Clinical implications of prolonged hyperglycaemia before basal insulin initiation in type 2 diabetes patients: An electronic medical record database analysis

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Summary

Aims: To assess the effect of duration of hyperglycaemia before basal insulin (BI) initiation on clinical outcomes in type 2 diabetes (T2D).

Materials and methods: Patients with T2D who initiated BI during 2009-2013, had continuous enrolment for ≥2 years preceding and ≥1 year following BI initiation (“index date”), and had ≥1 glycated haemoglobin (A1C) measure not at target (ie, ≥7.0%) within 6 months preindex date were included in the study. Patients were stratified by preindex-date duration of A1C ≥7.0%. Longitudinal A1C, weight, BMI, and diabetes medication were compared between cohorts for up to 15-month follow-up.

Results: Of 37 053 patients who initiated BI, 40.7%, 15.3%, 16.0%, and 28.0%, respectively, had uncontrolled A1C for <6, 6-<12, 12-<18 and 18-24 months preindex date. Baseline characteristics were similar between cohorts. Baseline A1C values were similar across cohorts (9.2%-9.6%). Mean follow-up A1C values were higher with longer preindex-date duration of uncontrolled A1C (8.0 ± 1.7%, 8.2 ± 1.6%, 8.5 ± 1.7%, and 8.6 ± 1.7% for <6, 6-<12, 12-<18, and 18-24 months); attainment of A1C <7.0% worsened with increasing preindex-date duration of A1C ≥7.0% (29.6%, 20.0%, 14.6%, and 11.5% for <6, 6-<12, 12-<18, and 18-24 months).

Conclusions: These data suggest that longer duration of uncontrolled A1C before BI initiation increases the risk of not reaching glycaemic targets. However, target attainment was poor in all cohorts, highlighting inadequate glycaemic control as an important unmet need in US patients with T2D.

KEYWORDS
basal insulin, clinical inertia, glycaemic control, treatment intensification, type 2 diabetes
1 | INTRODUCTION

Type 2 diabetes (T2D) is a chronic condition frequently characterized by progressive worsening of glycaemic control. The long-term positive effects of early interventions to correct hyperglycaemia have been recognized since the publication of the 10-year follow-up of the United Kingdom Prospective Diabetes Study (UKPDS). Among patients with newly diagnosed T2D who were randomized to intensive therapy (insulin, sulphonylurea, or metformin) or dietary restriction, long-term benefits of intensive therapy in terms of microvascular risk (vitreous haemorrhage, retinal photocoagulation, or renal failure), myocardial infarction, and death were evident even though differences in glycaemic control between groups quickly disappeared after trial end. More recently, in the ORIGIN trial, patients with T2D who were assigned to early intervention with insulin glargine were more likely to maintain glycaemic control for 5 years than those randomized to standard care. Two

Many patients with T2D ultimately require insulin therapy for adequate control of hyperglycaemia. However, despite the proven clinical benefits of insulin for patients with T2D, patients and physicians are often reluctant to initiate insulin—principally due to an interplay of attitudes related to injectable therapy, treatment complexity, and negative perceptions toward the meaning and consequences of insulin initiation.

Real-world data to illustrate the effect of duration of hyperglycaemia and the extent of clinical inertia, including the effects of glycaemic control, in patients with T2D would be useful. The aim of the current study was to examine the effects of different durations of hyperglycaemia on glycaemic control clinical treatment outcomes following initiation of basal insulin (BI).

2 | MATERIALS AND METHODS

2.1 | Study data source

This retrospective analysis used data derived from electronic medical records (EMRs) within the GE Centricity platform. GE Centricity is a large platform used by 35,000 clinicians to manage data from over 17 million patients across the USA. The database comprises a broad range of clinical and demographic information. Further, the data are captured longitudinally, so long-term outcomes can be studied.

2.2 | Study population

Data were selected from patients with ≥1 diagnosis of T2D (ICD-9-CM codes 250.x0 or 250.x2) between January 1, 2007, and December 31, 2014 (Figure 1A). Patients who initiated BI and who did not concomitantly receive a glucagon-like peptide-1 receptor agonist (GLP-1 RA) or a rapid-acting insulin on the index date were eligible. The date of first prescription of BI was defined as the "index date." Patients had to have ≥24 months of continuous health-plan enrolment preindex date and ≥12 months postindex date. All patients were required to have ≥1 glycated haemoglobin (A1C) test value of ≥7.0% within the 6 months preindex date and including the index date. Follow-up A1C values were reported only for patients who had ≥1 follow-up value and were persistent to BI therapy for ≥12 months. The closest A1C value before (or on) the index date was used as the index date value.

