The management of people with type 2 diabetes with hypoglycaemic agents in primary care: retrospective cohort study

Melanie J Calvert, Richard J McManus and Nick Freemantle


Background. Type 2 diabetes is common, largely managed in primary care and requires effective glycaemic control to reduce the risk of microvascular complications. Oral hypoglycaemic agents are typically the first pharmacological intervention used to improve glycaemic control.

Objectives. To evaluate the management of people with type 2 diabetes with oral hypoglycaemic agents in primary care.

Methods. This retrospective cohort study included people with type 2 diabetes treated with oral agents drawn from 243 general practices in the UK over a 5-year study period from 1999 to 2003. Primary outcome measures were glycaemic monitoring and control on oral hypoglycaemic agents.

Results. Of the 71 561 patients identified with prevalent type 2 diabetes, 20 922 received their first prescription for an oral hypoglycaemic agent during the study. Only 49% of patients had a recorded \( \text{HbA1c} \) within 6 months of starting therapy. Forty per cent of patients had poor glycaemic control (\( \text{HbA1c} > 7.5\% \)) after starting a single hypoglycaemic agent. There was a statistically significant association between post-therapy \( \text{HbA1c} \) with pre-therapy \( \text{HbA1c} \), metformin dose, age and geodemographical classification. Greater reductions in \( \text{HbA1c} \) were observed in older patients, those with a high pre-treatment \( \text{HbA1c} \) and those from less-deprived areas. Patients remained on a single therapy for a median of 3.8 years. During the study, 7009 of those who started a single agent were prescribed a second agent. Of those with a recorded \( \text{HbA1c} \), 50% had poor glycaemic control (\( \text{HbA1c} > 7.5\% \)) post-therapy.

Conclusions. Management of type 2 diabetes with oral hypoglycaemic agents appears to be suboptimal for many patients. Oral treatment is often not started until glycaemic control is poor, and many patients do not receive adequate monitoring or have poor glycaemic control following treatment with oral agents. Many patients with a high pre-treatment \( \text{HbA1c} \) are not controlled on a single oral agent even at high dose suggesting that earlier, more aggressive treatment in primary care is required.

Keywords. Diabetes mellitus, hypoglycaemic agents, primary health care.

Introduction

Type 2 diabetes is an increasingly common disease leading to micro- and macrovascular complications at significant cost to the National Health Service.\(^1\)\(^-\)^\(^4\) Tight glycaemic control reduces microvascular complications and is cost effective but often not achieved.\(^5\)^\(^-\)^\(^6\) Most people with type 2 diabetes in the UK are managed entirely within primary care.\(^7\) Treatment to control blood sugar typically comprises dietary advice with the addition of oral hypoglycaemic agents and/or insulin depending on subsequent glycaemic control measured by glycosylated haemoglobin levels (\( \text{HbA1c} \)).\(^8\) The most commonly prescribed oral hypoglycaemic treatments are sulphonylureas and metformin, which may be used alone or in combination. In addition, newer ‘third line’ oral medications such as meglitinides and glitazones may be used.\(^8\)
As with hypertension and other clinical specialities there is evidence of clinical inertia in the management of diabetes.9 Previous work from UK primary care has shown that glycaemic control is suboptimal for almost 40% of those with type 2 diabetes treated with medication.10 A recent study using primary care data has shown that many people receiving dual therapy with both a sulphonylurea and metformin remain poorly controlled and do not subsequently receive more intensive treatment.11 In North America, treatment with glucose-lowering agents appears to be delayed until HbA1c levels are considerably above recommended targets in both primary and secondary care.12,13

This study sought to evaluate the management of type 2 diabetes based on retrospective analyses of UK primary care data from 1999 to 2003. Glycaemic monitoring and control were assessed in patients starting hypoglycaemic medication during the study period. Predictors of response to first therapy were assessed, and progression to and glycaemic control on second agents were evaluated.

Methods

Population
Data were obtained from 243 general practices throughout England, Scotland and Wales providing continuous data to the DIN-LINK database over a 5-year period from 1999 to 2003. This database contains anonymized computer records from all patients registered with contributing practices which are similar to UK patients in terms of age and sex distribution.14 Contributing practices are asked to record all patient contacts onto their electronic clinical system and diagnoses, investigations and prescriptions are coded using Read Codes.15

Patients were identified with diabetes if they had a Read Code for diabetes or one or more prescriptions for oral antidiabetic agents, insulin or glucose testing kits.16,17 Patients were classified as having type 2 diabetes if they did not have a Read Code for gestational or type 1 diabetes or if they were prescribed an oral antidiabetic agent. Type 2 patients were classified as diet only if they had no prescription for an oral antidiabetic agent within the 5-year time frame.

