Short Report: Treatment

Trends in selection and timing of first-line pharmacotherapy in older patients with Type 2 diabetes diagnosed between 1994 and 2006

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Abstract

Aims To characterize temporal trends in the selection and timing of first-line pharmacotherapy among older patients with Type 2 diabetes.

Design and methods We studied five population-based cohorts every 3 years, from 1994 to 2006. In each of those years, we identified all subjects aged 66 years or older newly diagnosed with diabetes and determined the initial glucose-lowering drug and the time between diagnosis and drug initiation. We calculated the proportion of patients prescribed each agent and estimated time from diagnosis to initiation using Kaplan–Meier survival analysis.

Results We identified a total of 64,368 eligible people who initiated drug therapy during the study period. From 1994 to 2006, first-line metformin use increased from 20.1 to 79.0%. Glyburide (glibenclamide) decreased from 71.1% of all first-line therapies in 1994 to 9.8% in 2006, while first-line use of insulin or combination therapy have changed little at approximately 5% each. No other medication exceeded 2% of first-line therapies. The median time from diagnosis to initiation of pharmacotherapy increased dramatically during the study period, from 1.8 years in 1994 to 4.6 years in 2006.

Conclusions Metformin has become the most commonly used initial medication for the treatment of diabetes. Although guidelines have evolved to recommend more aggressive initiation and intensification of pharmacotherapy, our results suggest that the time from diagnosis to initiation has increased substantially.


Introduction

Diabetes is a chronic, progressive condition affecting over 300 million people worldwide and is a leading cause of blindness, end-stage renal disease and cardiovascular disease [1–4]. In 1998, the UK Prospective Diabetes Study (UKPDS) demonstrated that elevated glucose levels are a major determinant of long-term diabetes-related complications [5]. The UKPDS also found that reducing blood glucose using pharmacotherapy decreased the risk of microvascular complications and that intensive treatment with metformin demonstrated the greatest reduction in diabetes-related endpoints and all-cause mortality [6–9].

In light of the UKPDS findings, clinical practice guidelines worldwide were updated to urge prompt initiation of oral anti-hyperglycaemic agent therapy [10–14]. Evidence-based guidelines also ceased to recommend use of glyburide (glibenclamide), a sulphonylurea, for older patients with Type 2 diabetes, instead recommending first-line use of metformin for its lower risk of hypoglycaemia and reduction in morbidity and mortality [1–4,6,10,11,13,15].

Since 1998, new evidence has prompted significant changes in recommendations for diabetes pharmacotherapy and numerous new oral anti-hyperglycaemic agents have been introduced. However, little is known about how these
changes have affected the selection and timing of anti-hyperglycaemic pharmacotherapy. We therefore conducted a population-based study to examine how the selection and timing of first-line pharmacotherapy among older patients with Type 2 diabetes has changed over time in Ontario, Canada.

Subjects and methods

We conducted a series of population-based cohort studies using administrative databases to examine trends in first-line pharmacotherapy selection and timing among older patients with Type 2 diabetes in Ontario, Canada. We used the validated Ontario Diabetes Database to identify newly diagnosed diabetes patients and to determine the date of diagnosis. The Ontario Diabetes Database includes individuals with two or more diabetes-related physician service claims within 2 years or one diabetes-related hospitalization. Depending on the basis for entry to the Ontario Diabetes Database, the date of diagnosis was taken as the date of the first of two or more physician service claims, the date of hospitalization or the date of a diabetes-related physician service claim less than 2 years prior to hospitalization. Validation of the Ontario Diabetes Database against physician charts demonstrated sensitivity of 86% and specificity of 97% [5,16]. We used the Ontario Drug Benefit database to find diabetes-related drug claims and the Registered Persons Database to obtain demographic information and vital statistics for each patient [6–9,16].