Patients were stratified by duration of uncontrolled A1C (defined as ≥7.0% for <6, 6-<12, 12-<18, and 18-24 months) during the 2-year baseline period. Specifically, repeated A1C values recorded during the 24 months preindex date were evaluated based on increasing time from the index date. Patients were considered to have uncontrolled A1C until they had an A1C value <7.0%. Patients with no controlled A1C values (eg, no recorded value <7.0% during the 24 months preindex date) were considered to have uncontrolled A1C for 18-24 months. Patients with a single uncontrolled A1C value within 6 months preindex date, with no data available for the remaining baseline period, were conservatively classified in the <6-month cohort. When patients had a controlled A1C value(s) within the baseline period, the time of the closest uncontrolled A1C value before the index date was used for classification. All patients had uncontrolled A1C values exclusively (ie, A1C ≥7.0%) from the categorization date up to the index date.

Persistence was calculated as the duration of days from initiation to discontinuation of therapy postindex date. BI initiation was identified based on a physician order for BI. Each physician order and a corresponding number of refills prescribed were assumed to cover a 30-day supply. Patients were assumed to be persistent to BI until the assumed days’ supply of the order plus the number of days’ supply covered by any refills or subsequent orders ran out. Patients were considered to have discontinued treatment with BI if the physician entered a medication stop date for BI (regardless of any remaining days’ supply or refills) or if the days’ supply for the initial order, plus any refills or new orders, ran out without the presence of a new order or refill.

The following key baseline data were collected: age (at the index date); sex; race; weight; BMI; blood pressure (values closest to the index date, maximum 180 days before the index date); A1C (all values during the 2 years prior to the index date); comorbidities and Charlson comorbidity index (CCI) score (during the 6 months preindex date); and diabetes medications (during the 2 years prior to but excluding the index date and on the index date).

2.3 | Outcome measures

The following outcomes were studied for eligible patients in each of the four cohorts: A1C, weight, BMI, blood pressure, and diabetes medications. A1C data reported were: average A1C during the 730-366 days preceding the index date; average A1C during the 365 days up to and including the index date; the last A1C value before the index date; the most recent A1C values during days 1-93, 94-184, 185-276, and 277-365, respectively, for patients who were persistent to BI for ≥90, ≥180, ≥270, and ≥360 days; and the final A1C value during ≥12 up to 15-month follow-up (only for patients who were persistent to BI for ≥360 days).
Weight, BMI, and blood pressure data were reported at baseline (last value before the index date) and 12-month follow-up (last value up to 15 months postindex date for patients who were persistent to BI for ≥360 days.

2.4 | Data analyses

Descriptive analyses of patient demographics, clinical characteristics, and treatment characteristics included means and standard deviations (SDs) of continuous variables and frequency distributions for categorical variables.

3 | RESULTS

3.1 | Patient selection and baseline characteristics

Of over 22 million patients with ≥1 diagnosis of T2D, 37,053 were eligible for inclusion, of whom 15,081 (40.7%), 5,662 (15.3%), 5,939 (16.0%), and 10,371 (28.0%), respectively, had uncontrolled A1C for <6, 6-<12, 12-<18, and 18-24 months (Figure 1B).

The mean ± SD (range) age of the overall population was 60 ± 12 (60-80) years; 50.2% were female, with little variation by cohort (Table 1). Among those with known race, 83.0% were white and 14.9% were black, with little variation by cohort.

Mean A1C (last value before the index date) was slightly lower in the 6- to <12-month cohort than in the other three cohorts (9.2% vs 9.5%-9.6%; Table 1). Mean weight decreased slightly with increasing uncontrolled A1C duration, but mean BMI was similar in all cohorts. Most patients were obese (67.8% had a BMI ≥30 kg/m²) or overweight (24.0% had a BMI 25-<30 kg/m²). Other than diabetes, the most common Charlson comorbidity was chronic pulmonary disease (19.4%). This, along with the various other comorbidities, was slightly more common in the 6- to <12-month cohort, resulting in a slightly higher mean CCI score in this cohort than in the other three cohorts (1.1 vs 1.0; Table 1).

