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ISPOR EU
2-6 November
Copenhagen,
Denmark

Examining the Temporal Trends in Hypoglycaemia Events, Treatment Adherence, and HbA1c in Patients With T2D in the US

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INTRODUCTION

- Hypoglycaemia, typically defined as glycaemia <3.9 mmol/L (<70 mg/dL), and poor adherence to diabetes medication, (including insulin) which affects almost half of all patients with T2D, remain two important barriers to achieving optimal glycaemic control in patients with type 2 diabetes (T2D).[1,2,6]
  - Hypoglycaemia increases morbidity and mortality risk and is associated with poor quality of life.[3–5]
  - Poor adherence increases the risk of diabetes-related complications, mortality, and hospitalization.[1,7–9]
  - Hypoglycaemia and poor adherence to treatment increase overall cost of care.[3,7,8]

OBJECTIVE

To examine the temporal trends in hypoglycaemia events and medication adherence in patients with T2D initiating first-generation basal insulins (BIs), according to long-term patterns in HbA1c profile

METHODS

Study design

- In this retrospective, observational study, adults with a T2D diagnosis and a prescription for a first-generation BI (insulin glargine 100 U/mL or insulin detemir) were identified from the US-based Clinformatics™ Data Mart database between 1 January 2010 and 30 June 2018.
- The index date was defined as the date of the first BI prescription.

Inclusion criteria

- Age ≥18 years at index date.
- A primary or secondary diagnosis of T2D (ICD-9-CM codes 250.x0 or 250.x2, or ICD-10-CM code E11) covering the entire study period.
- ≥1 prescription for an oral antidiabetes drug (OAD) or glucagon-like peptide-1 receptor agonist (GLP-1 RA) during the baseline period.
- Continuous enrolment in a health insurance plan during the 12 months preceding the index date (baseline period) and the 18 months following the index date (follow-up period).
- ≥1 baseline HbA1c record and no missing HbA1c records in two consecutive quarters during follow-up.

Exclusion criteria

- Any insulin claims during the baseline period.
- A claim for both insulin glargine and insulin detemir on the index date.

Patient cohorts

- Participants were assigned to one of three glycaemic control cohorts ('Below Target', 'Above Target', and 'Fluctuating') (**Table 1**) based on their HbA1c profile during the 18-month follow-up period.

Table 1: Patient cohort definitions

Cohort	Definition
Below Target	HbA1c consistently <7.0% during Q2–Q6 or Q1–Q5
Above Target	HbA1c consistently ≥7.0% during Q2–Q6 or Q1–Q5
Fluctuating	More than 1 switch from below to above HbA1c target (or vice versa) during follow-up, or 1 switch during Q3–Q5

Study outcomes

- Temporal trends during the 18-month follow-up period:
  - The incidence of hypoglycaemia events, defined as any outpatient visit, inpatient admission, or emergency room visit with a diagnosis code for hypoglycaemia.
  - Adherence to BI therapy, reported as the proportion of days covered (PDC), defined as the number of days covered by any BI divided by the total number of days in the follow-up period.

Statistical analyses

- Study variables were examined descriptively.
  - Number and percentage were provided for dichotomous and polychotomous variables.
  - Mean and standard deviation (SD) were provided for continuous variables.
- Statistical tests of significance were conducted for differences among cohorts.
  - χ^2 tests were used for categorical variables.
  - Student t-tests were used for continuous variables.
  - In addition to p values, standardized differences, defined as the absolute difference in sample means divided by an estimate of the pooled SD of the variable, were also calculated for each variable.

RESULTS

Patients

- Of the 612,230 patients with T2D and ≥1 BI prescription during the identification period (1 January 2011–31 December 2016), 5785 met the study criteria and were included in the analysis.
- The number of patients in the 'Below Target', 'Above Target', and 'Fluctuating' cohorts was 579, 3691, and 1515 patients, respectively.
- Baseline demographics are shown in **Table 2**.
  - The mean age was 65.6 years; 53% were male.
  - More patients (41.7%) had Health Maintenance Organization insurance coverage than any other type of coverage; and 62.7% received Medicare.
  - Demographics were similar across the three HbA1c cohorts.

Table 2: Baseline demographics

Baseline demographics	Overall population N=5785
Age at index date, mean years (SD)	65.57 (11.93)
Age group, n (%)	
18–44 years	287 (5.0)
45–54 years	802 (13.9)
55–64 years	1367 (23.6)
65–74 years	1956 (33.8)
≥75 years	1373 (23.7)
Sex, n (%)	
Male	3047 (52.7)
Female	2737 (47.3)
Unknown	1 (0.02)
Insurance coverage plan, n (%)	
Indemnity	17 (0.3)
Point of Service	1386 (24.0)
Health Maintenance Organization	2413 (41.7)
Preferred Provider Organization	316 (5.5)
Exclusive Provider Organization	370 (6.4)
Other	1283 (22.2)
Plan type, n (%)	
Commercial	2157 (37.3)
Medicare	3628 (62.7)
Geographic location, n (%)	
Northeast US	487 (8.4)
South US	2883 (49.8)
Midwest US	376 (6.5)
West US	2016 (34.9)
Unknown	23 (0.4)

- Baseline clinical characteristics of each HbA1c cohort are shown in **Table 3**.
  - During the baseline period, and compared with the other cohorts, patients in the 'Below Target' cohort:
    - Had a significantly higher mean Charlson Comorbidity Index score.
    - Had a significantly lower mean HbA1c.
    - Used significantly fewer OADs.
    - Had lower use of GLP-1 RAs.
    - Had more hypoglycaemia events.