Procedure and analyses
Analyses were performed using SAS V8.2 (SAS Institute, Cary, NC). The prevalence of type 2 diabetes was estimated based on people registered with type 2 diabetes on December 31, 2003. Time to first HbA1c assessment was estimated for all patients who started their oral agent during the 5-year time period from the date of their first recorded prescription for an oral hypoglycaemic agent until their first recorded HbA1c after the prescription. Patients who started a second agent were censored on the date of prescription and patients with no recorded HbA1c were censored at the time of deregistration (if before the end of the study) or at the end of study.

Time to initiation of a second type of hypoglycaemic agent was estimated for all patients who started an oral agent during the 5-year time period from the date of their first prescription of a single agent until the date of prescription of a second agent. Patients who remained on a single agent were censored at the time of deregistration (if before the end of the study) or at the end of study.

The UK National Institute for Clinical Excellence guidance on the management of blood glucose for patients with type 2 diabetes, published in 2002, recommends that ‘For each individual, a target HbA1c (DCCT aligned) should be set between 6.5% and 7.5%, based on the risk of macrovascular and microvascular complications.’ Adequate glycaemic control was therefore defined in this study as an HbA1c < 7.5%. Glycaemic control after initiation of first or second therapy was evaluated based on all available HbA1c results at 6-month intervals. Two separate models were used to assess the relationship between HbA1c results in 3–6 months after starting metformin or sulphonylurea as first therapy, to pre-treatment HbA1c, drug dose, ACORN geodemographic classification18 (A Classification of Residential Neighbourhoods by postcodes, using census and lifestyle survey data) in 2001, age at first therapy, body mass index (BMI), gender, beta-blocker and diuretic use. These were evaluated using mixed models with an identity link, normal error and practice as a random effect (to account for any practice-related differences). A forward stepwise regression approach was used, with those variables identified as statistically significant in univariate analyses (P < 0.05) being entered into the final model until the addition of an extra variable was no longer significant.19 To evaluate whether any of the variables had a non-linear relationship with outcome, we assessed transformations of each variable using the natural logarithm and cubic spline.20 The Akaike Information Criteria (AIC) was used to determine the most appropriate transformation.21 The effect of metformin daily dose was assessed in the following categories: <=500 mg, >500 mg <=1 g, >1 g <=1.5 g or >1.5 g <=3 g. Since sulphonylurea doses vary across the class, we assessed whether patients were receiving half of the recommended maximal dose as reported in the British National Formulary.17

Results
During the 5-year study period, 71 561 people with type 2 diabetes were identified, of these 54 731 remained registered on December 31, 2003 from a total population of 1.95 million, giving an overall
prevalence of 2.8%. During the study, 50,406 (70.4%) received a prescription for an oral hypoglycaemic agent. For 20,922 patients, their first prescription of an oral agent (as opposed to diet alone) occurred during the study period, with 11,904 (57%) patients receiving metformin and 8839 (42%) a sulphonylurea. Patient demographics are shown with those prescribed metformin on average younger and with a higher BMI than those prescribed sulphonylureas (Table 1). Metformin use as a first therapy has steadily increased over time, with 37% of patients receiving this as a first therapy in 1999 compared to 75% in 2003. A corresponding decrease in the use of sulphonylureas as initial therapy was observed, from 61% in 1999 to 25% in 2003. Very few patients (~1%) were prescribed other oral agents (meglitinides, glitazones or other therapies) as a first therapy.

**HbA1c assessment and control on first therapy**
The median time to first HbA1c following initiation of an oral agent was 0.51 years [95% confidence interval (CI) 0.50–0.53]. Time to event analysis revealed that 10,252 (49%) patients had a recorded HbA1c within 6 months of starting therapy and 13,390 (64%) within the first year of therapy. In total, 5378 of 20,922 (26%) patients had a computer-recorded HbA1c both in the 6 months before (mean 9.15%, SD 1.9%) and after (mean 7.57%, SD 1.3%) starting their first therapy. For patients prescribed metformin with available HbA1c assessments (n = 3296), their mean HbA1c prior to therapy was 9.1% (SD 1.8%) which fell to 7.7% (SD 1.3%) in the 6 months following the initiation of therapy. The mean HbA1c prior to therapy for patients prescribed a sulphonylurea was slightly higher (mean 9.3%, SD 2.0%) which fell to 7.4% (SD 1.3%) post-therapy. Evaluation of all available HbA1c results for patients at 6-monthly intervals showed that approximately 40% of patients on a single agent with available HbA1c results were uncontrolled throughout the 5-year study period.

