Original article

Insulin therapy for diabetes mellitus: Treatment regimens and associated costs

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Abstract

Aims. – To describe insulin therapy in patients with diabetes, to determine treatment costs and to compare costs among treatment regimens.

Methods. – This observational study was performed by 734 French pharmacists. Adult patients filling an insulin prescription were invited to participate. Participants provided information on their diabetes history and management. Levels of intensification of insulin therapy were determined by the number of injections in type 1 diabetes mellitus (T1DM) patients, and by the different schemes used in type 2 (T2DM) patients, such as basal/intermediate-acting insulin only, and regimens using both basal and rapid-acting insulin. Costs were evaluated according to official medication costs, nurse visits and glucose monitoring kits.

Results. – A total of 361 patients with T1DM and 1902 with T2DM were enrolled in the survey. Patients with T1DM more frequently took 1–2 injections per day (46.3% of patients) and used single-dose basal insulin together with ≥ 1 dose of rapid insulin (43.8%). Patients with T2DM used multiple treatment regimens, with 58 different combinations documented. Most took basal/intermediate insulin only (42.5%) or combinations of basal/intermediate and rapid insulins (52.7%). Mean cost of insulin therapy was €27.4/week for T1DM and €45.4/week for T2DM. In T1DM, insulin was the biggest cost component and increased with the number of injections/day. In T2DM, nurse visits were the most important cost contributors irrespective of treatment regimen. Overall, the cost of insulin therapy increased with the complexity of the insulin schemes.

Conclusion. – Considerable heterogeneity is found in insulin treatment regimens used in everyday diabetes care. Payers should consider the full costs associated with the use of insulin rather than the cost of insulin alone. Treatment algorithms to harmonize insulin therapy should help to improve care, while encouraging patients to self-inject insulin should help to reduce costs.

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Keywords: Diabetes mellitus; Therapy; Insulin; Therapy; France; Epidemiology; Drug costs; Statistics and numerical data

Résumé

Traitement du diabète par l’insuline : schémas thérapeutiques et coûts associés.

Objectifs. – Décrire les pratiques d’insulinotherapie chez les patients atteints de diabète et déterminer les coûts de ce type de traitement selon les schémas utilisés.

Méthodes. – Cette étude d’observation a été réalisée chez 734 pharmaciens français. Ces derniers ont invité à participer tous les patients adultes qui se présentaient avec une prescription d’insuline sur la période d’inclusion. Les patients participants ont complété un questionnaire sur l’histoire de leur diabète et sa prise en charge. Différents niveaux d’intensité de l’insulinotherapie ont été distingués : dans le diabète de type 1, selon le nombre d’injections et dans le diabète de type 2 en distinguant les schémas ne faisant appel qu’aux insulines basales ou intermédiaires, les schémas combinant insuline basale et à action rapide, etc. Les coûts correspondant à ces schémas ont été évalués sur la base des tarifs officiels pour les médicaments, les visites de l’infirmière, et les dispositifs de surveillance de la glycémie.

Résultats. – Un total de 361 diabétiques de type 1 et 1902 diabétiques de type 2 a été inclus. Les patients diabétiques de type 1 était le plus fréquemment traités par une à deux injections quotidiennes (46,3 % des patients) et par une association d’insuline basale et au moins une dose d’insuline rapide (43,8 %). Les patients diabétiques de type 2 utilisaient de nombreux schémas de traitement, (58 combinaisons différentes documentées). Les schémas les plus utilisés comportaient uniquement une insuline basale/intermédiaire (42,5 %) ou une combinaison d’insuline basale/intermédiaire.

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et d’insuline rapide (52,7 %). Le coût moyen du traitement par insuline était 27,4 €/semaine dans le diabète de type 1 et de 45,4 €/semaine dans le diabète de type 2. Dans le diabète de type 1, le coût du traitement augmentait avec le nombre d’injections d’insuline/jour. Dans le diabète de type 2, le poste de coût le plus important concernait les visites de l’infirmière pour faire les injections indépendamment du schéma de traitement. Plus généralement, le coût du traitement par insuline augmentait avec la complexité des régimes utilisés.

