in terms of change in FBG (−2.6 mmol/L versus −2.2 mmol/L, p < 0.05), baseline FBG variability (1.2 mmol/L versus 0.8 mmol/L, p < 0.05), and change in the rate of minor hypoglycaemia (+0.8 versus −1.9 events per patient year, p < 0.005), respectively. There were no differences in age, sex, duration of diabetes, weight, previous medical history of macrovascular or microvascular complications, and baseline

### Table 1 – Demography for all patients completing (PHQ+) and not completing (PHQ−) the PHQ-9 questionnaire at baseline.

<table>
<thead>
<tr>
<th>Demographic</th>
<th>PHQ+ cohort</th>
<th>PHQ− cohort</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>942 (80.6%)</td>
<td>227 (19.4%)</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>60 ± 10</td>
<td>60 ± 10</td>
<td>0.5646</td>
</tr>
<tr>
<td>Male (%)</td>
<td>57.0</td>
<td>57.7</td>
<td>0.8477</td>
</tr>
<tr>
<td>Duration of diabetes (years)</td>
<td>7 ± 5</td>
<td>8 ± 4</td>
<td>0.3687</td>
</tr>
<tr>
<td>Previous medical history (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Macrovascular disease</td>
<td>37.4</td>
<td>38.6</td>
<td>0.7398</td>
</tr>
<tr>
<td>Microvascular disease</td>
<td>30.4</td>
<td>29.2</td>
<td>0.7300</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-insulin</td>
<td>8.4 ± 1.2</td>
<td>8.5 ± 1.3</td>
<td>0.3713</td>
</tr>
<tr>
<td>Change</td>
<td>−1.1 [−1.2; −1.0]</td>
<td>−1.1 [−1.3; −0.8]</td>
<td>0.5583</td>
</tr>
<tr>
<td>FBG (mmol/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-insulin</td>
<td>8.9 ± 2.1</td>
<td>8.7 ± 1.6</td>
<td>0.1251</td>
</tr>
<tr>
<td>Change</td>
<td>−2.6 [−2.8; −2.5]</td>
<td>−2.2 [−2.5; −2.0]</td>
<td>0.0157</td>
</tr>
<tr>
<td>FBG variability (mmol/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-insulin</td>
<td>1.2 ± 3.4</td>
<td>0.8 ± 1.5</td>
<td>0.0253</td>
</tr>
<tr>
<td>Change</td>
<td>−0.7 [−1.0; −0.4]</td>
<td>−0.4 [−0.6; −1.1]</td>
<td>0.0838</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-insulin</td>
<td>87.0 ± 17.6</td>
<td>86.8 ± 14.5</td>
<td>0.8780</td>
</tr>
<tr>
<td>Change</td>
<td>−1.2 [−1.4; −1.0]</td>
<td>−1.5 [−1.9; −1.0]</td>
<td>0.3038</td>
</tr>
<tr>
<td>BMI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-insulin</td>
<td>30.8 ± 5.3</td>
<td>30.3 ± 4.4</td>
<td>0.1488</td>
</tr>
<tr>
<td>Change</td>
<td>−0.4 [−0.5; −0.3]</td>
<td>−0.5 [−0.7; −0.4]</td>
<td>0.2462</td>
</tr>
<tr>
<td>Severe hypoglycaemia (events per patient year)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-insulin</td>
<td>0.00</td>
<td>0.00</td>
<td>N/A</td>
</tr>
<tr>
<td>Change</td>
<td>0.00</td>
<td>0.00</td>
<td>N/A</td>
</tr>
<tr>
<td>Minor hypoglycaemia (events per patient year)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-insulin</td>
<td>2.2 ± 11.8</td>
<td>2.70 ± 9.5</td>
<td>0.5691</td>
</tr>
<tr>
<td>Change</td>
<td>+0.77 ± 15.8</td>
<td>−1.87 ± 10.1</td>
<td>0.0039</td>
</tr>
<tr>
<td>Minor nocturnal hypoglycaemia (events per patient year)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-insulin</td>
<td>0.53 ± 5.0</td>
<td>0.29 ± 2.3</td>
<td>0.2868</td>
</tr>
<tr>
<td>Change</td>
<td>−0.05 ± 5.8</td>
<td>−0.20 ± 2.5</td>
<td>0.5747</td>
</tr>
</tbody>
</table>

PHQ, Patient Health Questionnaire; FBG, fasting blood glucose; BMI, body mass index.
glycaemic control between PHQ+ and PHQ− groups. The reasons for non-completion of the PHQ-9 were not recorded.

