Clinical Inertia in People With Type 2 Diabetes

A retrospective cohort study of more than 80,000 people

KAMLESH KHUNTI, MD1
MICHAEL L. WOLDEN, MSC2
BRIAN LARSEN THORSTED, MSC2

MARC ANDERSEN, PHD3
MELANIE J. DAVIES, MD4

OBJECTIVE—To determine time to treatment intensification in people with type 2 diabetes treated with one, two, or three oral antidiabetes drugs (OADs) and associated levels of glycemic control.

RESEARCH DESIGN AND METHODS—This was a retrospective cohort study based on 81,573 people with type 2 diabetes in the U.K. Clinical Practice Research Datalink between January 2004 and December 2006, with follow-up until April 2011.

RESULTS—In people with HbA1c ≥7.0, ≥7.5, or ≥8.0% (≥53, ≥58, or ≥64 mmol/mol), median time from above HbA1c cutoff to intensification with an additional OAD was 2.9, 1.9, or 1.6 years, respectively, for those taking one OAD and >7.2, >7.2, and >6.9 years for those taking two OADs. Median time to intensification with insulin was >7.1, >6.1, or >6.0 years for those taking one, two, or three OADs. Mean HbA1c at intensification with an OAD or insulin for people taking one, two, or three OADs was 8.7, 9.1, and 9.7%. In patients taking one, two, or three OADs, median time from treatment initiation to intensification with an OAD or insulin exceeded the maximum follow-up time of 7.2 years. The probability of patients with poor glycemic control taking one, two, or three OADs, intensifying at end of follow-up with an OAD, was 21.1–43.6% and with insulin 5.1–12.0%.

CONCLUSIONS—There are delays in treatment intensification in people with type 2 diabetes despite suboptimal glycemic control. A substantial proportion of people remain in poor glycemic control for several years before intensification with OADs and insulin.

Type 2 diabetes is a progressive disease that often requires stepwise intensification of treatment to maintain good glycemic control (1). It is also well established that timely treatment of people with type 2 diabetes has a beneficial effect on outcomes, so tight glycemic control is advocated to reduce the risk of development or progression of micro- or macrovascular complications (2,3). The recent American Diabetes Association guidelines recommend starting metformin alongside lifestyle modifications at diagnosis, aiming for an HbA1c target of <7% (<53 mmol/mol) (4). The joint American Diabetes Association/European Association for the Study of Diabetes Position Statement also endorses HbA1c <7% (<53 mmol/mol) for most people with diabetes but recommends individualized targets (5). Finally, the guidelines from the National Institute for Health and Care Excellence (NICE) in the U.K., most recently updated in 2009, recommend lifestyle measures as the first step in the clinical treatment algorithm. If HbA1c is then ≥6.5% (≥48 mmol/mol), metformin is recommended as the first-line oral antidiabetes drug (OAD) prescribed (6,7). Additional OADs may be added if glycemic control continues to remain above the recommended target of 6.5% (48 mmol/mol), and if HbA1c is ≥7.5% (≥58 mmol/mol) while the patient is already receiving at least two OADs, further intensification of treatment, including the use of insulin, is recommended (6,7).

Despite good-quality evidence of tight glycemic control, particularly early in the disease trajectory (3), people with type 2 diabetes often do not reach recommended glycemic targets. Baseline characteristics in observational studies indicate that both insulin-experienced and insulin-naïve people may have mean HbA1c above the recommended target levels, reflecting the existence of patients with poor glycemic control in routine clinical care (8–10). In a prospective, population-based study using retrospective observational data, it was reported that at insulin initiation people had experienced a high glycemic burden for 5 years with HbA1c >8% (>64 mmol/mol) and for 10 years with HbA1c >7% (>53 mmol/mol) (11). U.K. data, based on an analysis reflecting previous NICE guidelines, show that it takes a mean of 7.7 years to initiate insulin after the start of the last OAD (in people taking two or more OADs) and that mean HbA1c is ~10% (86 mmol/mol) at the time of insulin initiation (12). This is also reflected in poor HbA1c levels even after intensification of treatment. This failure to intensify treatment in a timely manner has been termed clinical inertia; however, data are lacking on clinical inertia in the diabetes-management pathway in a real-world primary care setting, and studies that have been carried out are, relatively speaking, small in scale (13,14). This retrospective cohort analysis investigates time to intensification of treatment in people with type 2 diabetes treated with OADs and the associated levels of glycemic control, and compares these findings with recommended treatment guidelines for diabetes.