Table 3: Baseline clinical characteristics

Baseline characteristics[a]	Below Target (n=579)	Above Target (n=3691)	Fluctuating (n=1515)
CCI, excluding diabetes-related items, mean (SD)	2.26 (2.28)	1.60 (1.96)	1.93 (2.12)
p value[b]	–	**<0.001**	**0.002**
Standardized difference	–	31.26	14.99
HbA1c (mmol/L) closest to index date, mean (SD)	8.26 (2.26)	9.54 (1.82)	8.81 (1.93)
p value[b]	–	**<0.001**	**<0.001**
Standardized difference	–	62.51	25.98
Number of OADs, mean (SD)	7.69 (5.65)	9.87 (6.29)	8.96 (6.07)
p value[b]	–	**<0.001**	**<0.001**
Standardized difference	–	36.42	21.53
GLP-1 RA use, n (%)	30 (5.2)	305 (8.3)	98 (6.5)
p value[b]	–	**0.013**	0.318
Standardized difference	–	12.33	5.50
Number of hypoglycaemia events, mean (SD)	0.28 (2.19)	0.18 (0.85)	0.22 (0.97)
p value[b]	–	**0.047**	0.385
Standardized difference	–	6.04	3.55

[a] Baseline period was the 12 months preceding the index date
[b] Versus 'Below Target' cohort

Outcomes

- During the follow-up period, the 'Below Target' cohort had:
  - A significantly higher mean number of hypoglycaemia events than the 'Above Target' cohort in Q1 (0.14 vs 0.08, respectively; p=0.009) and Q2 (0.12 vs 0.06, respectively; p=0.022) only (**Figure 1**).
  - A similar mean number of hypoglycaemia events to the 'Fluctuating' cohort in each quarter (**Figure 1**).
  - A significantly lower mean PDC for any BI after Q1 than the 'Above Target' and 'Fluctuating' cohorts (all p<0.001) (**Figure 2**).
- Decreasing mean numbers of hypoglycaemia events (0.10 in Q1 decreasing to 0.05 in Q6) and decreasing PDC (0.74 in Q1 decreasing to 0.49 in Q6) were observed in Q1–Q6 for the overall population (**Figure 3**).
- Among patients with a filled BI prescription in each quarter of the follow-up period, the 'Below Target' cohort had a higher mean number of hypoglycaemia events in Q1 than the 'Above Target' cohort (0.14 vs 0.08, p=0.009) (**Figure 4**).
- A decreasing trend for hypoglycaemia events during Q1–Q6 (0.10 decreasing to 0.04) was also observed among all patients with BI use in each quarter of the follow-up period.

Figure 1: Mean number of hypoglycaemia events in Q1–Q6 for the three HbA1c cohorts

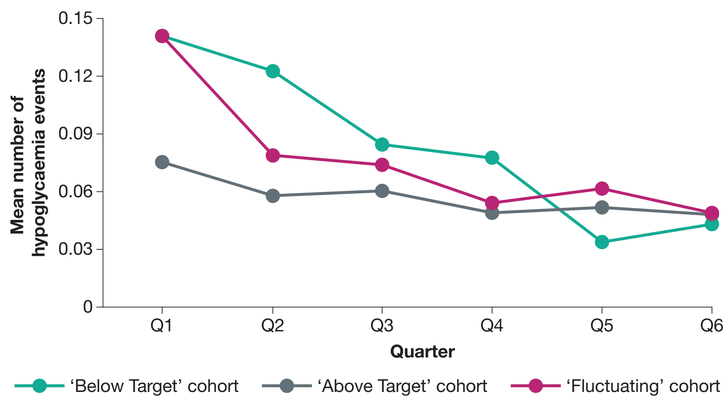
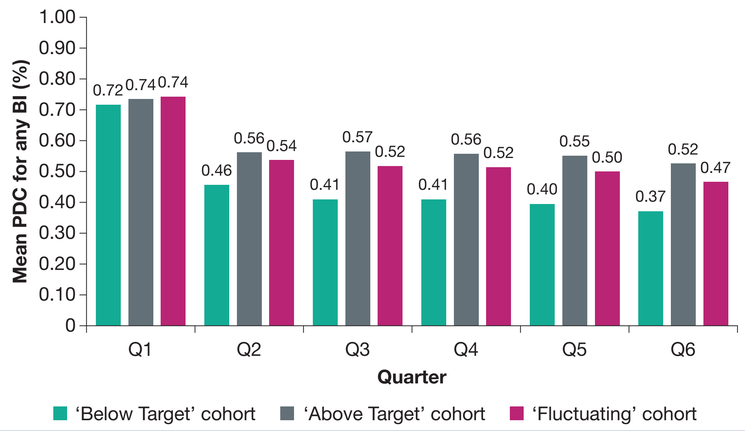
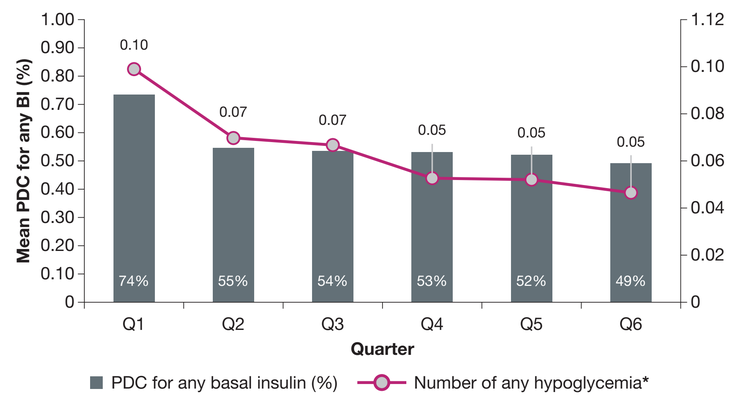