### 3.2. Depression frequency and PHQ-9 scores

Depressive symptoms were present in 45.6% (n=430) of patients at baseline, and 27.2% (n=223) of patients at final visit. At baseline, the majority (n=236, 54.8%) of patients with depressive symptoms had mild symptoms, with moderate/severe and severe symptoms present in 14.4% (n=62). Similarly, at final visit, symptoms were most commonly mild (n=178, 79.8%). The mean PHQ-9 score was 5.56 ± 4.95 at baseline and 3.24 ± 3.30 at final visit, a change of −2.38 [95% confidence interval (CI) −2.73, −2.02], p<0.001. The severity of depressive symptoms and the impact of symptoms on work, taking care of things at home, or getting along with other people (item 10) are shown in Table 2.

### 3.3. Multivariate predictors of depressive symptoms

Logistic regression analysis was performed to identify predictors of moderate/severe depressive symptoms at baseline and final visit (Table 3 and online Appendix). Female sex (odds ratio [OR] 1.61 [95% CI 1.16–2.24], p=0.004), a previous history of macrovascular disease (OR 2.14 [95% CI 1.53–2.99], p<0.001), and higher levels of HbA1c (OR 1.26 [95% CI 1.09–1.46], p=0.003), were all independently associated with the reporting of moderate/severe depressive symptoms at baseline.

At final visit, reporting of moderate/severe depressive symptoms was independently associated with moderate/severe depressive symptoms at baseline (OR 6.32 [95% CI 3.22–12.39], p<0.001), a previous history of microvascular disease at baseline (OR 2.45 [95% CI 1.27–4.73], p=0.016), the number of physician contacts during the study (OR 1.16 [95% CI 1.04–1.30], p<0.001), and the change in HbA1c (OR 0.60 [95% CI 0.39–0.94], p=0.025). The model shows that for every 1% reduction in HbA1c relative to baseline, the risk of moderate/severe depressive symptoms decreased by 40%.

### 3.4. Depressive symptoms and physician resource utilisation

Training times according to depressive symptom severity are shown in Table 4. The time spent training patients to
self-inject and self-adjust insulin doses, and the management of other aspects of insulin treatment increased as the severity of depressive symptoms increased.

Table 5 shows the results of physician resource utilisation at 12 weeks and final visit, according to the presence and/or persistence of moderate/severe depressive symptoms. Patients with moderate/severe depressive symptoms at both baseline and final visits (persistent depressive symptoms) had a higher number of telephone contacts and dose changes at final visit than patients without moderate/severe depressive symptoms.

4. Discussion

This sub-analysis of the SOLVE data shows that the use of PHQ-9 in Poland identified a large proportion of T2DM patients with depressive symptoms at the time of insulin initiation. The majority of patients had mild depressive symptoms; however, 6.6% of all PHQ-9 responders had depressive symptoms consistent with major clinical depression. Patients with moderate/severe depressive symptoms at baseline had higher pre-insulin HbA1c values. Moreover, the presence of moderate/severe depressive symptoms at baseline was a strong predictor of evidence of major clinical depressive symptoms at final visit. Such patients also appeared to have more frequent contact with physicians, after adjusting for a number of potential confounders including aspects of the patients’ previous medical history and clinical course during the 24-week observational period.

PHQ-9 is one of several validated tools for identifying and monitoring depressive symptoms in primary care [13,16]. However, several studies published while the SOLVE study was ongoing have reported that the PHQ-9 categorises more patients in the moderate to severe depression category than another self-assessment measure, the Hospital Anxiety and Depression Scale (HADS-D) [17–20]. Reddy et al. [20] also reported that PHQ-9 response rates appeared to be influenced by educational level, that there were more missing responses to individual items on PHQ-9 than the HADS-D tool, and that PHQ-9 may overestimate depression because it contains questions about symptoms common to diabetes.

