Effectiveness of Insulin Degludec in Thai Patients with Diabetes Mellitus: Real-World Evidence From a Specialized Diabetes Center

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Key words
insulin degludec, real-world evidence, Thai patients, continuous glucose monitoring, glycemic variability

Results A total of 55 patients (T2DM 76.4%, females 54.5%, mean age 57.1 ± 16.1 years, duration of diabetes 16.7 ± 8.8 years, BMI 27.3 ± 5.5 kg/m², baseline A1C 9.3 ± 2.3%, median duration of treatment 8 months) were included in the study. In T1DM patients (n = 13), the overall mean A1C reduction at 12 months was 0.5% with minimal weight gain of 0.9 kgs at 12 months. In T2DM patients (n = 42), the overall mean A1C reduction at 12 months was 0.8% with minimal weight loss of 0.4 kgs at 12 months. The proportion of T1DM patients who could achieve optimal glycemic control increased slightly from 14.3 to 18.2% but the proportion of T2DM patients who could achieve optimal glycemic control increased from 30.8 to 53.8%. Patient satisfaction showed a sustained improvement throughout the duration of study. In four T1DM patients who had paired CGM data, insulin degludec provided greater reductions in glycemic variability endpoints with increased time-in-range when compared with previous insulin glargine.

Discussion Our data suggested that the effectiveness of insulin degludec was consistent with the results seen in clinical trials with lower risk of patients-reported hypoglycemia, and a significant improvement in glycemic control. Patients also reported higher treatment satisfaction. More long-term and cost-effectiveness data are needed to establish the role of this ultra-long-acting insulin in real-world settings.

ABBREVIATIONS
A1C Glycated hemoglobin
CGM Continuous Glucose Monitoring
CV Coefficient of Variation
HAT the Hypoglycemia Assessment Tool
ICER Incremental Cost-Effectiveness Ratio
MAGE Mean Amplitude of Glycemic Excursions
MODD Mean Of Daily Differences
QALY Quality Adjusted Life Year
QOL Quality of Life
T1DM Type 1 Diabetes Mellitus
T2DM Type 2 Diabetes Mellitus
WHOQOL-THAI Thai version of abbreviated World Health Organization Quality Of Life.
Background

The evidence for improved glycemic control in reducing and halting the progression of diabetes-related microvascular complications is proven [1]. While insulin is the most potent glucose-lowering therapy, its clinical use is limited by associated hypoglycemia [2]. Advances in drug development have led to the availability of newer basal insulin analogue, namely insulin degludec (Tresiba®). Insulin degludec is an ultra-long-acting (pharmacokinetic half-life of 25 h) basal insulin designed to achieve a highly stable pharmacodynamic profile, with lower within-day and day-to-day glycemic variability [3, 4]. Two modifications included the deletion of the threonine amino acid residue at B30 and the addition of a fatty acid (hexadecanedioic acid) to the lysine at B29 via a glutamic acid spacer have been made to the human insulin structure to produce insulin degludec [5]. It has a soluble, stable dihexamer structure in the presence of phenol and zinc but forms a depot of multihexamer chains after subcutaneous injection. These multihexamer chains gradually disassemble into active monomers that are slowly absorbed into circulation, resulting in a glucose-lowering profile that is ultra-long and flat.

Clinical studies demonstrated that insulin degludec reduced rate of hypoglycemia especially nocturnal hypoglycemia in both patients with type 1 diabetes mellitus (T1DM) and patients with type 2 diabetes mellitus (T2DM) when compared with insulin glargine 100 U/mL (Glargine U100) [6–9]. Flexibility in the timing of injection also led to more convenience for some patients with shift works or frequent travelers. However, sometimes evidence from what happens in real-world studies might differ from data obtained from randomized control trials for novel medications and technologies [10]. Therefore, it is important to assess how novel therapeutic strategies can be applied from the research arena into the setting of everyday clinical practice. Moreover, the results of these studies can be used to inform the decisions of healthcare payers to prioritize novel treatments for universal coverage in the future.

