Abstract

Aims. – The purpose of this study was to investigate the time between the start of OAD treatment and the initiation of insulin therapy and to identify the factors associated with insulin prescription among Swedish patients with type 2 diabetes in Uppsala County.

Methods. – Retrospective, population-based, primary-care data gathered within the Swedish RECAP-DM study were used to identify type 2 diabetic patients who initiated OAD treatment. A Kaplan-Meier survival estimate for time to initiation of insulin therapy was generated and factors associated with insulin prescription were tested using a Cox proportional-hazards model.

Results. – Within 6 years of starting OAD treatment, an estimated 25% of Swedish patients with type 2 diabetes will be prescribed insulin (95% CI: 0.23–0.26) and, within 10 years, this figure will rise to 42% (95% CI: 0.39–0.45). The probability of insulin prescription was increased in patients aged less than 65 years (HR = 1.24, 95% CI: 1.03–1.50) and in those who initiated OAD treatment with more than one agent (HR = 2.71, 95% CI: 2.15–3.43). HbA1c at the time of starting OAD treatment was also related to the probability of insulin prescription (HR = 1.20, 95% CI: 1.146–1.25).

Conclusion. – Many type 2 diabetic patients who begin treatment with an OAD will eventually be prescribed insulin. Age, disease severity and the type of prior treatment may affect the rate of the transition.

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Keywords: Hyperglycaemia; Oral antidiabetic agents; Secondary failure; Insulin treatment; Type 2 diabetes mellitus; Sweden
1. Introduction

Diabetes and its associated complications impose substantial health and economic burdens on individual patients and their communities [1,2]. Comprising approximately 90% of such cases worldwide [3], type 2 diabetes is responsible for the largest proportion of this burden.

Treatment of type 2 diabetes is primarily aimed at glycaemic control and international guidelines recommend reducing HbA1c to 6.5–7% [4,5]. It is generally recognized that maintaining HbA1c at target levels can substantially reduce the risk of developing diabetes-related complications such as retinopathy, nephropathy and neuropathy [6–9]. Type 2 diabetes management should begin with lifestyle modifications and OADs such as metformin but, as the disease progresses and β-cell function deteriorates, insulin may be necessary for adequate glycaemic control [4].

Guidelines suggest that type 2 diabetic patients who are unable to achieve glycaemic targets with maximum doses of OADs are candidates for insulin therapy [4,5,10]. However, little is known of the progression of therapy in clinical practice. Identifying real-life patterns associated with insulin treatment—as opposed to protocol-defined algorithms or assuming that published guidelines represent everyday practices—forms a basis for understanding patient outcomes and identifying means of improving them. Furthermore, a profile of local treatment patterns provides a foundation for accurate health–economic modelling and for assessing the influence of new treatments.

Data collected within the Swedish RECAP-DM study provide information on diagnoses, prescriptions and resource use in a population-based setting [11,12]. Using such patient-based longitudinal data, the objectives of the present study were to examine the time to initiation of insulin treatment and to identify factors associated with insulin prescription among Swedish type 2 diabetic patients who had started OAD treatment.

2. Methods

2.1. Patients

The data collection methods and inclusion criteria for the Swedish RECAP-DM study have been described in detail elsewhere [11,12]. Briefly, 26 public primary-care centres in Uppsala County participated in this retrospective, population-based, cohort study. Each centre granted access to its computerized medical records, kept from 1993 to 2005. These de-identified records provided a complete account of drug prescriptions, laboratory measurements, diagnoses and biometrics recorded at the centres in association with patient contacts.

Patients were included in the RECAP-DM study if their primary-care records indicated that they met at least one of the following criteria:

- International Classification of Diseases (ICD) diagnostic code for type 2 diabetes (ICD-10 codes E11–E14; ICD-9 code 250);
- prescription of an OAD [Anatomical Therapeutic Chemical (ATC) code A10B];
- fasting blood or plasma glucose value indicative of type 2 diabetes, as defined in Swedish guidelines and by the World Health Organization (WHO) [13,14].