During the 2 years preindex date, the most common antidiabetes drugs used were biguanides (47.4%) and sulphonylureas (43.0%).

**FIGURE 1** (A) Trial design and (B) patient disposition. Abbreviations: A1C, glycated haemoglobin; d, days; GLP-1 RA, glucagon-like peptide-1 receptor agonist; mo, months; T2D, type 2 diabetes; y, years. †Index date = date of basal insulin prescription.
followed by dipeptidyl peptidase-4 inhibitors (21.9%) and thiazolidinediones (20.4%; Figure 2A). Fewer patients in the <6-month cohort received antidiabetes drugs during the 2 years preindex date compared with patients in the other three cohorts (Figure 2A). Any oral treatment was reported for 58.2% of those in the <6-month cohort vs 70.7%, 73.2%, and 69.3%, respectively, of those in the 6- to 12-, 12- to 18-, and 18- to 24-month cohorts. At index date, diabetes drug use in the <6-month cohort had increased to levels approaching those in the other three cohorts (Figure 2B).

3.2 | Basal insulin persistence

In the overall cohort, 94.0% of patients were persistent to BI for ≥90 days in the first 3 months, 90.0% for ≥180 days in the first 6 months, 86.9% for ≥270 days in the first 9 months, and 85.8% for ≥360-day follow-up. Within the four cohorts at each time point, persistence remained high (>80%) and was similar across the cohorts, with a trend towards a longer uncontrolled A1C period being associated with increased persistence (83.8%, 86.3%,
FIG URE 2 Proportions of patients receiving different antidiabetes drugs (A) during the 24 mo before the index date, (B) on the index date, and (C) the proportions of patients initiating different oral antidiabetes drugs during follow-up. A1C, glycated haemoglobin; DPP-4, dipeptidyl peptidase-4; FDC, fixed-dose combination; mo, months
87.2%, and 87.6%, respectively, were persistent for ≥360-day follow-up in the <6-, 6- to <12-, 12- to <18-, and 18- to 24-month cohorts).

3.3 | A1C control

During the 1-2 years preindex date, mean A1C was higher in the 12- to <18- and 18- to 24-month cohorts (Figure 3A). By the index date, mean A1C was similar across the <6-, 12- to <18-, and 18- to 24-month cohorts, but slightly lower in the 6- to <12-month cohort (Figure 3A).

Patients in the <6-month cohort demonstrated the best glycaemic control at all time points during follow-up, followed by those in the 6- to <12-, 12- to <18-, and 18- to 24-month cohorts (A1C 8.0%, 8.2%, 8.5% and 8.6%, respectively; Figure 3A). Thus, a trend of rising A1C was observed with longer duration of hyperglycaemia. Similarly, achievement of A1C <7.0% during follow-up increased in line with decreased duration of time with uncontrolled A1C preindex date (29.6%, 20.0%, 14.6%, and 11.5%, respectively, in the <6-, 6- to <12-, 12- to <18-, and 18- to 24-month cohorts; Figure 3B).

3.4 | Weight, BMI, and blood pressure

Mean weight increased slightly between baseline and follow-up in all cohorts (Figure 4A). Mean ± SD weight gain among those with both baseline and follow-up weight measurements (n = 22 507) was similar across cohorts (1.4 ± 23.7, 1.1 ± 23.8, 1.5 ± 25.0, and 0.8 ± 24.0 kg, respectively, for the <6-, 6- to <12-, 12- to <18-, and 18- to 24-month cohorts).

![Figure 3](image-url)
The mean BMI (mean ± SD) was similar at baseline and follow-up across cohorts (Figure 4B). Among patients with both baseline and follow-up BMI measurements (n = 26,177), mean ± SD BMI increase was 0.1 ± 3.2 kg/m². At follow-up, 64.7% of patients were obese, 21.2% overweight, and 14.1% in the healthy range.