Conclusions. — Une hétérogénéité considérable existe en France dans les schémas d’utilisation de l’insuline chez les patients diabétiques. Pour les payeurs, il importe de considérer que les coûts associés à ces schémas ne correspondent pas seulement au coût de l’insuline. La définition d’algorithmes destinés à harmoniser les pratiques d’insulinothérapie pourrait contribuer à améliorer les soins délivrés. Il conviendrait également d’encourager l’apprentissage et la réalisation de l’auto-injection d’insuline afin de réduire les coûts de traitement.

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Mots-clés : Diabète ; Traité ; Insuline ; Traitement ; France ; Épidémiologie ; Coûts des médicaments

1. Introduction

The prevalence of diabetes in Western Europe has been rising over the past two decades in association with the rise in obesity and increasing sedentary [1]. In France, data from the national prescription claims database indicates that the prevalence of treated diabetes rose from 2.8% in 1998 to 4.4% in 2009 [2–4], while a general population survey conducted in 2006 [5] reported a prevalence rate of 4.6% for type 2 diabetes mellitus (T2DM).

Treatment standards have also evolved over this period, notably with an emphasis on ‘treating-to-target’ regimens in which treatment is adjusted in a dynamic fashion to achieve a glycosylated haemoglobin (HbA1c) target, thereby reducing the risk of diabetic complications over the long term. In addition, insulin therapy is more frequently initiated earlier in T2DM in cases where HbA1c targets cannot be achieved with oral antidiabetic drugs (OADs) alone. French treatment guidelines recommend starting insulin therapy in all patients in whom HbA1c levels ≥ 7% persist in spite of treatment with appropriate doses of two OADs for at least 6 months [6]. This has led to a rise in the proportion of patients with T2DM treated with insulin, which now represents around one-fourth of all patients with T2DM [7]. At the same time, modified recombinant insulins with tailored pharmacodynamic and pharmacokinetic profiles have been developed—specifically, basal and rapid/ultra-rapid insulins—the use of which allows the natural physiological pattern of insulin secretion to be reproduced more faithfully than with the standard neutral protamine Hagedorn (NPH) insulins [8,9].

While the number of diabetes patients treated with insulin has grown over the recent years together with the number of therapeutic options, information on how insulin therapy is used in everyday clinical practice is limited, and the cost consequences for the healthcare system are not well understood. In the SCHEMA study, performed in 1999 before the introduction of basal and rapid insulins, insulin therapy regimens were evaluated in 1263 patients treated by diabetologists in France [10]. It was observed that 54% of patients with type 1 diabetes (T1DM) were taking three or more injections daily, whereas this was the case for only 17% of patients with T2DM treated with insulin. Wide variation in the types of insulin used was also observed. However, since the time of that study, basal and premixed insulins have replaced NPH insulins as the most frequent types of insulin prescribed. A new survey was conducted in 2005 [11,12] in patients with T2DM requiring insulin therapy (14% of all patients with T2DM). Of these, 44% were treated at that time with one injection daily and only 20% with three or more injections per day. In addition, a cross-sectional survey of a large randomized national sample of patients treated with hypoglycaemic drugs was conducted in 2007 [13]. Of these, 5.6% were identified as T1DM and 91.9% as T2DM, of whom 19% were treated with insulin [14]. However, no information was included on how these insulin treatments were prescribed, and data on the current costs associated with these treatments are very limited [15].

For this reason, the objectives of the present study were to describe the insulin therapy regimens used by diabetes patients (types 1 and 2) in France in 2010 to determine the cost of insulin therapy in terms of medications, nurse visits and blood glucose monitoring, and to compare these costs among the various treatment regimens.

2. Methods

This was a cross-sectional observational study of the treatment of diabetes in patients requiring insulin therapy that was performed by community pharmacists during the summer of 2010. The pharmacists were recruited from a panel of 4500 pharmacies representative of the 22,500 pharmacies in France in terms of geographical location, size of the community served and turnover. Panel members have regularly participated in research protocols in France.

During the study period, the participating pharmacists were asked to invite all patients coming to the pharmacy to fill out an insulin prescription for their own use to participate in the study. Only patients aged ≥ 18 years were eligible. Individuals collecting insulin prescriptions on behalf of someone else were excluded, as were the patients also being treated concomitantly with glucagon-like peptide-1 (GLP-1) analogues and/or using insulin pumps.