RESEARCH DESIGN AND METHODS

Data source
We used the Clinical Practice Research Datalink (CPRD) database. This is the world’s largest computerized database,
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representing the primary care longitudinal records of >13 million patients from across the U.K. The CPRD is representative of the U.K. general population, with age and sex distributions comparable with those reported by the U.K. National Population Census (15). All information collected in the CPRD has been subjected to validation studies and been proven to contain consistent and high-quality data (16).

This retrospective cohort analysis used the CPRD covering the period from January 2004 to December 2006, with follow-up to April 2011 (so that maximum follow-up time was 7.3 years). The analysis was approved by the Independent Scientific Advisory Committee (see Authors’ Note). The CPRD is a computerized database containing approximately 5 million anonymized, longitudinal, primary care medical records from people in the U.K. It is linked with other health care data, making it the largest in the world. These contemporary data can aid interpretation of the impact of new guidelines.

People included in this analysis were diagnosed with type 2 diabetes according to Read/Oxford Medical Information System codes using algorithms based on age at diagnosis, type of treatment, and age at treatment. The algorithms also distinguished between people with types 1 and 2 diabetes (17). People with type 2 diabetes had a diagnosis of diabetes and were treated with diet only or with an OAD. People with a diagnosis of type 1 diabetes were omitted from the analysis, as were people treated with insulin only. As all people by definition were prescribed at least one OAD and did not receive insulin, people with a missing diagnosis code were classified as having type 2 diabetes; however, it is acknowledged that a small number of these patients potentially may not have had diabetes (e.g., people with prediabetes and women with polycystic ovary syndrome receiving metformin). People <18 years of age or of unknown sex were excluded.

Prescriptions were used to identify episodes of drug treatment. If there were <120 days between the (estimated) end of one prescription and the start of the next prescription, the prescriptions were considered to make up one episode of drug treatment. The end of one prescription was estimated from the number of days and amount prescribed or, if that information was not available, as the median duration of prescription of the drug.

OAD regimens were defined as the time period in which the same OAD prescriptions were used without use of insulin, classified by the number of different OAD active ingredients (to account for combination products). The end of an OAD regimen was categorized as treatment intensification, end due to change not representing intensification in OAD prescriptions (i.e., being treated with fewer OADs), or end of follow-up or acceptable data. Treatment intensification was defined as either addition of further OAD prescription without change in current OAD prescription or initiation of insulin irrespective of changes in OAD regimen.

People who started an OAD regimen between 1 January 2004 and 31 December 2006 were included. All prescription data until April 2011 were included. So that all of the patients followed in this study actually had their first prescription on the given regimen within the analyzed time period, people had to be registered in the CPRD database ≥6 months prior to inclusion. People <18 years of age or of unknown sex were excluded.

People were stratified by the number of different OAD active ingredients, and the first use of a given number was identified. A subset of the OAD regimens was selected from the NICE guidelines (Supplementary Data). Only OAD regimens with at least 6 months of acceptable data before start were included. One patient could contribute in more than one OAD category.