The apparent discrepancy between small weight gain and similar BMI may be due to missing data. Although 92% patients had a follow-up BMI (and 83% had a baseline BMI), only 74.3% had a baseline weight (and 70% a follow-up weight).

Among patients with systolic blood pressure readings at baseline and follow-up (n = 30,095), the mean ± SD increase was 0.1 ± 92.6 mm Hg; for diastolic blood pressure (n = 30,125), the mean decrease was 0.8 ± 16.3 mm Hg. There was little clinically relevant difference between cohorts.

### 3.5 Oral antidiabetes treatment during follow-up

The mean numbers of oral antidiabetes medications received in the baseline period were 2.10, 2.32, 2.40, and 2.46, respectively, in the <6-, 6- to <12-, 12- to <18-, and 18- to 24-month cohorts. Few patients initiated additional antidiabetes drugs during follow-up, but treatment initiation was slightly more common in the <6-month cohort (Figure 2C).

### 4 DISCUSSION

In this retrospective cohort analysis, in patients with A1C >7% at baseline, shorter time spent with uncontrolled A1C before the initiation of BI was associated with better glycaemic control and improved achievement of target A1C during follow-up. Despite similar baseline A1C levels in the four cohorts, by the end of up to the 12-month (up to 15-month) follow-up, mean A1C levels were higher with longer duration of uncontrolled A1C before initiation of BI. Similarly, A1C target attainment (<7.0%) at the end of follow-up worsened with longer durations of uncontrolled A1C.

Our results are in line with various studies of patients with T2D who failed to reach target A1C with metformin, which reported that earlier intensification results in better glycaemic control. Using US EMR data, Rajpathak et al. reported that additional oral therapy within 3 vs 10-15 months significantly improved attainment of glycaemic goals (47% vs 42%). Pantalone et al. used US EMR data to show that earlier intensification (mainly additional antidiabetes medication or titration of metformin dosage) vs after 6 months resulted in significantly faster time to A1C goal attainment. Lastly, Fu and Sheehan reported a greater A1C reduction among patients whose treatment was intensified (oral or injectable drugs) within 6 months of baseline vs after 6 months or with no intensification) using US insurance claims data.
Overall, it seems that starting insulin before A1C becomes too high (>8.0%) and in a timely manner after A1C control is lost is likely to result in better glycemic control. This may be because patients with a longer duration of uncontrolled A1C before BI initiation may have suffered more glucotoxicity, leading to increased loss of β-cell mass. This could potentially affect target A1C attainment or maintenance of glycemic control—particularly in those patients receiving insulin secretagogues as next intensification. Numerous studies have established that after treatment intensification, delays have been shown to be associated with poorer response to the added therapy. Thus, delaying treatment intensification exposes patients to avoidable hyperglycaemia both during and after the delays. These results highlight the benefit of early initiation of intensification therapy in patients not at target, and demonstrate that prolonged hyperglycaemia may be associated with decreased ability to reach target.

It should be noted that glycemic goal attainment was quite poor (12%-30%) in all cohorts in the current study—this is in line with a previous US claims database analysis by Dalal et al., in which 27% of patients who initiated BI reached A1C <7.0%. It is also in line with National Health and Nutrition Examination Surveys (NHANES) data, in which 30% of diabetes patients on insulin attained A1C <7.0%.

It is also notable that A1C reductions observed in the current study occurred in the first 3-6 months following BI initiation, after which time mean A1C levels plateaued. Similar results have recently been reported among a cohort of real-world patients with T2D initiating BI.

Both poor A1C target attainment and A1C plateau may be due to insufficient insulin intensification. This reluctance to intensify insulin regimens may be due to factors including fear of hypoglycaemia, weight gain, burdensome regimens, or cost. In this regard, currently available second-generation BIs have sought to reduce hypoglycaemia risk without compromising A1C reduction; however, it remains to be determined whether these novel insulins (eg, insulin glargine 300 units/mL and insulin degludec) will overcome such reluctance to intensify insulin therapy.