2.1. Data collection

At the time of the pharmacy visit, the pharmacist and patient completed an anonymous questionnaire to collect data on sociodemographic features, diabetes history and treatment (insulin and OAD use, including posology and administration regimens), type of prescribing physician (diabetologist or general practitioner), glucose monitoring, HbA1c monitoring (last
known HbA1c value declared by the patient), hypoglycaemic episodes with current treatment, hospitalizations in the preceding 6 months, and cardiac and cerebrovascular co-morbidities. Questionnaires were sent to the study’s operational centre for data entry and analysis. All data were reviewed centrally; any potentially incoherent or incorrect data were clarified by the pharmacists.

2.2. Evaluation criteria

An algorithm designed for use in epidemiological studies in France was used to categorize respondents as having either T1DM or T2DM [16]. This algorithm was developed on the basis of age at diagnosis, and the delay between the initial diagnosis and initiation of insulin therapy. Patients diagnosed before the age of 45 years or for whom the interval between diagnosis and start of insulin therapy was < 2 years were considered to have T1DM if they were not treated simultaneously by OADs other than metformin; the remaining patients were categorized as having T2DM. Similar algorithms have been developed in other countries [17,18].

For patients with T1DM, insulin treatment regimens were divided into three classes based on the number of injections per day: one or two injections; three injections; and four or more injections. For patients with T2DM, insulin treatment regimens were divided into three classes according to the combination of types of insulin used. Basal insulin regimens were defined as the use of basal or intermediate insulin only (with no other type of insulin), and subdivided into regimens using insulin glargine, regimens using insulin detemir and regimens using NPH insulin. Enhanced basal regimens were defined as either the use of basal or intermediate insulin together with rapid-acting or ultra-rapid-acting insulin, or the use of premixed insulin, and divided into regimens using one injection of rapid-acting insulin per day and regimens using two or more rapid-acting insulin injections per day. Regimens based on rapid-acting insulin only were considered separately.

Weekly treatment costs were evaluated using the official tariffs for medication costs, nurse visits and kits for self-monitoring of blood glucose [19]. Medication costs were estimated from the number of injections per days and the dose, excluding waste costs. The cost analysis was therefore performed from a social security perspective.

2.3. Sample size determination

The target sample size for the study was determined by \( a \) \_priori power calculations to estimate the variables of interest in subgroups of patients using different insulin treatment regimens with a precision of ± 8% for a frequency estimate of 50% and an \( a \) risk of 0.05.

2.4. Statistical analysis

Treatment regimens were described according to the proportion of patients using them together with their 95% confidence intervals (95% CI). Treatment costs were described as mean values with the 95% CI. For treatment regimens used by \( \geq 100 \) patients, these costs were compared between treatment regimens in a two-by-two fashion, using a log-transformed general linear model adjusted for other patient variables collected by the questionnaire. Patients declaring a dose of insulin \( \geq 200 \) units per injection were excluded from the economic analysis. Data analyses were performed using SAS software version 9.1 (Cary, NC, USA).

2.5. Ethical considerations

The survey protocol was submitted for evaluation to the CCTIRS (National Ethics Advisory Board). Procedures for data collection and management were approved by the Commission Nationale de l’Informatique et des Libertés (CNIL; the French Data Protection Authority).

3. Results

Overall, 734 pharmacists participated in the study and enrolled at least one patient over a 1-week period. Each pharmacy included an average of 3.3 patients (median: 3; range: 1–48). In general, the participating pharmacies were representative of all French pharmacies in terms of turnover, although pharmacies located in the Île-de-France (Paris) region and in middle-sized towns (5000–30,000 inhabitants) were slightly underrepresented (data not shown).

During the inclusion period, a total of 2457 patients were enrolled. Of these, 194 patients were excluded because of missing data for the evaluation criteria, leading to an analyzed population of 2263 patients, of whom 361 were assigned a diagnosis of T1DM and 1902 a diagnosis of T2DM. The demographic characteristics and diabetes features of these patients are presented in Table 1. The mean age was lower in type 1 patients (41.9 ± 15.4 years) than in type 2 patients (68.3 ± 12.2 years). Men were slightly overrepresented in both groups (54.5% of all patients included). Although the mean time since diagnosis was similar in patients with T1DM (14.4 ± 12.1 years) and T2DM (15.6 ± 11.0 years), the duration of insulin therapy was longer in the former vs the latter (14.3 ± 12.1 years vs 8.5 ± 8.2 years). Recent data on HbA1c were only available for around one-fourth of the study sample, and approximately one-third had values within the target range (≤ 7%). Around three-fourths of the sample were being followed by a diabetologist. The vast majority of patients (96.4% overall) monitored their blood glucose themselves, but over a quarter of patients with T2DM required nurse assistance for some or all of their injections. Since the beginning of their current insulin treatment, around one-fourth experienced a hypoglycaemic episode requiring help from a third party and, for 14% of the overall patient population, the hypoglycaemic episode led to hospitalization.