Insulin degludec has been available in Thailand since October 2016. Although the clinical trial results revealed less nocturnal hypoglycemia, the data from real-world settings is limited especially in Asian patients [11, 12]. To gain further knowledge on clinical effectiveness, treatment patterns, satisfaction with new insulin treatment and quality of life (QOL) among Thai patients with diabetes (both T1DM and T2DM) initiating insulin degludec in a real-life clinical setting, we conducted a 12-month, prospective non-interventional study in a single specialized diabetes center in Bangkok, Thailand. The primary objective of the study is to evaluate effectiveness and rate of hypoglycemia after starting insulin degludec in routine clinical practice. Secondary objectives include to access patient satisfaction with insulin degludec, quality of life (QOL) changes after treatment, and evaluate glycemic fluctuation from continuous glucose monitoring (CGM) in a subset of patients with T1DM.

Methods

This prospective observational study recruited all patients who had been prescribed insulin degludec and continued the use for at least 3 months between October 2016 to September 2017 at Theptarin Hospital, one of the largest and most comprehensive diabetes centers in Bangkok, Thailand. The index date for each patient was the date of starting insulin degludec. The characteristics of patients, reasons for starting insulin degludec, frequency of self-reported hypoglycemia episodes before and after starting insulin degludec, changes in glycemic control (Glycated hemoglobin; A1C) and body weight at baseline, 3, 6, and 12 months were evaluated. Frequency of self-report hypoglycemic episodes was pre-defined by the patient recall the number of hypoglycemic episodes during the previous 12 weeks. Hypoglycemic episodes were divided from none, at least once a month, at once a week, and at least 3 times per week.

Severe hypoglycemia was defined as plasma glucose level less than 54 mg/dL, irrespective of symptoms, or if the hypoglycemia was severe, requiring assistance from a third party. Nocturnal hypoglycemia was defined as occurring between 00:00 and 05:59 AM.

QOL was evaluated with validated Thai version of the brief form of World Health Organization quality of life (WHOQOL-BREF-THAI) assessment instrument at baseline, 3, 6, and 12 months [13]. The WHOQOL-BREF-THAI consists of 26 items, each with 5-point Likert scale (a higher score indicating a better QOL). The instrument assesses 4 domains - physical health (7 items), psychological well-being (6 items), social relationships (3 items), and satisfaction with the environment (8 items). The overall QOL score is the summation of all 4 domains plus another two global item scores. Level of satisfaction with current anti-diabetic medications at baseline was assessed using 7-point Likert scale and then after starting insulin degludec at 3, 6, and 12 months.

Glycemic fluctuation from paired iPro® 2 (Medtronic, USA) 6-day CGM system obtained 4–6 weeks apart were evaluated from a subset of patients with T1DM who switched from insulin glargine to insulin degludec. The parameters of glucose variability included coefficient of variation (CV), mean amplitude of glycemnic excursions (MAGE), and mean of daily differences (MODD) were compared before and after insulin degludec [14]. Times spent in the target glucose range (70–180 mg/dL) were also compared.

This study was carried out in accordance with the Declaration of Helsinki and the International Conference of Harmonization-Good Clinical Practice, and was approved by the ethics board committee of Theptarin Hospital (No. 06/2016).

Statistical Analysis

Descriptive statistics were used to summarize baseline characteristics as percentages or mean (± standard deviation) as appropriate. Comparisons between T1DM and T2DM patients were done using an unpaired Student’s t test in continuous data and using a Chi square test in categorical data. At the last visit, changes from baseline in A1C and body weight were analyzed using paired t-test. The overall QOL score at baseline and at last follow-up time point were also compared. Glucose variability end points (CV, MAGE, and MODD) and time spent within, below, and above target were compared at baseline and 4–6 weeks later in a subset of T1DM patients who had CGM data. A p-value of < 0.05 was considered statistically significant. All statistical analyses were conducted using the Statistical Package for the Social Sciences (version 22.0; SPSS, Chicago, IL, USA).
Results