Despite these controversies, the overall prevalence of depressive symptoms reported here is consistent with that reported previously. In a meta-analysis performed by Ali et al. [21], the overall prevalence of depression in patients with T2DM was 17.6%, with individual studies reporting prevalence from 6% to 52% depending on the patient cohort and assessment method. This finding is consistent with the rate of moderate/severe depressive symptoms (20.6% of patients at baseline) in our study, taking into account differences in the duration of diabetes, level of glycaemic control, prevalence of macrovascular and microvascular disease, and degree of obesity, which are known to be correlates for depression in diabetes [22,23]. Severity of depression in patients with diabetes is known to fluctuate over time [24]. This fluctuation may occur for a variety of reasons related or unrelated to the disease; however, associations between depressive symptomatology and glycaemic control, weight, and hypoglycaemia have been reported.

The relationship between depressive symptoms and glycaemic control also remains controversial, with results from several large studies showing contrasting results [25–27]. These differences may be explained by confounding factors such as the use of insulin and the frequency of healthcare contact [28], the natural history and underlying cause of comorbid depression in diabetes [29], and the diagnostic overlap with other psychological problems such as anxiety and diabetes distress [30]. Papelbaum et al. [31] reported higher levels of HbA1c in T2DM patients with depression than those without mood disorder; however, HbA1c levels were not higher in patients with a history of depression who were not depressed at the time of clinical evaluation. A study by Aikens et al. [32], which assessed depressive symptoms using PHQ-9 found that depressive symptoms were not prospectively associated with 6-month glycaemic control; however, among insulin users, glycaemic control was predictive of depressive symptoms. These results suggest that the direction of association is that of glycaemic control on depressive symptoms, which may be mediated by hyperglycaemic and hypoglycaemic symptoms [33–36]. The Whitehall II study reported higher depression scores for patients with both the lowest and highest blood glucose levels (both fasting and post-prandial), with the lowest depression scores in the range of normoglycaemia [35]. Associations between HbA1c and moderate/severe depressive symptoms in our study are consistent with these earlier reports.

Similarly, associations between moderate/severe depressive symptoms and both macrovascular and microvascular disease have been reported [37,38]. Recently published data from the ACCORD (Action to Control Cardiovascular Risk in Diabetes) Health-Related Quality of Life sub-study also suggest a possible association between depression and an increased risk of macrovascular events among adults with T2DM already at high risk for cardiovascular events [14]. Microvascular and macrovascular disease might reflect the overall psychological burden of diabetes as well as being surrogate markers of previously poorly controlled disease [38]. Alternatively, the susceptibility to developing depression may be a consequence and an early manifestation of cerebral microvascular disease [39,40]. Another theory is that patients with depression may be predisposed to poor control and the development of microvascular and macrovascular complications as a result of poor self-care behaviour [41].
Weight (in the presence or absence of diabetes mellitus) [42–44] and hypoglycaemia [45] have also been associated with depression. In our study, neither weight loss nor the presence of hypoglycaemia was identified as an independent predictor of moderate/severe depressive symptoms during follow-up. The reasons for this are not known, but may have been because of the relatively small absolute change in weight relative to the aforementioned studies, and the relatively low number of reported hypoglycaemic events. Notably, the frequency of healthcare contact (adjusted for in our analysis) may have been overlooked as an important confounder in randomised studies comparing more intensive treatment with usual care [46, 47]. Graco et al. [28] found that glycaemia improved more in patients who were seen earlier in their disease course and were managed more intensively, regardless of their psychometric status.

Patients with moderate/severe depressive symptoms had increased resource utilisation as represented by the total number of physician contacts (Table 5). Patients with chronic diseases account for approximately 26% of out-of-hours calls to primary healthcare services – the third most frequent single diagnosis being diabetes after lung disease and cancer [48]. In randomised clinical trials, contact frequency is highly correlated with improvement in glycaemic control in insulin-treated patients with T2DM [49]. However, in real-life observational studies, increased telephone and office visits are likely to result in other healthcare costs in addition to those associated with healthcare personnel time. An evaluation of diabetes disease management programmes found that members who received more telephone contact demonstrated 20–24% higher low-density lipoprotein and HbA1C testing rates than members who received mailings alone [50].