Patients initiating metformin in 2003 (n = 891) had slightly but significantly lower pre-treatment HbA1c (mean 8.9%, SD 1.8%) than those initiating metformin earlier in the study (9.1%, SD 1.7%) (P = 0.004). Post-therapy mean HbA1c was also lower in those initiating therapy in 2003 (mean 7.6%, SD 1.2%) compared to those prior to 2003 (mean 7.7%, SD 1.3%) (P = 0.058). A non-significant decrease in pre-treatment HbA1c was also observed in patients prescribed sulphonylureas with available results in 2003 (n = 273) (mean 2003 9.2%, SD 2.0% compared to a mean prior to 2003 of 9.3%, SD 2.0%; P = 0.23). Similar results were observed post-treatment (mean 7.39% both during and prior to 2003).

**Prediction of response to first therapy in people with type 2 diabetes receiving metformin or sulphonylureas**
Analyses of the relationship between post-therapy HbA1c (assessed 3–6 months after initiation) and Table 1 Patient demographics of those initiating first therapy during the study and those included in final regression models to predict post-treatment HbA1c, following initiation of metformin or sulphonylureas

<table>
<thead>
<tr>
<th>All patients initiating first therapy (n = 20,922)</th>
<th>Patients initiating metformin (n = 1762)</th>
<th>Patients initiating sulphonylureas (n = 1207)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>62.2 (14.8)</td>
<td>62.0 (11.4)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>9864 (47.15)</td>
<td>785 (44.55)</td>
</tr>
<tr>
<td>ACORN geodemographic classification, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wealthy achievers</td>
<td>3714 (17.75)</td>
<td>333 (18.90)</td>
</tr>
<tr>
<td>Urban prosperity</td>
<td>747 (3.57)</td>
<td>50 (2.84)</td>
</tr>
<tr>
<td>Comfortably off</td>
<td>4611 (22.04)</td>
<td>415 (23.55)</td>
</tr>
<tr>
<td>Moderate means</td>
<td>1905 (9.11)</td>
<td>222 (12.60)</td>
</tr>
<tr>
<td>Hard pressed</td>
<td>3523 (16.84)</td>
<td>353 (20.03)</td>
</tr>
<tr>
<td>Unclassified</td>
<td>6422 (30.69)</td>
<td>589 (22.08)</td>
</tr>
<tr>
<td>BMI, mean (SD)a</td>
<td>31.0 (7.2)</td>
<td>32.86 (6.5)</td>
</tr>
<tr>
<td>Systolic blood pressure, mean (SD)b</td>
<td>144.4 mm Hg (19.7)</td>
<td>144.8 (17.9)</td>
</tr>
<tr>
<td>Diastolic blood pressure, mean (SD)b</td>
<td>82.5 mm Hg (10.7)</td>
<td>83.3 (10.3)</td>
</tr>
<tr>
<td>Blood pressure &gt;140/80 mm Hg(^{\text{c}})</td>
<td>5712 (51.34)</td>
<td>739 (54.2)</td>
</tr>
<tr>
<td>Beta-blocker or diuretic use, n (%)</td>
<td>8878 (42.43)</td>
<td>805 (45.7)</td>
</tr>
<tr>
<td>First therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metformin, n (%)</td>
<td>11904 (56.90)</td>
<td>1762 (100.0)</td>
</tr>
<tr>
<td>Sulphonylurea, n (%)</td>
<td>8839 (42.25)</td>
<td>N/A</td>
</tr>
<tr>
<td>Other</td>
<td>179 (0.86)</td>
<td>N/A</td>
</tr>
</tbody>
</table>

\(^{a}\)All patients n = 15566, metformin patients n = 1583, sulphonylurea patients n = 1007.

\(^{b}\)All patients n = 11126, metformin patients n = 1364, sulphonylurea patients n = 829.