Baseline characteristics of the patients

During the study period, a total of 59 patients were prescribed insulin degludec but 4 patients were lost to follow-up before 3 months. Therefore, the full analysis were studied in the remaining 55 patients (T2DM 76.4 %, females 54.5 %, mean age 57.1 ± 16.1 years, duration of diabetes 16.7 ± 8.8 years, BMI 27.3 ± 5.5 kg/m², baseline A1C 9.3 ± 2.3 %, median duration of treatment 8 months). The clinical characteristics of the patients are shown in Table 1. In patients with T2DM (n = 42), insulin degludec was prescribed in 9 insulin-naïve patients. The reasons to start insulin degludec from treating physicians were compared between T1DM and T2DM patients as shown in Fig. 1. While brittle diabetes (extreme swings in blood glucose levels) was the most common reason to switch from previous basal insulin regimen to insulin degludec in T1DM patients (54 %), de-escalation from complex insulin regimens (insulin regimen ≥ 2 times per day) was the most common reason in T2DM patients (33 %). The subset of T1DM patients (4 from 13 T1DM patients) who switched from insulin glargine to insulin degludec were evaluated glycemic fluctuation from paired iPro®2 CGM obtained 4–6 weeks apart.

Table 1  Baseline characteristics of T1DM and T2DM patients who were treated with insulin degludec in this study (n = 55).

<table>
<thead>
<tr>
<th></th>
<th>Total (n = 55)</th>
<th>T1DM (n = 13)</th>
<th>T2DM (n = 42)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>57.1 ± 16.1</td>
<td>36.9 ± 6.5</td>
<td>63.3 ± 12.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>% Female</td>
<td>30 (55 %)</td>
<td>9 (69 %)</td>
<td>21 (50 %)</td>
<td>0.224</td>
</tr>
<tr>
<td>Duration of diabetes (years)</td>
<td>16.7 ± 8.8</td>
<td>11.7 ± 6.7</td>
<td>18.3 ± 8.9</td>
<td>0.017</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.3 ± 5.5</td>
<td>23.3 ± 3.9</td>
<td>28.5 ± 5.3</td>
<td>0.002</td>
</tr>
<tr>
<td>Baseline A1C (%)</td>
<td>9.3 ± 2.3</td>
<td>7.9 ± 1.9</td>
<td>9.7 ± 2.2</td>
<td>0.011</td>
</tr>
<tr>
<td>Previous CV event (%)</td>
<td>3 (5 %)</td>
<td>0 (0 %)</td>
<td>3 (7 %)</td>
<td>0.322</td>
</tr>
<tr>
<td>Chronic kidney disease (%)</td>
<td>15 (27 %)</td>
<td>0 (0 %)</td>
<td>15 (36 %)</td>
<td>0.012</td>
</tr>
<tr>
<td>Baseline anti-diabetic medications</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Metformin (%)</td>
<td>23 (42 %)</td>
<td>0 (0 %)</td>
<td>23 (55 %)</td>
<td></td>
</tr>
<tr>
<td>Sulfonylurea (%)</td>
<td>7 (13 %)</td>
<td>0 (0 %)</td>
<td>7 (17 %)</td>
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<tr>
<td>Pioglitazone (%)</td>
<td>14 (25 %)</td>
<td>0 (0 %)</td>
<td>14 (33 %)</td>
<td></td>
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<tr>
<td>DPP4 inhibitor (%)</td>
<td>25 (45 %)</td>
<td>0 (0 %)</td>
<td>25 (60 %)</td>
<td></td>
</tr>
<tr>
<td>GLP1 receptor agonist (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>SGLT2i (%)</td>
<td>6 (11 %)</td>
<td>0 (0 %)</td>
<td>6 (14 %)</td>
<td></td>
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<tr>
<td>Insulin usage</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
<td></td>
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<tr>
<td>Glargine only (%)</td>
<td>5 (9 %)</td>
<td>0 (0 %)</td>
<td>5 (12 %)</td>
<td></td>
</tr>
<tr>
<td>Detemir only (%)</td>
<td>3 (5 %)</td>
<td>0 (0 %)</td>
<td>3 (7 %)</td>
<td></td>
</tr>
<tr>
<td>Basal plus regimen (%)</td>
<td>11 (20 %)</td>
<td>0 (0 %)</td>
<td>11 (26 %)</td>
<td></td>
</tr>
<tr>
<td>Basal bolus regimen (%)</td>
<td>20 (36 %)</td>
<td>12 (92 %)</td>
<td>8 (19 %)</td>
<td></td>
</tr>
<tr>
<td>Mixed Split regimen (%)</td>
<td>7 (13 %)</td>
<td>1 (8 %)</td>
<td>6 (14 %)</td>
<td></td>
</tr>
</tbody>
</table>