Patients with a diagnosis code for any other type of diabetes, those who were aged less than 30 years and those aged less than 40 years who were prescribed insulin, but not an OAD, were excluded.

To assess the time from initiation of OAD treatment to the start of insulin therapy, we identified all RECAP-DM patients with at least one record of an OAD prescription (ATC code A10B) and no previous insulin prescription (ATC code A10A) during the study period. Also, the date of the first OAD prescription was required to have been at least 1 year after the beginning of the observation period (the period for which primary-care data were available). No inferences could be made concerning medication prior to the observation period but it was assumed that patients taking continuous OADs need to refill their prescriptions at least once a year, so requiring one initial prescription-free year should identify those commencing OAD treatment.

Data for patients included in the study cohort were also obtained from national registries through linking records via Swedish national personal-identification numbers. For this particular analysis, the National Causes of Death Registry provided mortality data through 31 December 2003.

2.2. Time to insulin treatment

Time from the initiation of OAD treatment to the start of insulin therapy was determined through survival analysis, with time zero defined as the date of the first OAD prescription in the primary-care records. The event of interest was the subsequent prescription of insulin (ATC-code A10A). Thus, for patients prescribed insulin during the observation period, the analysis began with time zero and ended on the date of insulin prescription. For patients not prescribed insulin during the observation period, analysis time started with time zero and ended on 7 October 2005, the final date for which prescription data were available, or on the date of death, as recorded in the National Causes of Death Registry. For patients who were prescribed insulin on the same date as the initial OAD prescription, analysis time was set...
to 1 day instead of 0 days to prevent those observations from being inadvertently excluded from the analysis.

2.3. Factors associated with insulin treatment

A Cox proportional-hazards model was developed to test for factors associated with being prescribed insulin that, in this case, included: gender; age expressed as categorical variables for those aged less than 65 years, 65–79 years (reference group) and 80 years and above; body mass index (BMI) and HbA1c at baseline (time of OAD treatment initiation); and type of initial OAD treatment, expressed as categorical variables for metformin monotherapy as the first-line agent (metformin: 1; all other treatments: 0) and for combination therapy, defined as the prescription of more than one OAD at time zero (initiation of combination therapy: 1; initiation of all other single or combination treatments: 0).

Baseline HbA1c was defined as the measurement taken within 60 days before to 30 days after the date of the initial OAD prescription. If there was more than one measurement available during this period, the mean value was used. HbA1c values were converted from the Mono-S scale used in Sweden to the more commonly used Diabetes Control and Complications Trial (DCCT) scale, using an established formula [15].

Patients who lacked a baseline HbA1c measurement or baseline BMI measurement were excluded from the base-case Cox proportional-hazards model. However, the effect of missing data was explored through the addition of indicator variables, which took the value 1 if baseline HbA1c/BMI were missing and the value 0 otherwise.

Possible changes over time in the propensity of general practitioners to prescribe insulin treatment were also explored through the use of an indicator variable, taking the value 1 for patients starting OAD treatment after 1 January 2000 and 0 for patients starting treatment before that date. The applied proportional-hazards model used the Breslow method for ties and the statistical significance of the model’s covariates was evaluated using a Wald test, with $\alpha = 0.05$.

3. Results

3.1. Study sample

Of the 11,856 type 2 diabetic patients included in the Swedish RECAP-DM study, 5403 were identified as initiating OAD treatment during the study period and were thus included in the present analysis. The mean ± S.D. age of those starting OAD treatment was 66 ± 13 years and 45% were women, which is in line with findings from the Swedish National Diabetes Registry [16]. Mean HbA1c at the time of starting OAD treatment was 8.33 ± 1.69% ($n = 4126$ with HbA1c values) and mean BMI was 30.0 ± 5.4 kg/m² ($n = 3250$ with BMI measurements).