Recorded HbA1c measurements were used to define poor control during each OAD regimen. Time in poor control was defined as the time from the first HbA1c measurement above or equal to a given cutoff point (HbA1c ≥7.0% [≥53 mmol/mol], ≥7.5% [≥58 mmol/mol], and ≥8.0% [≥64 mmol/mol]) until 1) the first time a subsequent HbA1c measurement was below the cutoff point, 2) the end of the OAD regimen (intensification with another OAD or insulin), or 3) censoring due to end of follow-up. As only one period of poor control experienced by the patient is used for the analysis, the study does not account for patients oscillating above and below the given cutoff point. The annual frequency of HbA1c testing during follow-up among all patients on one, two, or three OADs, respectively, was assessed for the groups. Furthermore, the same assessment was done for the subgroup of patients in poor glycemic control (according to the three HbA1c cutoff points). The most recent measurement within 6 months before the start of an OAD regimen was used as the baseline value. If no baseline value was available, people were regarded as being in glycemic control if they had an HbA1c value <7% (<53 mmol/mol) at any point previously.

The primary endpoint was time to intensification from the time of being in poor control (defined as HbA1c ≥7.0% [≥53 mmol/mol], ≥7.5% [≥58 mmol/mol], and ≥8.0% [≥64 mmol/mol]) within each OAD regimen until return to below HbA1c target, end of current OAD regimen, or end of follow-up data. The secondary endpoint was time to intensification from the start of an OAD regimen (people treated with one, two, or three OADs).

Statistical methods
Baseline characteristics for subjects at initiation of treatment with either one, two, or three OADs were reported as the mean and SD. For baseline HbA1c, we reported the mean and number of people with a nonmissing value in a period of 6 months prior to initiation of treatment. For primary as well as for secondary endpoints, we used a competing risk approach to estimate the cumulative incidence function for each event type: this enabled us to differentiate between various ways of intensifying treatment regimens. This approach is preferable to the Kaplan-Meier estimation procedure, which estimates each event type separately and regards other events as censoring (18–20). Only results describing intensification of treatment were reported. As it was not possible to estimate the median time to event in all subcohorts, the results were represented in three different ways for the primary endpoint: 1) graphs with 1 minus cumulative incidence functions, 2) median time to event, and 3) probability of having intensified at end of follow-up. For the secondary endpoint, only graphs with 1 minus cumulative incidence function were presented. For the analysis of clinical inertia, we chose to report the time to event using three different HbA1c levels for glycemic control (≥7.0% [≥53 mmol/mol], ≥7.5% [≥58 mmol/mol], and ≥8.0% [≥64 mmol/mol]), reflecting the different cutoff points in different guidelines. All statistical analyses were performed using SAS, version 9.3 (SAS institute, Cary, NC).

RESULTS—In each of the three respective regimens, 50,476 people taking one
**Table 1—Baseline characteristics of people included in the analysis**

| Number of people (OAD regimens from January 2004 to December 2006) | Number of OADs in regimen* |
|---------------------------------------------------------------|----------------------------|
|                                                              | 1 | 2 | 3 | 4 |
| Female/male sex, %                                            | 49.5/50.5 | 44.7/55.3 | 42.6/57.4 |
| Duration of regimen (years), mean ± SD                       | 1.9 ± 2.0 | 1.9 ± 2.0 | 1.3 ± 1.6 |
| Time since diabetes diagnosis (years), mean ± SD             | 2.6 ± 4.1 | 3.8 ± 4.3 | 5.2 ± 5.1 |
| Age at diabetes diagnosis (years), mean ± SD                 | 62.6 ± 13.4 | 61.5 ± 12.8 | 59.0 ± 11.9 |
| Age (years), mean ± SD                                       | 62.6 ± 15.7 | 65.0 ± 12.9 | 63.8 ± 11.8 |
| Baseline HbA1c (%), mean (N)                                 | 8.4 (32,173) | 8.8 (20,818) | 9.0 (4,905) |
| Baseline HbA1c (mmol/mol), mean (N)                          | 68 (32,173) | 73 (20,818) | 75 (4,905) |

*For list of OADs included, see Supplementary Data.

OAD, 25,600 people taking two OADs, and 5,677 people taking three OADs were analyzed. Mean baseline HbA1c (the most recent measurement within 6 months before starting OADs) was 8.4% (68 mmol/mol), 8.8% (73 mmol/mol), and 9.0% (75 mmol/mol) in people taking one, two, or three OADs, respectively. Baseline characteristics are presented in Table 1.