Assuming that resource utilisation is a surrogate marker for self-efficacy, the findings of our study suggest that whatever the causal relationship between depression and self-efficacy, resolving depressive symptoms may lead to lower levels of physician resource utilisation. However, resource utilisation may not necessarily be patient initiated. Having identified depressive symptoms, physicians may be more concerned about patient welfare and therefore plan more frequent contact. Last, since the insulin doses at the final visit were still relatively low, and many patients had not reached target HbA1C levels of <7.0% (<53 mmol/mol), it could be argued that both patients with and without depressive symptoms may have benefited from more intensive follow-up and dose adjustment.

Our study has a number of important limitations and results should be interpreted as hypothesis generating. The study was observational; therefore, it is not possible to attribute the improvement in depressive symptoms to any specific intervention or treatment effect. Neither is it possible to exclude a placebo effect of initiating a new treatment and participating in a clinical study. Notably, only two of the countries participating in the SOLVE study (Israel and Poland) performed the PHQ-9 assessment. The small number of responses and the risk of selection bias meant that data fromIsrael was excluded from this analysis. In addition, imputation of missing data assumes that the loss of data was completely at random. The healthcare resource utilisation questionnaires used in our study have not been previously validated; however, a part of the assessment did include direct measures of healthcare utilisation such as duration of time spent training patients in various aspects of insulin treatment and patient contact frequency. Last, the PHQ-9 scale alone cannot be used to make a firm diagnosis of depression, but it remains a well-researched and validated tool for identifying and monitoring depressive symptoms.

### Table 5 – Physician resource utilisation at 12-weeks and final (24-weeks) visit, according to the presence and/or persistence of moderate/severe depressive symptoms.

<table>
<thead>
<tr>
<th>No depressive symptoms at baseline or final visit</th>
<th>Depressive symptoms at baseline only</th>
<th>Depressive symptoms at final visit only</th>
<th>Depressive symptoms at baseline and final visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>579</td>
<td>130</td>
<td>18</td>
</tr>
<tr>
<td>Office visits</td>
<td>0.57 [0.49; 0.66]</td>
<td>0.61 [0.54; 0.76]</td>
<td>0.75 [0.59; 1.21]</td>
</tr>
<tr>
<td>Telephone contacts</td>
<td>1.24 [1.13; 1.35]</td>
<td>1.48 [1.31; 1.65]</td>
<td>1.18 [0.52; 1.84]</td>
</tr>
<tr>
<td>Number of dose changes</td>
<td>1.24 [1.13; 1.35]</td>
<td>1.11 [0.65; 1.57]</td>
<td>1.36 [0.82; 1.90]</td>
</tr>
</tbody>
</table>

* p < 0.05 compared to reference group: no depressive symptoms at baseline or final visit.

### 5. Conclusion

Depressive symptoms are common in patients with T2DM in Poland, and are associated with female sex, a history of macrovascular disease, and evidence of poor glycaemic control. Mean PHQ-9 scores improved during the course of the 24-week observational period, which may be associated with an improvement in glycaemic control and diabetes symptoms. Incident and persistent depressive symptoms were associated with increased healthcare utilisation. To the best of our knowledge, an improvement in depressive symptoms despite of insulin initiation has not been reported previously. Given the complexities involved in managing depressive symptoms in people with T2DM, patients should receive holistic care from an interdisciplinary team.
Conflict of interest

The SOLVE study was sponsored by Novo Nordisk A/S (NCT00825643 and NCT00740519). All external authors have received consulting fees and support for travel to meetings from Novo Nordisk in association with the SOLVE study. Grzegorz Dzida consults for Lifescan and Novo Nordisk; and has received lecture fees from Bioton, Eli Lilly, Novo Nordisk, Sanofi Aventis and Servier. Norbert Hermanns consults for Eli Lilly and Novo Nordisk; and has received lecture fees and grants/grants pending with Berlin Chemie and Eli Lilly. Eddy Karnieli has received consulting and lecture fees from Novo Nordisk, BI, and AstraZeneca. Anne Louise Svendsen and Kristine Steensen Selje are employees and shareholders of Novo Nordisk A/S.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.pcd.2015.01.002.

REFERENCES