Every 3 years between 1994 and 2006, we created an annual cohort of patients newly diagnosed with Type 2 diabetes in the calendar year using the Ontario Diabetes Database [10–14,16]. We excluded patients < 66 years of age to avoid incomplete medical records, and those who received an anti-hyperglycaemic agent in the year prior to diabetes diagnosis to remove patients with inaccurate dates of diagnosis. Patients were followed forward until the first of initiation of first-line glucose-lowering therapy, death or the end of follow-up (31 December 2011). These databases are linked anonymously using encrypted health card numbers and are used routinely to study drug safety and utilization [17–19].

For each patient, we identified the initial diabetes therapy and determined the time elapsed from diagnosis to initiation of therapy. In each annual cohort, we calculated the distribution of initial treatment selection and used the Kaplan–Meier method to analyse the time from diagnosis to therapy initiation. We used the log-rank test to determine if there were significant differences in time to therapy initiation among the five cohorts. All analyses were conducted using SAS version 9.2 (SAS Institute, Cary, NC, USA). This study was approved by the research ethics board at Sunnybrook Health Sciences Centre and performed at the Institute for Clinical Evaluative Sciences, both in Ontario, Canada.

Results

We identified a total of 64 368 people who were newly diagnosed and were eligible for one of our five annual cohorts (1994, 1997, 2000, 2003 and 2006). Among those diagnosed in 1994, 71.1% of all new users of drug therapy were treated with glyburide as their first-line agent, falling to 9.8% in the 2006 cohort. Conversely, use of metformin as a first-line agent steadily increased from 20.1 to 79.0% over the same period. First-line use of insulin dropped slightly from 5.4 to 3.2%, while initiation with more than one anti-hyperglycaemic agent increased from 3.1 to 4.7%. Treatment initiation with other oral anti-hyperglycaemic agents as first-line agents was rare over the study period, with no other drug exceeding 2% of first-line therapy (Table 1). Time from diagnosis to initiation of therapy increased significantly from each cohort to the next, from a median of 1.8 years in the 1994 cohort to a median of 4.6 years in the 2006 cohort ($P < 0.0001$, Fig. 1).

Discussion

Our findings indicate that, over the past two decades, metformin has become the dominant first-line agent for Type 2 diabetes and that the time from diagnosis to treatment initiation has increased significantly. The dramatic increase in first-line metformin use was paralleled by similar drops in glyburide initiation, which accounted for only one in 10 new therapies by 2006. These observed trends likely reflect the recommendations for preferential metformin use in clinical practice guidelines [12,20,21]. Despite the introduction of new oral anti-hyperglycaemic agents over time, metformin and glyburide continued to represent the vast majority of first-line agents for individuals diagnosed with diabetes in 2006. Although accounting for only a small
proportion of first-line agents, use of pioglitazone or rosiglitazone increased 16-fold over the study period. Pioglitazone and rosiglitazone carry a relatively low risk of hypoglycaemia, may be used when metformin is contraindicated and were included in the Ontario Public Drug Program’s general benefit formulary from October 2006 to June 2009 (pioglitazone) and January 2007 to June 2009 (rosiglitazone). In light of growing concerns of cardiovascular safety and their 2009 exclusion from the Ontario Public Drug Program’s general benefit formulary, it is likely that this upward trend has begun to reverse [22–25]. Similarly, a 15-fold increase was noted in gliclazide use over the study period. As gliclazide was classified as general benefit under the Ontario Drug Benefit in 2007, it is not surprising that its first-line use became more common among later cohorts [26] (Table 1).

The increasing time from diagnosis to first-line therapy during this period contradicts the predicted trend toward swifter oral anti-hyperglycaemic agent initiation (Fig. 1). Earlier diagnoses and decreased disease severity at diagnosis may contribute to this delay by precluding the perceived necessity of prompt pharmacotherapy. Yet in light of the progressive nature of Type 2 diabetes, the large observed time lag in treatment initiation suggests clinical inertia is a factor [9,27]. Notably, a 2005 survey of diabetes management in Ontario primary care facilities found that the predominant plan for patients not at blood glucose target was lifestyle management, with physicians citing patient non-compliance to diet and exercise as the primary barrier to glycaemic control [27].