\(^{c}\)Number and per cent of those with raised blood pressure of those with recorded systolic and diastolic blood pressure in the 6 months before starting their first therapy.
predicators of response to metformin \((n = 1762)\) revealed a statistically significant association between post-therapy HbA\(_1c\) with pre-therapy HbA\(_1c\) metformin dose, geodemographic classification, age, BMI and beta-blocker/diuretic use. The natural logarithm of age led to improved model fit as judged by the AIC. A forward stepwise approach was used to generate a final model, in which pre-therapy HbA\(_1c\), geodemographic classification, log age and metformin dose were significantly associated with post-therapy HbA\(_1c\) (Table 2). BMI and beta-blocker/diuretic use were no longer significant in the final model but were correlated with age (beta-blocker/diuretic use was correlated with age, while BMI was inversely correlated with age). On average, greater reductions in HbA\(_1c\) were observed in older patients, those with a high pre-treatment HbA\(_1c\), and those not classified as hard-pressed or moderate means. Assessment of interaction terms revealed a significant association between pre-treatment HbA\(_1c\) and metformin dose, with those patients with a higher pre-treatment HbA\(_1c\) prescribed higher doses (mean pre-treatment HbA\(_1c\) for those patients prescribed: \(\leq 500 \text{mg} \ 8.4\%\); \(>500 \text{mg} \leq 1 \ g \ 8.8\%\); \(1 \ g \leq 1.5 \ g \ 9.4\%\); \(1.5 \ g \leq 3 \ g \ 9.5\%\)).

Analysis of the relationship between post-therapy HbA\(_1c\) and sulphonylureas \((n = 1207)\) showed a significant association with pre-treatment HbA\(_1c\), gender and dose, however, no association was observed with the remaining variables (Table 3). On average, female patients had a slightly higher HbA\(_1c\) following therapy. Univariate analyses clearly show that the decrease in HbA\(_1c\) is strongly associated with pre-treatment HbA\(_1c\), with those patients with the highest pre-treatment HbA\(_1c\) experiencing the greatest reductions. The final model is more complex with sulphonylurea dose and the interaction between pre-treatment HbA\(_1c\) affecting outcome. Those patients with a high pre-treatment HbA\(_1c\) were more likely to be prescribed the half maximal recommended dose of sulphonylurea. Post hoc analysis of the effect of sulphonylurea category on post-therapy HbA\(_1c\) showed no significant differences between therapies compared to the most commonly prescribed sulphonylurea: glicazide.

**Patient progression to and control on a second type of hypoglycaemic agent**

In total, 7009/20 922 (34\%) patients were prescribed a second oral agent during the study; of these, 3022 (43\%) received metformin, 2964 (42\%) a sulphonylurea, 127 (2\%) a meglitinide, 820 (12\%) a glitazone and 76 (1\%) other diabetes drugs or combination therapies. The median time from prescription of a first agent to prescription of a second agent was 3.86 years (95\% CI 3.82–3.90). Only 2634 (38\%) had HbA\(_1c\) assessments in both the 6 months before (mean 8.99\%, SD 1.7\%) and in the 6 months following therapy (mean 7.74\%, SD 1.35). Of these patients, 1372 (52\%) were uncontrolled post-therapy. Assessment of all available HbA\(_1c\) results at 6-month intervals for those patients remaining on a second agent revealed approximately 50\% had poor glycaemic control (HbA\(_1c\) \(\geq 7.5\%\)).

**Discussion**

Management of type 2 diabetes with oral hypoglycaemic agents appears to be suboptimal for many patients in UK Primary Care. For patients starting an oral agent during the study, both glycaemic monitoring and control were poor. Fewer than half of the patients had a computer-recorded HbA\(_1c\) within 6 months of starting therapy, and many patients had no recorded HbA\(_1c\) at 1 year. For those patients with available HbA\(_1c\) assessments, around 40\% remained uncontrolled on a single agent. Evaluation of predictors of response to first therapy indicates that some patients with high pre-treatment HbA\(_1c\) are unlikely to be controlled by a single therapy even at high dose. Despite this, many patients remained on a single agent for long periods of time (median almost 4 years). Of those
patients who did receive a second agent 50% remained poorly controlled following therapy.