3.1. Insulin treatment regimens

The insulin treatment regimens used by patients participating in the study are shown in Fig. 1. Patients with T1DM were more frequently taking one or two injections per day (46.3%, 95%
Characteristics of patients with type 1 (T1DM) and type 2 (T2DM) diabetes mellitus.

Data are presented as mean ± SD, median [range], unless otherwise specified.

<table>
<thead>
<tr>
<th>Study population</th>
<th>T1DM (n = 361)</th>
<th>T2DM (n = 1902)</th>
<th>Total (n = 2263)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>n = 360</td>
<td>n = 1898</td>
<td>n = 2258</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>41.9 ± 15.4</td>
<td>68.3 ± 12.2</td>
<td>64.1 ± 16.0</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td>n = 359</td>
<td>n = 1870</td>
<td>n = 2229</td>
</tr>
<tr>
<td>Women</td>
<td>146 (40.7%)</td>
<td>868 (46.4%)</td>
<td>1014 (45.5%)</td>
</tr>
<tr>
<td>Men</td>
<td>21 (59.3%)</td>
<td>1002 (53.6%)</td>
<td>1215 (54.5%)</td>
</tr>
<tr>
<td><strong>Body mass index (kg/m²)</strong></td>
<td>n = 357</td>
<td>n = 1873</td>
<td>n = 2230</td>
</tr>
<tr>
<td>&lt; 18.5 kg/m²</td>
<td>17 (4.8%)</td>
<td>13 (0.7%)</td>
<td>30 (1.3%)</td>
</tr>
<tr>
<td>18.5–25 kg/m²</td>
<td>201 (56.3%)</td>
<td>397 (21.2%)</td>
<td>598 (26.8%)</td>
</tr>
<tr>
<td>25–30 kg/m²</td>
<td>95 (26.6%)</td>
<td>774 (413%)</td>
<td>869 (39.0%)</td>
</tr>
<tr>
<td>&gt; 30 kg/m²</td>
<td>44 (12.3%)</td>
<td>689 (36.8%)</td>
<td>733 (32.9%)</td>
</tr>
<tr>
<td><strong>Time since diagnosis (years)</strong></td>
<td>n = 360</td>
<td>n = 1898</td>
<td>n = 2258</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>14.4 ± 12.1</td>
<td>15.6 ± 11.0</td>
<td>15.5 ± 11.2</td>
</tr>
<tr>
<td>Median [range]</td>
<td>12 [0–64]</td>
<td>13 [0–76]</td>
<td>13 [0–76]</td>
</tr>
<tr>
<td><strong>Insulin therapy duration (years)</strong></td>
<td>n = 360</td>
<td>n = 1898</td>
<td>n = 2258</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>14.3 ± 12.1</td>
<td>8.5 ± 8.2</td>
<td>9.4 ± 9.2</td>
</tr>
<tr>
<td>Median [range]</td>
<td>12 [0–64]</td>
<td>6 [0–55]</td>
<td>6 [0–64]</td>
</tr>
<tr>
<td><strong>HbA1c (%)</strong></td>
<td>n = 129</td>
<td>n = 409</td>
<td>n = 538</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>7.4 ± 1.0</td>
<td>7.4 ± 1.1</td>
<td>7.4 ± 1.0</td>
</tr>
<tr>
<td>≤ 7%</td>
<td>41 (33.6%)</td>
<td>118 (31.4%)</td>
<td>159 (31.9%)</td>
</tr>
<tr>
<td><strong>Treated by diabetologist</strong></td>
<td>301 (84.8%)</td>
<td>1302 (70.0%)</td>
<td>1603 (72.4%)</td>
</tr>
<tr>
<td><strong>Aid from nurse for injections</strong></td>
<td>26 (7.2%)</td>
<td>532 (28.0%)</td>
<td>558 (24.7%)</td>
</tr>
<tr>
<td><strong>Self-monitoring of blood glucose</strong></td>
<td>335 (93.1%)</td>
<td>1844 (97.1%)</td>
<td>2179 (96.4%)</td>
</tr>
<tr>
<td><strong>Cardiac complications</strong></td>
<td>37 (10.4%)</td>
<td>525 (28.3%)</td>
<td>562 (25.4%)</td>
</tr>
<tr>
<td><strong>Cerebrovascular complications</strong></td>
<td>5 (1.4%)</td>
<td>100 (5.4%)</td>
<td>105 (4.7%)</td>
</tr>
<tr>
<td><strong>Hypoglycaemia</strong></td>
<td>n = 345</td>
<td>n = 1858</td>
<td>n = 2203</td>
</tr>
<tr>
<td>Requiring help from third party</td>
<td>135 (39.2%)</td>
<td>486 (26.3%)</td>
<td>621 (28.3%)</td>
</tr>
<tr>
<td>Requiring hospitalization</td>
<td>60 (17.8%)</td>
<td>233 (13.0%)</td>
<td>293 (13.8%)</td>
</tr>
<tr>
<td><strong>Hospitalization in preceding 6 months</strong></td>
<td>81 (22.8%)</td>
<td>599 (32.1%)</td>
<td>680 (30.6%)</td>
</tr>
</tbody>
</table>