Several limitations of our study merit emphasis. First, while the Ontario Diabetes Database is a validated registry, the accuracy of the timing of diabetes diagnosis is uncertain. We expect that entry of individuals with two diabetes physician service claims within 2 years or one diabetes-caused hospitalization represents the latest possible date of clinical recognition of diabetes. Second, changes in diagnostic criteria may have influenced the number and character of patients diagnosed with diabetes. The 1998 Canadian Diabetes Association clinical practice guidelines suggested that a fasting plasma glucose level of 7.0 mmol/l or higher suffice for a diagnosis of diabetes, rather than the more stringent 1992 Canadian Diabetes Association criterion of fasting plasma glucose \( \geq 7.8 \) mmol/l [10,15]. The expected result of this change is diagnosis of diabetes in hyperglycaemic individuals who previously would not have met the fasting plasma glucose criteria. Indeed, the incidence of diabetes in the Ontario Diabetes Database stayed constant from 1992 to 1997 and increased from 6.6 per thousand in 1997 to 8.2 per thousand in 2003 [16,28]. Although we expect that, after 1998, some older individuals were diagnosed with Type 2 diabetes at a lesser degree of hyperglycaemia than those diagnosed prior to 1998, the changes in diagnostic criteria were accompanied by a push for early and aggressive treatment [10]. Therefore, the

<table>
<thead>
<tr>
<th>Year of diagnosis</th>
<th>Total no. of people starting first-line therapy</th>
<th>Metformin</th>
<th>Glyburide/repaglinide</th>
<th>Gliclazide</th>
<th>Rosiglitazone/pioglitazone</th>
<th>Acarbose</th>
<th>Combination of drugs</th>
<th>Insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>1994</td>
<td>12,164</td>
<td>8,646</td>
<td>15,741</td>
<td>6,822</td>
<td>6,654</td>
<td>0</td>
<td>6</td>
<td>50</td>
</tr>
<tr>
<td>1997</td>
<td>12,087</td>
<td>4,651</td>
<td>14,087</td>
<td>5,124</td>
<td>4,969</td>
<td>0</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>2000</td>
<td>12,588</td>
<td>6,951</td>
<td>15,108</td>
<td>7,682</td>
<td>6,949</td>
<td>0</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>2003</td>
<td>12,656</td>
<td>9,092</td>
<td>15,102</td>
<td>7,682</td>
<td>6,949</td>
<td>0</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>2006</td>
<td>14,873</td>
<td>11,749</td>
<td>14,873</td>
<td>7,682</td>
<td>6,949</td>
<td>0</td>
<td>5</td>
<td>6</td>
</tr>
</tbody>
</table>

Small cell sizes are suppressed in accordance with privacy legislation.
continuing increase in time to pharmacotherapy remains surprising. Third, we examined older patients with diabetes and it is uncertain whether our findings are applicable to younger patients. Fourth, drugs not covered on the Ontario Drug Benefit formulary (e.g. incretins) as well as drugs paid for ‘out of pocket’ or by private insurance providers were not captured and therefore we are unable to describe these prescribing patterns. Finally, in the absence of blood glucose measures or other laboratory data, we cannot comment on whether patients reached recommended blood glucose targets or whether treatment was entirely consistent with established guidelines for diabetes management [29].

From 1994 to 2006, evidence-based guidelines have changed to urge rapid initiation of metformin in patients with newly diagnosed Type 2 diabetes. While metformin replaced glyburide as the most common first-line anti-hyperglycaemic agent, time from diagnosis to treatment initiation increased significantly. As prior studies have found inadequate glycaemic control in a majority of elderly patients with Type 2 diabetes, further investigation of the observed deviation from recommended pharmacotherapy aggressiveness may improve glycaemic control in these individuals [27,30–33].

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**Competing interests**

MMM has served as an advisory board member for AstraZeneca, Bristol-Myers Squibb, Eli Lilly and Company, GlaxoSmithKline, Hoffman La Roche, Novartis, Novo Nordisk and Pfizer. PDF, DNJ, BRS, JMP and TG have nothing to declare.

**References**