Table 1 presents the frequencies of initial OAD prescriptions for the studied patients. Sulphonylureas as a group (glibenclamide, glipizide, gliclazide and chlorpropamide) were the most commonly prescribed first-line treatments (52%), followed by metformin (36%) and combination treatments (11%). Initial prescriptions were written between 22 June 1994 and 7 October 2005 and there was a clear shift towards an increased use of metformin as the first-line agent over time. Metformin alone

<table>
<thead>
<tr>
<th>Initial treatment</th>
<th>$n$</th>
<th>Mean (S.D.) age</th>
<th>Percent female</th>
<th>Mean (S.D.) baseline HbA1c (%)</th>
<th>Percent of all oral treatment initiators</th>
<th>Percent prescribed insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Monotherapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metformin (A10BA02)</td>
<td>1930</td>
<td>61 (12)</td>
<td>46</td>
<td>8.2 (1.6)</td>
<td>35.7</td>
<td>13.0</td>
</tr>
<tr>
<td>Glipizide (A10BB07)</td>
<td>1461</td>
<td>69 (13)</td>
<td>46</td>
<td>8.5 (1.8)</td>
<td>27.0</td>
<td>22.4</td>
</tr>
<tr>
<td>Glibenclamide (A10BB01)</td>
<td>1257</td>
<td>70 (13)</td>
<td>45</td>
<td>8.4 (1.7)</td>
<td>23.3</td>
<td>21.0</td>
</tr>
<tr>
<td>Glimepiride (A10BB12)</td>
<td>90</td>
<td>65 (11)</td>
<td>40</td>
<td>8.8 (1.9)</td>
<td>1.7</td>
<td>26.7</td>
</tr>
<tr>
<td>Repaglinide (A10BX02)</td>
<td>41</td>
<td>64 (12)</td>
<td>46</td>
<td>8.6 (1.9)</td>
<td>0.8</td>
<td>24.4</td>
</tr>
<tr>
<td>Acarbose (A10BF01)</td>
<td>17</td>
<td>62 (15)</td>
<td>65</td>
<td>8.2 (1.3)</td>
<td>0.3</td>
<td>29.4</td>
</tr>
<tr>
<td>Rosiglitazone (A10BG02)</td>
<td>9</td>
<td>70 (12)</td>
<td>11</td>
<td>7.6 (1.4)</td>
<td>0.2</td>
<td>0</td>
</tr>
<tr>
<td>Pioglitazone (A10BG03)</td>
<td>5</td>
<td>67 (13)</td>
<td>40</td>
<td>9.3 (2.6)</td>
<td>0.1</td>
<td>0</td>
</tr>
<tr>
<td>Chlorpropamide (A10BB02)</td>
<td>4</td>
<td>75 (11)</td>
<td>50</td>
<td>6.4 (–)</td>
<td>0.1</td>
<td>25.0</td>
</tr>
<tr>
<td><strong>Combination treatment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metformin + glipizide</td>
<td>316</td>
<td>63 (12)</td>
<td>37</td>
<td>8.4 (1.8)</td>
<td>5.9</td>
<td>41.5</td>
</tr>
<tr>
<td>Metformin + glibenclamide</td>
<td>226</td>
<td>67 (11)</td>
<td>45</td>
<td>8.0 (1.7)</td>
<td>4.2</td>
<td>40.7</td>
</tr>
<tr>
<td>Metformin + repaglinide</td>
<td>10</td>
<td>58 (10)</td>
<td>10</td>
<td>7.6 (1.4)</td>
<td>0.2</td>
<td>30.0</td>
</tr>
<tr>
<td>Metformin + glicepride</td>
<td>9</td>
<td>71 (12)</td>
<td>78</td>
<td>7.8 (1.3)</td>
<td>0.2</td>
<td>22.2</td>
</tr>
<tr>
<td>Metformin + rosiglitazone</td>
<td>8</td>
<td>71 (10)</td>
<td>25</td>
<td>6.7 (0.5)</td>
<td>0.2</td>
<td>12.5</td>
</tr>
<tr>
<td>Metformin + chlorpropamide</td>
<td>4</td>
<td>76 (8)</td>
<td>25</td>
<td>6.1 (–)</td>
<td>0.1</td>
<td>50.0</td>
</tr>
<tr>
<td>Metformin + pioglitazone</td>
<td>2</td>
<td>63 (6)</td>
<td>50</td>
<td>5.7 (–)</td>
<td>&lt;0.1</td>
<td>0</td>
</tr>
<tr>
<td>Glimepiride + acarbose</td>
<td>2</td>
<td>59 (4)</td>
<td>0</td>
<td>6.8 (0.6)</td>
<td>&lt;0.1</td>
<td>0</td>
</tr>
<tr>
<td><strong>Other double or triple oral combinations</strong></td>
<td>12</td>
<td>65 (11)</td>
<td>50</td>
<td>7.4 (1.1)</td>
<td>0.2</td>
<td>16.7</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>5403</td>
<td>66 (13)</td>
<td>45</td>
<td>8.3 (1.7)</td>
<td>100</td>
<td>1115</td>
</tr>
</tbody>
</table>