Data are presented as n (%) unless otherwise specified.

CI: 41.0–51.6%), 66 patients (18.3%, 95% CI: 14.4–22.7%) were taking three injections per day and 128 patients (35.5%, 95% CI: 30.5–40.6%) were taking four or more injections per day. The mean daily dose of insulin was 38.7 ± 21.7 units for patients taking one or two daily doses, 62.7 ± 27.9 units for those taking three daily doses, and 61.8 ± 40.1 for those taking more than three daily doses. Overall, 48 different combinations of basal, rapid, NPH and premixed insulins were reported. The most frequently encountered combinations were one dose of basal insulin with one or more doses of rapid insulin (158 patients), premixed insulins alone or in combination (73 patients) and rapid insulins only (41 patients). Insulin glargine (180 patients) was more frequently used as a basal insulin than insulin detemir (45 patients), whereas NPH insulin, alone or in combination, was used by only two patients.

For patients with T2DM, a large number of treatment regimens were documented, involving 58 different combinations of basal, rapid, NPH and premixed insulins. Most patients were taking basal/intermediate insulin only (809 patients, 42.5%, 95% CI: 40.3–44.8%) or a combination of basal/intermediate and rapid insulins (enhanced basal regimens; 1002 patients, 52.7%, 95% CI: 50.4–54.9%). Over half the basal regimens involved insulin glargine (551 patients, 29.0%, 95% CI: 26.9–31.1%), whereas 135 patients (7.1%, 95% CI: 6.0–8.3%) were using NPH insulins and 123 were taking insulin detemir (6.5%, 95% CI: 5.4–7.7%). Insulin glargine and insulin detemir were most frequently injected once a day (89.5 and 74.0%, respectively, of patients using these insulins) whereas NPH insulin was used most frequently twice a day (50.4% of patients). The mean daily dose of insulin was similar across the three insulins, ranging from 32.2 ± 21.4 units/day for insulin glargine to 40.3 ± 24.4 units/day for NPH insulin.

For patients using enhanced basal treatment regimens, these involved two injections a day for 378 patients (19.9%, 95% CI: 18.1–21.7%), most frequently one basal insulin and one rapid insulin (179 patients) or premixed insulin once daily (114 patients). When three or more injections were taken (624 patients, 32.8%, 95% CI: 30.7–35.0%), they most frequently involved premixed insulin twice a day (203 patients) or one
basal and three rapid insulins per day (166 patients). The mean daily insulin dose was 47.0 ± 31.0 units/day for patients taking insulin twice daily, and 70.7 ± 43.7 units/day for those taking three or more injections a day. Also, 91 patients were taking rapid insulin only (4.8%, 95% CI: 3.9–5.8%), most frequently once a day (59 patients).