The duration of uncontrolled A1C before BI initiation did not appear to differ by various baseline factors including age, sex, race, blood pressure, and CCI. Patients with the shortest duration of uncontrolled A1C (<6 months), however, used fewer oral antidiabetes drugs vs the other cohorts (58.1% vs 71.0%, respectively). Additionally, patients with the longest duration of uncontrolled A1C (18-24 months) were more likely to have a diagnosis of "diabetes with chronic complications" than those with the shorter period of uncontrolled A1C (27.2% vs 21.9%). More detailed information on the types of complications was unfortunately not available, but these results are in line with prior findings that elevated A1C can cause various microvascular complications (eg, retinopathy, neuropathy, and nephropathy) and macrovascular complications (eg, coronary artery disease, peripheral arterial disease, and stroke).

Although mean baseline BMI was relatively consistent across cohorts, patients in the two shorter-duration cohorts tended to have a slightly higher mean baseline weight vs those in the longer-duration cohorts. Among patients with both baseline and follow-up BMI data, mean changes in BMI were very small in all four cohorts. Among patients with both baseline and follow-up weight measurements, mean ± SD weight gain was 1.2 ± 24.0 kg. Clearly, weight change varied widely among patients, but weight gain after initiating insulin is as would be expected. BMI data show that 67.8% of our study population was obese at BI initiation. Newer fixed-ratio coformulation therapies using BI and glucagon-like peptide-1 receptor agonists can offer an alternative therapy for targeting glycemic control while mitigating or reducing weight gain, which may be of use in this population.

Patients in the shortest-duration cohort received fewer noninsulin diabetes drugs during the 2 years before BI initiation, presumably because diabetes was diagnosed during this time for some patients. This is supported by the fact that only 39.5% of patients in the <6-month cohort had an available A1C measurement during the 1-2 years before their index date, compared with 56.2%, 100%, and 100%, respectively, in the 6- to <12-, 12- to <18-, and 18- to 24-month cohorts.

4.1 | Limitations

As with all retrospective observational studies, where randomization is not undertaken, there is a risk of selection bias. Further, as our aim was to examine the effects of increasing periods of hyperglycaemia in as large a population as possible, techniques such as propensity score matching—which may have somewhat ameliorated bias—were not undertaken. Also, as the EMR data were office-based, detailed information on other services (eg, inpatient and emergency department visits as well as visits to other health-care providers) is limited. As data were captured in real-world medical practice, not all patients had all data available. These missing data could have affected the results—especially as patients with more severe diabetes were more likely to have undergone more regular testing, or less testing because of failure to adhere to clinical visit recommendations. Additionally, persistence to treatment was based on physician orders for medication and an assumed refill supply of 30 days per refill, and no information was available regarding whether patients took medication as prescribed. Further, there was a likely a “survivor phenomenon” whereby patients who remained on treatment and in the database could have differed from those who did not. However, these factors would likely have affected all four cohorts similarly. Finally, the collection of data relating to insulin dose at index date and again at follow-up would have been useful in exploring the association between diabetes management, duration of uncontrolled A1C, and attainment of glycemic targets.

5 | CONCLUSION

Our retrospective, real-world data analyses suggest that delaying treatment intensification (BI initiation in this study) increases the risk of not meeting glycemic targets; in addition, there is a trend of rising A1C after BI initiation in patients with longer-duration uncontrolled A1C. This does not change significantly, even with continued treatment with BI beyond 6 months up to 1 year. Thus, uncontrolled
A1C duration may be an important indicator to the clinician and could serve as a call to action to review the clinical care and need for intensification of therapy. These results point towards the need for earlier therapy intensification in this population. Moreover, our observation that attainment of A1C <7.0% during follow-up increased in line with decreased duration of time with uncontrolled A1C before starting BI highlights that glycaemic control does not change much after 6 months; thus, other intensification therapies are needed.

While patients have uncontrolled A1C, they are at increased risk of micro- and macrovascular complications as well as disease progression. Such patients would benefit from initiating treatments that can improve glycaemic control without a high risk of hypoglycaemia or weight gain.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTION

EL and AS contributed to designing the study. AM and JM contributed to designing the study and acquiring the data. All authors contributed to the data analysis and interpretation and critically reviewed the manuscript.

ETHICAL APPROVAL

This study was conducted in compliance with the ethics guidelines for research in humans as recorded in the Helsinki Declaration of 1964. Given the observational retrospective nature of this study, individual consent was not required after ensuring for anonymization of data.

DATA ACCESSIBILITY

All data are included within the manuscript.

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