Our results clearly show that those patients with a high pre-treatment HbA1c are more likely to receive higher doses of metformin or sulphonylureas and have the greatest decreases in HbA1c in response to therapy. Our results also suggest older patients and those from less-deprived areas have decreased HbA1c compared to younger patients and those from deprived areas when prescribed metformin. While male patients appear to have decreased HbA1c compared to females prescribed sulphonylureas. These differences may reflect a difference in case mix of patients prescribed metformin versus sulphonylureas, their standard of care, patients’ lifestyles or compliance to therapy.22

The finding that those receiving metformin as their first oral hypoglycaemic agent were younger with a higher BMI than those receiving sulphonylureas is consistent with other findings from the UK.23 It suggests preferential prescription of metformin to those with higher BMI while the younger age may reflect earlier failure of diet alone in the obese.

Population-based studies such as this depend on the quality of data used, careful diagnostic categorization and the ability to generalize from the results. The data suggest that many patients received suboptimal monitoring, however, this might reflect poor data recording, the use of self-monitoring or assessments taking place in secondary care.24 The anonymized nature of the data means that it is not possible to cross check with paper records but some evidence suggests that electronic records may be more complete than manual records.25 Some people may have been misclassified as having diabetes on the basis of prescribing data (for instance, those receiving metformin for polycystic ovary syndrome) but this is unlikely to have made much impact on the results, as judged by the similarity of the observed prevalence (2.8%) with data from another large-scale cross-sectional study of people with type 2 diabetes and also with the recently published prevalence figures from the Quality and Outcomes Framework.26

This study included all practices which contributed full data throughout the study period rather than applying data quality criteria.27 The large population increases generalizability but may mean that actual performance has been underestimated if included practices have not electronically recorded all results. However, the inclusive methodology used mirrors the data collection for the new General Medical Services (GMS) contract and electronic coding by practices for diabetes has been shown to be better than in other conditions.28

A further potential limitation of this study is that patients were evaluated only until the end of 2003. Practice may have changed in response to incorporation of National Institute of Clinical Excellence guidelines issued in 2002, which recommend HbA1c assessments for people with type 2 diabetes at 2- to 6-monthly intervals and a target HbA1c between 6.5% and 7.5%, and the new GMS contract, although the results presented are consistent with those from the first year of the new contract.26 29 It is encouraging that patients in 2003 were being prescribed oral agents at lower HbA1c levels than those earlier in the study, although this may reflect differences in reporting. In the past, GPs may have been more likely to request or report HbA1c where control was perceived to be poor.

Comparable work from the US suggests that the problems identified here are not confined to the UK: Brown and Nichols12 evaluated patients receiving second-line therapy with metformin for people already receiving a sulphonylurea and found that mean HbA1c prior to metformin was 9.4% and had been over 8% for many months. Shah et al.13 found that fewer than half of patients with diabetes over 65 with high HbA1c levels had intensification of treatment. Similarly in Europe, a Danish study including people with both type 1 and type 2 diabetes found the majority to be poorly controlled and French work suggests that less than 40% of people with type 2 diabetes have HbA1c monitored.29 30 These poor results from daily practice are despite the clear advantages to patients from good glycaemic control in terms of reduction in complications.5

The reasons for the observed suboptimal diabetes control are not clear from our data. Other work has suggested that clinical inertia is an important factor and that people with chronic disease are often reviewed without inadequate control being acted upon.9 This may at least partly explain our data, in which case, more aggressive treatment with the earlier addition of insulin treatment may improve the situation. However, insulin alone is unlikely to be adequate: the UK Prospective Diabetes Study comparing initial treatment of type 2 diabetes with insulin or oral hypoglycaemics found that after 9 years of treatment, while more patients remained controlled on insulin monotherapy than oral agents, the majority of participants required multiple therapies whatever the initial agent.31 Moreover, studies of adherence to medication suggest that average non-adherence rates in diabetes are approximately 25%.32 Improving control may therefore require interventions at both physician and patient level.

In conclusion, patients with type 2 diabetes receive suboptimal monitoring and management of blood glucose levels. In order to achieve improved glycaemic control and meet national targets, such patients should receive more active monitoring of the progress of their diabetes and where appropriate progress more rapidly through the available treatment options.6 Further research is required to assess the impact of clinical guidelines, incentives on HbA1c monitoring and glycaemic control and to evaluate patient progression to and control on additional therapies such as insulin.
Declaration

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Conflicts of interest: NF has received funding for research from Pfizer and devices for the treatment of diabetes. MJC and RJM have received funding for research from Pfizer and sanofi-aventis.

References