Forty-five patients with T1DM (12.5%) and 967 patients with T2DM (51.0%) were being treated concomitantly with OADs.

### 3.2. Treatment costs

The mean cost of insulin therapy was €27.4/week for patients with T1DM and €45.4/week for patients with T2DM (Table 2). The difference was accounted for principally by the cost of nurses to help with injections, which was more than threefold higher in the T2DM group, and accounted for more than half the total cost for these patients. Greater use of OADs contributed marginally to the higher cost of insulin treatment in type 2 patients.

In patients with T1DM, the cost of insulin was the biggest cost component. The cost of therapy increased significantly \((P < 0.0001)\) with the number of injections per day (Table 2). This difference was mostly accounted for by the increased cost of medication. After adjusting for non-treatment-related variables, two-by-two comparisons revealed that administration three times daily or \(\geq 4\) times daily was significantly more costly than administration once or twice a day \((P < 0.0001)\); however, the cost of a \(\geq 4\)-times-daily regimen did not differ significantly from that of a three-times-daily regimen. No significant difference was observed in the overall cost of treatment between regimens using insulin glargine, insulin detemir, NPH insulin or premixed insulins (data not shown).

In patients with T2DM, nurse visits were the most significant contributors to cost in all of the treatment regimens evaluated. The overall cost of insulin therapy differed significantly among the three regimens \((P < 0.0001)\), being highest in those using both basal and rapid insulins (enhanced basal regimen: €52/week), and lowest in the small group of patients using rapid insulin only (€33.5/week). Again, the difference was primarily attributable to nurse visits, which were twice as frequent in the enhanced-basal-regimen group as in the

**Table 2**

Weekly costs of insulin therapy (€) in type 1 (T1DM) and type 2 (T2DM) diabetes patients.

<table>
<thead>
<tr>
<th></th>
<th>Insulin</th>
<th>OAD</th>
<th>Nurse visits</th>
<th>Glucose tests</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall T1DM costs</strong></td>
<td>12</td>
<td>2</td>
<td>23</td>
<td>6</td>
<td>43</td>
</tr>
<tr>
<td>1 or 2 injections/day</td>
<td>9.0</td>
<td>0.3</td>
<td>3.7 ± 4.2</td>
<td>21.5 ± 35.2</td>
<td>38.9</td>
</tr>
<tr>
<td>3 injections/day</td>
<td>14.6</td>
<td>0.3</td>
<td>3.8 ± 4.1</td>
<td>20.1 ± 31.5</td>
<td>37.4</td>
</tr>
<tr>
<td>(\geq 4) injections/day</td>
<td>14.4</td>
<td>0.1</td>
<td>4.9 ± 5.4</td>
<td>25.7 ± 39.9</td>
<td>45.7</td>
</tr>
<tr>
<td><strong>Overall T2DM costs</strong></td>
<td>11.5</td>
<td>2.5</td>
<td>25.8 ± 49.5</td>
<td>7.1 ± 5.0</td>
<td>32.6</td>
</tr>
<tr>
<td>Basal regimen</td>
<td>9.0</td>
<td>0.3</td>
<td>3.7 ± 4.2</td>
<td>21.5 ± 35.2</td>
<td>38.9</td>
</tr>
<tr>
<td>Insulin glargine</td>
<td>9.1</td>
<td>0.3</td>
<td>3.8 ± 4.1</td>
<td>20.1 ± 31.5</td>
<td>37.4</td>
</tr>
<tr>
<td>Insulin detemir</td>
<td>9.8</td>
<td>0.4</td>
<td>4.9 ± 5.4</td>
<td>25.7 ± 39.9</td>
<td>45.7</td>
</tr>
<tr>
<td>NPH</td>
<td>7.8</td>
<td>1.7</td>
<td>1.7 ± 2.5</td>
<td>23.4 ± 43.9</td>
<td>38.3</td>
</tr>
<tr>
<td>Enhanced basal regimen</td>
<td>14.0</td>
<td>1.6</td>
<td>1.6 ± 3.0</td>
<td>29.7 ± 59.1</td>
<td>51.8</td>
</tr>
<tr>
<td>2 injections/day</td>
<td>10.9</td>
<td>1.6</td>
<td>1.6 ± 3.1</td>
<td>21.1 ± 38.5</td>
<td>38.6</td>
</tr>
<tr>
<td>(\geq 3) injections/day</td>
<td>15.7</td>
<td>1.6</td>
<td>1.6 ± 3.3</td>
<td>34.4 ± 67.2</td>
<td>58.9</td>
</tr>
<tr>
<td>Rapid insulin only</td>
<td>6.2</td>
<td>1.8</td>
<td>1.8 ± 3.0</td>
<td>20.1 ± 42.3</td>
<td>33.5</td>
</tr>
</tbody>
</table>