Fig. 1  Reasons to start insulin degludec from treating physicians.
Effectiveness of insulin degludec on glycemic control and body weight

As shown in ▶ Fig. 2, A1C levels improved from baseline up to period of 12 months (p = 0.005) in both T1DM and T2DM patients. In T1DM patients (n = 13), the overall mean A1C reduction at 12 months was 0.5 % (p = 0.206) with minimal weight gain of 0.9 kgs at 12 months (p = 0.385). The total dose of daily insulin decreased slightly from the median dose of 30 units (0.49 units/kg/day) at baseline to 24 units (0.53 units/kg/day) at 12 months (p = 0.246). The dose of insulin degludec slightly reduced from the median dose of 15 units at baseline to 14 units at 12 months (p = 0.116). In T2DM patients (n = 42), the overall mean A1C reduction at 12 months was 0.8 % (p = 0.021) with minimal weight loss of 0.4 kgs at 12 months (p = 0.627). For insulin-treated T2DM patients who switched from previous insulin regimens to insulin degludec (n = 33), the total dose of daily insulin decreased slightly from the median dose of 50 units (0.66 units/kg/day) at baseline to 33 units (0.53 units/kg/day) at 12 months (p = 0.357). The dose of insulin degludec also slightly reduced from the median dose of 26 units at baseline to 24 units at 12 months in insulin-treated T2DM patients (p = 0.843). The proportion of T1DM patients who could achieve optimal glycemic control (A1C < 7.0 %) increased slightly from 14.3 to 18.2 % (p = 0.082), but the proportion of T2DM patients who could achieve optimal glycemic control (A1C < 7.0 %) increased from 30.8 to 53.8 % (p = 0.022).

Frequency of self-reported hypoglycemia

The overall frequency of self-reported hypoglycemic events was improved after starting insulin degludec as revealed in ▶ Fig. 3. The percentage of severe hypoglycemia in the subgroup of patients who frequently experienced hypoglycemia at least 3 times per week reduced from 5 % at baseline to 2 % at 12 months after starting insulin degludec as shown in ▶ Fig. 4a. The percentage of nocturnal hypoglycemia at least 1 time per month improved from 17 % at baseline to 9 % at 12 months (47 % reduction of nocturnal hypoglycemia) and subgroup of patients who frequently experienced nocturnal hypoglycemia at least once a week reduced from 2 % at baseline to none at 12 months after starting insulin degludec as shown in ▶ Fig. 4b.

Patient-reported outcome measurements

The overall QOL scores evaluated with WHOQOL-BREF-THAI did not differ significantly from baseline to the last follow-up at 12 months. Subscale QOL scores in each domain also did not differ significantly before and after insulin degludec treatment as shown in ▶ Table 2. However, patient satisfaction evaluated with 7-point Likert scale showed a sustained improvement throughout the duration of study as revealed in ▶ Fig. 5.