For the subgroup of patients in poor glycemic control, the mean interval between HbA1c measurements was lower than for the entire population; the mean interval between testing ranged from 5.3 months for people with HbA1c ≥7% to ≥7.5% to 4.9 months for people with HbA1c ≥7.5% to 4.7 months for people with HbA1c ≥8%. The frequency of HbA1c testing did not differ substantially between people treated with one, two, or three OADs. The mean time between HbA1c measurements varied between 7.0-month intervals for patients on one OAD and 6.2-month intervals for patients treated with three OADs.

The median time to intensification from HbA1c cutoff ≥7.0% (≥53 mmol/mol), ≥7.5% (≥58 mmol/mol), or ≥8.0% (≥64 mmol/mol) is presented in Table 2. By end of follow-up, treatment of 17.5% of people with HbA1c ≥7.0% (≥53 mmol/mol) taking three OADs was intensified with insulin, treatment of 20.6% of people with HbA1c ≥7.5% (≥58 mmol/mol) taking three OADs was intensified with insulin, and treatment of 22.0% of people with HbA1c ≥8.0% (≥64 mmol/mol) taking three OADs was intensified with insulin. There were minimal differences in the proportion of patients intensified between the groups.

In people taking one OAD, the probability of an additional OAD or initiation of insulin was 23.9% after 1 year, increasing to 48.7% by end of follow-up; in people taking two OADs, the probability of an additional OAD or initiation of insulin was 11.4% after 1 year, increasing to 30.1% after 2 years; and in people taking three OADs, the probability of an additional OAD or initiation of insulin was 5.7% after 1 year, increasing to 12.0% by the end of follow-up (Fig. 2).

Mean ± SD HbA1c in patients taking one OAD was 8.7 ± 1.6% in those

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**Table 2—Probability at end of follow-up/median time (in years) of going from HbA1c above cutoff to intensification, reaching glycemic target, or end of follow-up data**

| Cutoff HbA1c (%) | Number of OADs* | Patients with treatment intensified with additional OAD | Patients with treatment intensified with insulin | Patients with treatment intensified with additional OAD or insulin |
|-----------------|-----------------|------------------------------------------------------|--------------------------------------------------|---------------------------------------------------------------|
| ≥7% (≥53 mmol/mol) | n = 35,988 | 65.0, 7.2*                                | 6.5, >7.2*                                       | 71.5, 2.2                                                   |
|                 | n = 21,838 | 31.5, >7.2*                                | 13.7, >7.2*                                      | 45.2, >7.2*                                                |
|                 | n = 5,050  | —                                              | 17.5, >7.1*                                      | 17.5, >7.1*                                                |
| ≥7.5% (≥58 mmol/mol) | n = 31,375 | 66.9, 1.9                                 | 7.6, >7.1*                                       | 74.5, 1.5                                                  |
|                 | n = 20,164 | 32.1, >7.2*                                | 17.1, >7.2*                                      | 49.2, >7.2*                                                |
|                 | n = 4,733  | —                                              | 20.6, >6.1*                                      | 20.6, >6.1*                                                |
| ≥8% (≥64 mmol/mol) | n = 25,096 | 67.0, 1.6                                 | 8.8, >6.9*                                       | 75.8, 1.1                                                  |
|                 | n = 16,991 | 30.1, >6.9*                                | 20.2, >6.9*                                      | 50.3, 6.3                                                  |
|                 | n = 4,112  | —                                              | 22.0, >6.0*                                      | 22.0, >6.0*                                                |