All data are presented as means ± SD unless otherwise specified; OAD: oral antidiabetic drug. OAD: oral antidiabetic drug.
rapid-insulin-only group. After adjusting for non-treatment-related variables, a significant difference in cost was observed between the enhanced-basal-regimen group and the other two groups ($P < 0.0001$), which had similar average adjusted costs. Costs also differed among the various basal insulin regimens, being higher in patients using insulin detemir than in the other two groups even after adjusting for non-treatment-related variables ($P = 0.0004$; detemir: €45; glargine: €37; NPH: €32), due to more frequent nurse visits and greater use of adjunct OADs. For patients using enhanced basal regimens, those using three or more injections incurred more costs than those using two injections per day ($P < 0.0001$); in this case, this was principally attributable to the higher costs of insulin.

4. Discussion

The two principal objectives of the present study were to describe the insulin treatment regimens used by patients with diabetes in France and to evaluate their costs. The principal findings were the wide variety of treatment regimens used in everyday practice, and the important contribution of nurse visits to the cost of insulin therapy, especially for type 2 patients.

It was observed that 48 different insulin treatment regimens were used by 361 patients with T1DM, and 58 different regimens by 1902 patients with T2DM. In type 1 patients, basal-bolus schemes were used by less than a third of patients (29%). Since the SCHEMA study was performed in 1999 in France, before basal and rapid insulins were introduced, a number of other studies have documented and deployed the multiplicity of insulin treatment regimens used in everyday practice [10,12,15], and the situation does not appear to have been improved. A wide variety of treatment regimens has also been observed in other countries, as reported in a survey conducted between December 2007 and February 2008 in a sample of 9179 patients with T2DM in seven countries (USA, France, Germany, UK, Italy, Japan, Spain) [12].

In T2DM, the most frequently used schemes—for example, one basal insulin injection and one or more injections of rapid insulin or two daily injections of premixed insulin; a single daily injection of basal insulin or two of NPH insulin; and one or more injections of rapid insulin only—appear to be appropriate. Such regimens were used by around three-fourths of all patients in our present study. On the other hand, some of the other regimens documented in our study, such as the use of three injections of basal insulin every day, or combinations of basal, rapid and premixed insulins, appear to be less clearly justifiable. National treatment guidelines for T2DM [6] recommend starting insulin therapy in all patients who do not achieve satisfactory glycaemic control with two OADs with a single daily injection of basal or intermediate insulin. If this is insufficient to achieve the desired objective, a rapid-acting insulin or further intermediate insulin should be added. However, it is clear that a significant minority of patients are receiving insulin treatment regimens inconsistent with this recommendation. In this respect, there is clearly room for better physician education and more precise treatment algorithms, such as those recently produced by the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) for the treatment of T2DM [20].

The second major finding of the present study was that the cost of nurse visits to help with injections is the main contributor to the cost of insulin therapy in type 2 patients. In this group, 28% of patients made use of a nurse for their insulin injections compared with only 7% of patients with T1DM. This observation is consistent with data from the Échantillon national témoin représentatif des personnes diabétiques (ENTRED; National Representative Sample of Diabetic Patients) study which showed that the per capita expenditure for nursing care was 15-fold higher in T2DM patients using insulin than in those using only OADs [21]. Thus, if more patients could be encouraged to inject their insulin on their own, considerable cost savings would be made. The extent of nurse intervention is a major factor that explains the differences in costs incurred between type 1 and type 2 patients, and between insulin treatment regimens of different intensities. The contribution of the cost of insulin itself to the total cost of T2DM was half that of nurse visits and varied with the number of injections.

Another important finding was that the costs, after adjustments, differed among the various basal insulin regimens (higher for insulin detemir than for insulin glargine, and higher for insulin glargine than for NPH), while the costs of the various enhanced basal regimens were similar regardless of the type of insulin used.