Glycemic fluctuation from paired 6-day CGM data

Four T1DM patients who switched from insulin glargine to insulin degludec over 4–6 weeks due to brittle diabetes were evaluated glycemic fluctuation. As shown in ▶ Fig. 6, CGM data showed that treatment with insulin degludec allowed these patients to maintain blood glucose within target range throughout the day (13 % increment of percentage in target range) but provided slightly reductions in mean interstitial glucose (171 ± 34 mg/dL compared with 176 ± 20 mg/dL before treatment, p = 0.601). Regarding glycemic variability indexes, all endpoints (CV, MAGE, and MODD) improved after switching to insulin degludec but did not reach statistically significance (p > 0.05 in all parameters. Inter-day variability assessed by MODD was the most pronounced change parameter (30 % reduction of MODD) but did not reach statistically significance (p = 0.090).
Discussion

In this prospective study, we demonstrated that insulin degludec attained beneficial effects on glycemic control, minimal weight gain, and reduction in hypoglycemic events especially nocturnal hypoglycemia in both T1DM and T2DM patients as previously seen in clinical trials [6–9]. Moreover, study on glycemic variability in the subset of T1DM patients confirmed significant improvements in all glycemic variability endpoints and showed the increment of time in range after switching from insulin glargine to insulin degludec in T1DM patients. The improvement in treatment satisfaction was improved and sustained up to 12 months after starting insulin degludec. However, there was no change over time in terms of QOL from WHOQOL-BREF-THAI assessment instrument. Given that there is little data on the long-term use of insulin degludec in routine clinical practice among Asian patients, our study generated supplement real-world data in heterogeneous types of patients and also confirmed all benefits of insulin degludec observed from efficacy-focused randomized controlled trials.

Previous reports have shown that insulin glargine 100 U/mL once daily is not enough to achieve adequate glucose control in some patients especially in T1DM patients who often require a twice daily dosing [15, 16]. In contrast to previous basal insulin, insulin degludec has a unique structure and binds to circulating albumin upon absorption which facilitates its ultra-long and flat action [5]. The extensive phase 3 clinical trial programs in both T1DM and T2DM patients with participants from various ethnicities consistently demonstrated non-inferiority glycemic control when compared with insulin glargine 100 U/mL but showed lower rates of hypoglycemia.

![Fig. 3](image-url) Summary of frequency of overall self-reported hypoglycemia before and after insulin degludec.

![Fig. 4](image-url) a Frequency of severe hypoglycemia before and after insulin degludec b Frequency of nocturnal hypoglycemia before and after insulin degludec.

![Table 2](image-url) The overall QOL scores evaluated with WHOQOL-BREF-THAI and subscale QOL scores in each domain before and after insulin degludec treatment.
nocturnal hypoglycemia and severe hypoglycemia [6–9, 17]. The burden and fear of hypoglycemia become the biggest preventing patients from reaching the recommended A1C level [18]. According to the Hypoglycemia Assessment Tool (HAT) study [19], global hypoglycemia rates among T1DM patients were very high and varied greatly between geographical regions (ranged from less than 20 events per patient-year in South East Asia to almost 100 events per patient-year in Latin America). Therefore, insulin degludec could help these vulnerable patients achieve glycemic control with lower risk of hypoglycemia. Our study also confirmed the utility of insulin degludec in improving glucose variability based on CGM data in T1DM patients. CGM is a standard method of measuring glucose variability which is advocated as a standard of care in the management of T1DM patients. Data from CGM profiling enhance our confidence in the use of the newer basal insulin in clinical practice by providing physiological context to real-world observations [20–22].

For patients with T2DM, priority should be set to identify individuals at higher risk of hypoglycemia, such as elderly individuals with cognitive impairment or patients with chronic kidney disease [2]. These patients could be harmed by the use of complex insulin regimens. From our study, one-third of T2DM patients were offered insulin degludec as a step-down from multiple insulin injections. We found that switching to insulin degludec resulted in clinically significant reductions in reported hypoglycemia, achieving better glycemic control, and improved treatment satisfaction. This finding is of great importance in confirming that the lower rates of hypoglycemia observed in these cases are not achieved at the cost of poor glycemic control. Our previous study in elderly Thai patients with T2DM found that complex insulin regimens and overtreatment still represented major problems for management of older people.

![Fig. 5](image) Changes of level of satisfaction evaluated with 7-point Likert scale over study period.