Figure 2: Mean adherence (PDC) to any BI in Q1–Q6 for the three HbA1c cohorts



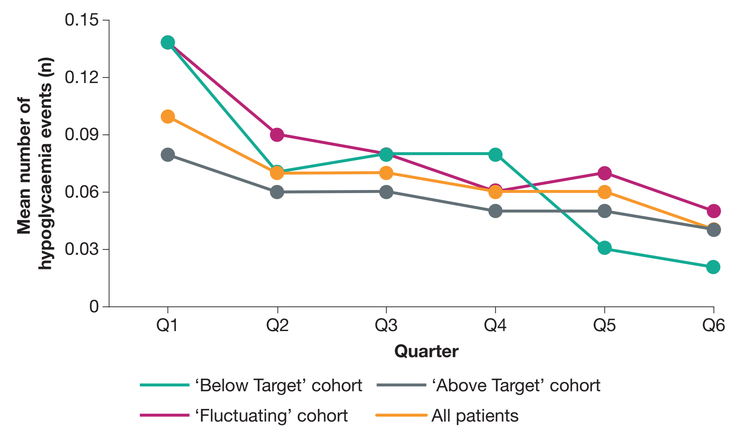
BI, Basal Insulin

Figure 3: Mean adherence (PDC) to any BI and mean number of hypoglycaemia events during Q1–Q6 for the overall population



* Including outpatients, in-patients, and emergency department related-hypoglycaemia events

Figure 4: Mean number of hypoglycaemia events in patients with prescription for BI filled in each quarter during follow-up



LIMITATIONS

- Characterizing the 'Fluctuating' cohort of patients is a challenge, as some patients showed a fluctuating HbA1c trend (below and above the target) across the 18-month follow-up, defined as having at least 2 switches from below to above HbA1c target, or vice versa.
- The number of fluctuations and the degree of fluctuation is likely to vary between patients.
- The included patients were grouped based on their long-term glycaemic control profile. As this study represents a descriptive analysis only, without adjustment for additional differences in the study population, this grouping method may mask other heterogeneous factors that might impact their response to treatment.
- Results are derived from a claims database and are therefore subject to possible coding errors or missing data.

DISCUSSION AND CONCLUSIONS

- **Among patients with T2D treated with a first-generation BI, hypoglycaemia was more common in the 'Below Target' cohort than the 'Above Target' cohort; these findings are consistent with previous reports[10]. Differences at baseline, higher event rates, more comorbidities together with lower medication use, in the 'below target' cohort suggest that this group may have a more complex relationship between Hb1c and hypoglycaemia.**
- **'Below Target' patients also had lower adherence to BI than 'Above Target' patients.**
- **The consistently lower PDC seen in the 'Below Target' cohort may be related to the higher rate of hypoglycaemia events in this group.**
- **These findings highlight temporal trends in two important barriers to optimal glycaemic control in patients with T2D.**

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Acknowledgements and disclosures

This study was sponsored by Sanofi. The authors received editorial assistance and printing support in the preparation of this poster from Joseph Worrall, PhD, of Excerpta Medica, funded by Sanofi.
Charlie Nicholls and Jukka Westerbacka — Employees and stock/shareholders: Sanofi. **Jasmanda Wu** — Employee: Sanofi U.S., Inc. **Lin Xie, Yuexi Wang, and Huiqi Wang** — Employees: STATinMED Research, under contract with Sanofi U.S., Inc.

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