It should be noted that the only costs evaluated in the present study were the day-to-day ‘running costs’ of insulin therapy, and did not take into account the general costs incurred in the management of diabetes, such as physician visits and laboratory tests, or the costs associated with hypoglycaemia and the long-term complications of diabetes. These other costs may have an impact on the relative cost-effectiveness of the different insulin treatment regimens.

Also, the patients included in the present study were unelected, being recruited when they spontaneously visited the pharmacy for a prescription refill. How representative the participating pharmacies were may be questioned, as participation was voluntary and little information was collected on their specific characteristics. Furthermore, no information was collected on the number of potentially eligible patients who declined to participate in the study, so there may be a participation bias if, for example, patients who were more ill were less likely to agree to completing the questionnaire. Moreover, as only patients going in person to the pharmacy to get insulin for their own use were included, the more severely ill patients who were unable to get to the pharmacy on their own were not represented in our study sample.

For this reason, the characteristics of our patients were compared with those treated with insulin in the ENTRED 2007 study [13], where data were partly obtained from a prescription claims database without the need for patients’ consent. The mean age of our sample was similar to that of the ENTRED population, although women were less well represented (45.5% vs 49.2% in ENTRED); also, our patients had, on average, a shorter history of diabetes (15.5 years vs 17.1 years in ENTRED) and, in T2DM...
patients, had been treated with insulin for longer (8.5 years vs 6.5 years, respectively). In addition, the proportion of patients with T1DM with HbA1c values ≤ 7% was higher in the present study (33.6%) than in the ENTRED population (26.5%). However, it should be noted that, in the ENTRED study, HbA1c was documented by the physician who ordered the test whereas, in our study, this information was provided by the patient during the pharmacy visit without access to records. This may have led to errors in the information provided.

These study differences may reflect changes in the diabetes population over time, with diabetes being diagnosed at a younger age than previously [4] and insulin therapy being started earlier. For patients with T1DM, but not those with T2DM, glycaemic control, as evaluated by the proportion of patients with HbA1c levels ≤ 7%, appeared to be better in our study population than in the ENTRED population, which may also reflect improvements in standards of care between the two studies or, perhaps, underrepresentation of less compliant patients in our sample. The level of glycaemic control in our study was nonetheless similar to that reported in the SCHEMA study [10], conducted before the introduction of recombinant modified basal and rapid-acting insulins, where 33% of the sample presented with HbA1c levels < 7.5%, thereby supporting the presence of a sampling bias rather than improvement of glycaemic control in diabetes patients over time.

In conclusion, our present study revealed considerable heterogeneity in the type of insulin treatment regimens used in the everyday care of diabetes in France. Use of treatment algorithms to simplify and harmonize insulin therapy may help to improve patient care and reduce costs. A large proportion of patients (especially older ones) have recourse to private nurses to perform their injections, and this situation is likely to worsen over time because of the ageing of the population of patients with diabetes. Encouraging patients to self-inject insulin would generate substantial cost savings in patients with T2DM in France.

Disclosure of interest

Bernard Charbonnel has received fees for consultancy, speaking, travel or accommodation from Takeda, GlaxoSmithKline, Merck Sharpe & Dohme, AstraZeneca, Bristol Myers Squibb, Boehringer Ingelheim, Novo Nordisk, Roche, Sanofi-Aventis, Novartis.

A. Penfornis has received honoraria for lectures and consultations from Abbott, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly, LifeScan, Merck-Serono, Merck Sharp & Dohme, Novartis, Novo Nordisk, Roche, Sanofi-Aventis, Takeda.

M Varroud-Vial has received honoraria for lectures and consultations from AstraZeneca, Bristol Myers Squibb, Eli Lilly, LifeScan, Merck-Serono, Merck Sharp & Dohme, Novo Nordisk, Sanofi-Aventis, Takeda.

O. Kusnik-Joinville was a consultant at Cemka-Eval, a contract research organisation, working for most of the private companies and public institutions involved in health care in France. She is currently employed by AG2R La Mondiale Inc.

B. Detournay is an Associate of Cemka-Eval, a contract research organisation, working for most of the private companies and public institutions involved in health care in France.

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