\[a\] 24% missing observations.  
\[b\] Where $n = 1.$
accounted for 17% \((n = 420)\) of initial prescriptions before the year 2000 and 52% \((n = 1510)\) of initial prescriptions since then.

Of the 5403 patients initiating OAD treatment, 21% \((n = 1115)\) were subsequently prescribed insulin during the study period, with 181 patients \((3.3\%)\) prescribed insulin on the same date as the initial OAD prescription. For the majority of patients \((n = 752)\), the first insulin prescription was for intermediate-acting human insulin \((\text{ATC code A10AC01})\) alone. The second most common type of prescription \((n = 196)\) was for premixed combinations of rapid- and intermediate-acting insulin \((\text{ATC code A10AD})\). Relatively few patients \((n = 36)\) received prescriptions for both intermediate-acting \((\text{ATC code A10AC})\) and rapid-acting insulin \((\text{ATC code A10AB})\), although this figure is likely to have been higher had the analysis not been restricted to prescriptions written the very day of starting treatment. Only a small number of patients \((n = 18)\) were prescribed long-acting insulin \((\text{ATC code A10AE})\).

At initiation of insulin treatment, the mean HbA1c in the studied patients was 8.7 ± 1.47% \((n = 867\) with values). Three to 6 months after the first insulin prescription, mean HbA1c had dropped to 7.82 ± 1.19% \((n = 790\) with measurements).

### 3.2. Time to insulin initiation

The mean analysis time—defined as the number of days from the initial OAD prescription to the event of insulin prescription, patient death or end of the observation period—was 1467 ± 1011 days \((4.0 ± 2.8\) years). The median analysis time was 1319 days \(3.6\) years. According to the estimated survival function based on the present sample from Uppsala County, 25% of patients with type 2 diabetes will be prescribed insulin treatment within 6 years \((2200\) days) of starting OAD treatment \((95\%\ CI: 0.23–0.26\). At 10 years, the estimated proportion prescribed insulin will be 42% \((95\%\ CI: 0.39–0.45\), corresponding to an annual rate of insulin initiation of 4%. The Kaplan-Meier estimate of the survival function for time to initiation of insulin treatment is plotted in Fig. 1.

<table>
<thead>
<tr>
<th>Table 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Covariate &amp; HR &amp; SE &amp; (P &gt;</td>
</tr>
<tr>
<td>Female gender &amp; 1.033 &amp; 0.094 &amp; 0.723 &amp; 0.864–1.234</td>
</tr>
<tr>
<td>Age &lt; 65 years &amp; 1.244 &amp; 0.119 &amp; 0.022 &amp; 1.032–1.501</td>
</tr>
<tr>
<td>Age ≥ 80 years &amp; 0.923 &amp; 0.163 &amp; 0.650 &amp; 0.652–1.306</td>
</tr>
<tr>
<td>Oral combination treatment &amp; 2.714 &amp; 0.325 &amp; 0.000 &amp; 2.146–3.433</td>
</tr>
<tr>
<td>Metformin &amp; 0.881 &amp; 0.099 &amp; 0.260 &amp; 0.708–1.098</td>
</tr>
<tr>
<td>Baseline HbA1c &amp; 1.198 &amp; 0.027 &amp; 0.000 &amp; 1.146–1.253</td>
</tr>
<tr>
<td>Baseline body mass index &amp; 0.982 &amp; 0.009 &amp; 0.061 &amp; 0.964–1.001</td>
</tr>
</tbody>
</table>