Data are probability (%), median (years) unless otherwise indicated. *The symbol > indicates that <50% of subjects have intensified treatment. Differences in this value are due to variation between subcohorts.
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CONCLUSIONS—This analysis shows that there is a delay in intensifying treatment in people with type 2 diabetes with suboptimal glycemic control, with patients remaining in poor glycemic control for >7 years before intensification of treatment with insulin. In patients taking one, two, or three OADs, median time from initiation of treatment to intensification with an additional OAD for any patient exceeded the maximum follow-up time of 7.2–7.3 years, dependent on sub-cohort. As <50% of the people treated with two or more OADs had treatment intensified after 7 years (i.e., they remained in poor glycemic control for >7 years before intensification of treatment), no exact median value was estimated. A longer follow-up time is warranted in future analysis to estimate the exact time that patients remain in poor glycemic control before intensified treatment. Despite having HbA1c levels for which diabetes guidelines recommend treatment intensification, few people appeared to undergo intensification (4,6,7). The highest proportion of people with clinical inertia was for insulin initiation in people taking three OADs. Consequently, these people experienced prolonged periods in poor glycemic control before intensification.
glycemic control, which is detrimental to long-term outcomes. A protracted period of poor control can have adverse effects; the follow-up data from the UK Prospective Diabetes Study (UKPDS) have demonstrated the beneficial legacy effect of good glycemic control early in the course of type 2 diabetes, potentially conferring protection against, or delaying, long-term diabetes complications (3).

A number of limitations should be considered with this analysis. 1) We had to estimate the duration of drug supply to define the end of one prescription and the start of another; however, allowing for a gap does partially overcome this drawback. 2) Data were subject to several possible confounders, including age, duration of diabetes, BMI, previous treatment for diabetes, comorbidities, and other medications. 3) In this study, only the addition of another OAD or insulin initiation was viewed as intensification. Increases of the dose of an OAD were not accounted for, as active dose titration is part of any current regimen (6). Furthermore, increases in dose are not identifiable in routine databases. 4) The treatment continuum started with OADs, as prescription of diet and exercise to patients was not included. 5) Interval-censored data are treated as continuous (HbA1c has been measured at different points and is a likely source of bias, given that high HbA1c leads to frequent measurements). Despite these limitations, the large patient population captured from the independent and validated CPRD database should be considered a representative sample and, as such, provides a good clinical picture of the state of diabetes control in routine practice. Data derivation from the CPRD also required a very complex analysis; our analyses are robust and the results internally consistent (i.e., with increasing cutoff points for HbA1c, the event probability changed as expected). Surveillance bias did not appear to be an issue in our analysis (i.e., the interval between HbA1c measurements was shorter in the subgroup of patients in poor control). Finally, the primary strength of our analysis is that it determines inertia for the entire type 2 diabetes treatment continuum from OADs to insulin.

Previous studies in U.K. general practice have shown similar findings. A retrospective study involving 14,824 people with type 2 diabetes from 154 general practice centers contributing to the Doctors Independent Network Database (DIN-LINK) between 1995 and 2005 observed that median time to insulin initiation for people prescribed multiple OADs was 7.7 years (95% CI 7.4–8.5 years); mean HbA1c before insulin was 9.85% (84 mmol/mol), which decreased by 1.34% (95% CI 1.24–1.44%) after therapy (12). A longitudinal observational study from health maintenance organization data in 3,891 patients with type 2 diabetes in the U.S. observed that, despite continued HbA1c levels >7% (>53 mmol/mol), people treated with sulfonylurea and metformin did not start insulin for almost 3 years (21). Another retrospective cohort study, using data from the Health Improvement Network database of 2,501 people with type 2 diabetes, estimated that only 25% of people started insulin within 1.8 years of multiple OAD failure, if followed for 5 years, and that 50% of people delayed starting insulin for almost 5 years after failure of glycemic control with multiple OADs (22). The U.K. cohort of a recent, 26-week observational study examining insulin initiation in clinical practice reported a large proportion of insulin-naive people with HbA1c >9% (>75 mmol/mol) at baseline (64%); the mean HbA1c in the global cohort was 8.9% (74 mmol/mol) (10). Consequently, our analysis supports previous findings concerning clinical inertia in both U.K. and U.S. general practice and reflects little improvement in recent years, despite updated treatment guidelines recommending tight glycemic control. There has been an increasing emphasis on the individualization of treatment regimens, but our results suggest that, if this is the case, the targets set for patients may be lacking in rigor.