![Fig. 6](image) a Comparison of a paired 6-day CGM graphic display in a case of brittle T1DM patient who switched from insulin glargine to insulin degludec at 6 weeks later (same total daily insulin dose) b Comparisons of glycemic variability endpoints from paired CGM data in a subset of T1DM patients who switched from insulin glargine to insulin degludec over 4–6 weeks due to brittle diabetes (n = 4).
with diabetes [23]. Safer and simpler basal insulin treatment would be alternative options for elderly patients with frailty as shown in elderly Japanese patients [24, 25]. Regarding the results of QOL scores which did not see any improvement over the study period even the significant reduction in hypoglycemia, we hypothesize that WHOQOL-BREF-THAI might be suitable for general population, but selected group of patients such as our brittle diabetes might need a more specific tool or full WHOQOL tool to capture any change in QOL [26]. However, at least QOL scores in this study showed no further deterioration over 12 months period. Further different tools should be studied to focus QOL in Thai DM patients.

Establishing cost-effectiveness of any novel treatment is important from a healthcare provider’s perspective [27, 28]. Previous studies in Caucasian patients consistently showed incremental cost-effectiveness ratio (ICER) and gained more Quality Adjusted Life Year (QALY) from insulin degludec due to lower rate of hypoglycemia without compromising glycemic control [29, 30]. In the era of value-based healthcare and patients being increasingly mindful of health care-related expenses, additional cost-effectiveness analyses in the context of Thai patients who switch from other basal insulin regimens to insulin degludec should be conducted in future multi-center study to establish the role of insulin degludec and determine the optimal clinical algorithm for healthcare providers in order to consider insulin degludec as the first option in some patients.

Our study has some strength to highlight. To the best of our knowledge, this study is the first prospective real-life experience of insulin degludec in Southeast Asian patients. In addition, this study has subset of T1DM with paired CGM data to verify the effect of insulin degludec toward glycemic variability. However, we acknowledged several limitations. First, the study was limited by its observational design from a single hospital in a private setting located in the central of Bangkok which might limit the generalizability of the findings. Most patients in this study would be considered difficult diabetes patients from their unstable blood glucose levels so the benefits might be over-estimated from this particular group of patients. Second, the sample size was still limited and the length of the present study was relatively short in view of the required lifelong treatment for patients with diabetes; however, this is the longest study to date in Southeast Asian patients. Third, new insulin glargine 300U formulation which became available in Thailand later than insulin degludec (available in late 2017) should be compared in the future real-life study whether both novel insulin analogs are comparable in term of effectiveness and safety as seen in a recent head-to-head clinical trial. In conclusion, our prospective data suggested that effectiveness of insulin degludec was consistent with the results seen in clinical trials with less risk of patient-reported hypoglycemia, and achieve more optimal glycemic control in both patients with T1DM and T2DM. Patients also reported higher treatment satisfaction. More long-term data are needed to establish the role of this ultra-long acting insulin in real-world settings.

Authors’ Contributions
TY performed the statistical analyses, interpreted the data and drafted the manuscript. YB, MA, and BS collected and analyzed all data. YB and CP contributed to the statistical analyses, interpretation of the data and revised the manuscript critically before submission. KS, CT and HT made substantial contributions to the discussion of results. They revised the manuscript critically before submission. All authors read and approved the final manuscript.

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Declarations
Ethics Approval and Consent to Participate
This prospective observational study is approved by the ethics board committee of Theptarin Hospital (No.06/2016). All studied patients gave consent to participate in this study.

Consent For Publication
All authors have contributed significantly to this study and they are in agreement with the consent for publication.

Availability of Data and Material
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Parts of this manuscript had previously been presented as a poster in the 12th International Diabetes Federation Western Pacific Region Congress (IDF-WPR 2018), Kuala Lumpur, Malaysia and also as a poster in the 34th annual meeting of the Royal College of Physicians of Thailand (RCPT) 2018, Chonburi, Thailand.

Conflict of Interest
Authors declare that they have no conflict of interest.

One Sentence Summary: Our data suggested that the effectiveness of insulin degludec in Thai patients with diabetes was consistent with the results seen in clinical trials with less risk of patient-reported hypoglycemia, and a significant improvement in glycemic control. Patients also reported higher treatment satisfaction.
References