Model inputs: number of subjects = 2812; number of failures (subjects prescribed insulin) = 532; total patient-time at risk = 10,999 years.

SE: standard error.

\(a\) 1 if patient was female, 0 if male.

\(b\) 1 if patient started with more than one oral antidiabetic agent, 0 if otherwise.

\(c\) 1 if patient started with metformin monotherapy, 0 if otherwise.

### 3.3. Factors associated with insulin initiation

The number of patients with complete data for baseline HbA1c and BMI, who could therefore be included in the base-case Cox proportional-hazards model, was 2812, of which 532 were prescribed insulin subsequent to initiating OAD treatment. Neither gender nor older age had a statistically significant effect on the chances of being prescribed insulin (Table 2). However, patients aged less than 65 years at the time of starting OAD treatment had a 24% greater probability of insulin prescription than the reference group of patients aged 65–79 years \((HR = 1.24, 95\%\ CI: 1.03–1.50)\). In addition, baseline HbA1c and initiation of OAD treatment on a combination of oral agents were independently associated with the probability of insulin prescription, with starting on a combination of OADs being associated with a 2.7-fold greater probability of insulin prescription (Table 2). The association between BMI and insulin prescription was of borderline statistical significance, but the trend appeared to be slightly negative \((HR = 0.98, 95\%\ CI: 0.96–1.00)\).

When BMI was excluded from the model, the number of patients that could be included was 4126, of which 804 were prescribed insulin subsequent to starting OAD treatment. This alternative was explored as approximately 40% of patients lacked BMI data, leading to the exclusion of a large number of observations from the base-case model. With the increased sample size following the dropping of BMI as a model covariate, being prescribed metformin monotherapy as a first-line treatment was associated with a statistically significant 20% decreased probability of insulin prescription compared with other treatments \((HR = 0.80, 95\%\ CI: 0.67–0.95)\).

Missing baseline HbA1c or BMI data was not significantly associated with the probability of being prescribed insulin \((HR = 1.02, 95\%\ CI: 0.88–1.16\) for missing HbA1c: \(HR = 1.04, 95\%\ CI: 0.92–1.18\) for missing BMI; 5403 observations in the model). Thus, the 2591 patients omitted from the base-case Cox proportional-hazards model because of missing HbA1c and/or BMI data did not appear to differ from the 2812 included patients in terms of rates of insulin prescription. Also, there appeared to be no change in insulin prescription rates over time, as the indicator variable for OAD treatment initiation prior to year 2000.
was not significant when added to the model (HR = 1.03, 95% CI: 0.85–1.25).

4. Discussion

In the present study of patients with type 2 diabetes in Uppsala County, we found that an estimated 25% of patients starting OAD treatment will be prescribed insulin within 6 years. The strength of our study lies in the use of population-based data derived from day-to-day clinical practice. These real-life data reflect actual treatment patterns and allow for observation of patients over time.

ADA/EASD guidelines for the initiation and adjustment of treatment in type 2 diabetes recommend starting with lifestyle interventions and metformin and then changing these interventions at as rapid a pace as medication titration allows to maintain HbA1c below 7%, thereby protecting patients from the increased risk of complications that ensue from inadequate control of glycaemia [4]. The fact that the mean HbA1c value among patients initiating insulin was 8.79% in our present study suggests that the transition to new treatment regimens may not be taking place rapidly enough.