Several factors may influence the need for intensification of treatment, including ineffective diet and exercise initiatives, limited pharmacologic armamentarium, conservative management, adverse events, poor compliance, underlying physiopathology, limited resources, and suboptimal healthcare systems (23). In particular, adherence to therapy and the complexity of multidrug regimens appear to play a role in delaying timely treatment intensification (24,25). In an inception cohort of 2,065 people with type 2 diabetes and elevated HbA1c, previous medication adherence predicted subsequent treatment intensification (24). Physician factors may also influence treatment intensification, with disparities between primary and specialist care (13,14). Inertia surrounding insulin initiation is a specific problem. Physicians may be reluctant to initiate insulin owing to a belief about patient risk, including risks in people with
comorbidities, excess weight gain, hypoglycemia, impaired quality of life, beliefs about patient competence, and resource issues (26–28). Patient factors, such as fear of hypoglycemia or weight gain, also contribute to clinical inertia when initiating insulin (26). The Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) and Action to Control Cardiovascular Risk in Diabetes (ACCORD) studies have raised the debate about whether extremely tight glucose control is beneficial in type 2 diabetes (29,30). The ADVANCE trial found that tight glucose control in type 2 diabetes resulted in no change in the incidence of retinopathy or macrovascular complications (29). The ACCORD trial reported that tight glucose control resulted in increased mortality in high-risk patients with type 2 diabetes (30). Conversely, a recent 10-year follow-up of the UKPDS confirmed the utility of long-term glycemic control in type 2 diabetes in preventing cardiovascular disease (3). The treatment guidelines are moving toward more individualized treatment, where certain patient characteristics justify less stringent efforts to lower HbA1c (5), and future studies should attempt to analyze whether the importance of clinical inertia differs between different patient types. Still, the issues of clinical inertia must be addressed in order to keep people from experiencing the glycemic burden of inadequate control from diagnosis or a “bad glycemic legacy” (23). The concept of a bad glycemic legacy stems from the long-term follow-up results of the large Diabetes Complications and Control Trial in patients with type 1 diabetes and the UKPDS in patients with type 2 diabetes (23,31), in which patients on an intensive regimen during the active study not only retained the significant reduction of risk of microvascular complications seen in the original studies, but also had a greatly reduced risk of myocardial infarction and all-cause mortality (3,32). Another study has indicated that if glycemic control is not established early in the disease pathology, there may be a long-term increase in the risk of diabetes-related complications (31). Importantly, the CPRD database used in our analysis contains a very large cross-section of general practices across the U.K. and thus should reflect current practice. However, it would be interesting to explore whether there would be any regional or sociodemographic differences in terms of clinical inertia, given the large dataset.

Various approaches have been proposed to help overcome clinical inertia, including use of guidelines and recommendations, motivation and support of patient self-management, and education for both physicians and people with diabetes (33). Specifically, patient education programs should target the concerns surrounding the intensification of therapy. Effective use of electronic medical records to assist physicians when making decisions about a patient’s care pathway has also been proposed. However, there is, as yet, little hard evidence to support this (34).

In conclusion, this analysis demonstrates that there is a delay in intensifying treatment in people with type 2 diabetes with suboptimal glycemic control: these people experienced prolonged periods of poor glycemic control. A greater effort must be made to motivate both people with diabetes and physicians to improve diabetes management, and that motivation needs to be translated into action by striving for the recommended treatment goals in a timely manner.

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K.K. reviewed data and wrote the manuscript. M.L.W., B.L.T., and M.A. analyzed data and wrote the manuscript. M.J.D. reviewed data and wrote the manuscript. K.K. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Authors’ Note—This article deviates from the accepted Independent Scientific Advisory Committee protocol in that the order of the primary and secondary endpoints have been switched. This change was made in response to the reviewers’ comments.

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