Patients less than 65 years of age had a greater probability of insulin prescription, which is to be expected, as the administration of insulin requires certain visual and motor skills. As for the fact that patients with elevated baseline HbA1c and/or who initiated OAD treatment with a combination of agents had a greater probability of insulin prescription, this probably reflects the fact that diabetes had progressed further in these patients. Clearly, the analysis would have benefited from including diabetes duration in the model, but these data were not available from the primary-care records.

Our finding that patients prescribed metformin as the first-line antidiabetic treatment had a lower probability of insulin prescription compared with those who started with other OADs (in the model excluding BMI) is consistent with the results of Canadian and Scottish retrospective studies, which found that type 2 diabetic patients who initiated antidiabetic treatment with metformin monotherapy were less likely than those starting with a sulphonylurea to begin insulin treatment during their study periods, which were approximately 5.7 and 1.6 years, respectively [17,18]. It may, however, be that diabetes duration confounds this variable, as metformin is often prescribed relatively early in the treatment of type 2 diabetes and patients initiating treatment with this medication alone are likely to be in the earlier stages of the disease.

As for timing, the rate of insulin initiation in the present studied Swedish population is comparable to those observed in other studies [18,19]. With a median of 1.6 years of data, the retrospective Scottish study estimated that 5.8% of OAD treatment initiators would start insulin each subsequent year [18], a higher rate than that observed for Uppsala County in the present study. However, data from the prospective Australian Fremantle Diabetes Study suggest a slightly lower rate than that found in our sample, with approximately 15% of patients taking OADs starting insulin within 5 years, though these patients were not necessarily OAD treatment initiators at baseline [19].

Some studies suggest that early initiation of insulin treatment—even temporarily—can aid in establishing glycaemic control by more rapidly reducing HbA1c levels and preserving β-cell function, leading to more effective glycaemic control over time [20–22]. Even if not instituted immediately, insulin may currently be prescribed earlier for some patients to complement OAD treatment or because of earlier recognition of inadequate glycaemic control. A study of type 2 diabetic patients included in the Swedish National Diabetes Registry reported an increased use of OADs combined with insulin between 1996 and 2003 (6.8% vs 13.0%, respectively, for patients in primary care) and a decreased use of insulin alone (15.8% vs 12.5%, respectively) [23]. Furthermore, additional antidiabetic treatment was added at lower HbA1c levels in 2003 compared with 1996 [16]. These patterns suggest that physicians may be introducing insulin treatment earlier, while OADs are still somewhat effective, rather than waiting for secondary failure.

The medical records used in the present study are representative of local treatment practices. However, these data should be interpreted in the context of the information source. The prescription data available to this study were restricted to primary care and, although this captures the majority of diabetic patients in Uppsala County [24,25], some may have received insulin prescriptions from specialists, which would mean that the time to insulin initiation in our study has been underestimated. Also, as no data for prescriptions prior to our observation period were available, it is also possible that some patients had received previous prescriptions of insulin or were not true initiators of OAD treatment. Another possible source of bias was the lack of mortality data beyond December 2003, which precluded the assessment of mortality after that date.

In addition, whether or not patients switched to insulin or only added it to their oral medication was not assessed. Furthermore, the specific reasons for starting insulin were not available from the medical records and physicians may have prescribed particular OADs to patients with certain underlying characteristics that may have predisposed them to insulin treatment. Moreover, other possible confounding factors, such as obesity and renal dysfunction, were not accounted for in the proportional-hazards model.

In conclusion, the present study estimates that 25% of Swedish type 2 diabetic patients in Uppsala County who start OAD treatment will be prescribed insulin within 6 years. The probability of being prescribed insulin was found to be associated with age, HbA1c, and the type of initial oral treatment given. Knowledge of these real-life treatment patterns is useful for explaining treatment outcomes and may also form a basis for assessing the influence of new therapies.

Conflict of interest

A.R. and P.L. have served as consultants to and received research grants from, Merck & Co., Inc and D.D.Y. is a full-time employee of Merck & Co., Inc. M.M. and J.S. have no conflicts of interest to declare.
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