A Prospective, Longitudinal, Multicenter, Observational Study to Assess Insulin Treatment Patterns in Diabetic Patients in Thailand: Results from the TITAN Study

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Objective: *To assess usage patterns, effectiveness, and safety of newly prescribed insulin treatment in patients with diabetes in Thailand.*

Material and Method: *Type 1 or type 2 diabetes mellitus patients who failed achievement of HbA_{1c} <7%, and were about to start or switch to a new insulin treatment were enrolled into this prospective, longitudinal, multicenter, observational study. Data regarding insulin usage pattern, HbA_{1c}, fasting plasma glucose (FPG), and hypoglycemia were collected at enrollment, three and six-month.*

Results: *Between July 2008 and February 2010, 751 patients were recruited. Mean (SD) age was 57.0 (12.8) years. Mean BMI was 26.1 (5.0) kg/m^2. At enrollment, 269 (35.8%), 241 (32.1%), 206 (27.4%), and 35 (4.7%) patients were prescribed neutral protamine Hagedorn (NPH) insulin, long-acting insulin analogues (LAA), premixed insulin (Premixed), and insulin combinations, respectively. Significant HbA_{1c} and FPG reductions were noted at six-month (-1.4% and -56.2 mg/dl, respectively, $p<0.01$). After stratifying patients into three subgroups according to insulin, the patients could continue throughout six months (588 patients, 211 NPH-group, 201 LAA-group, and 176 Premixed-group). Patients in LAA-group attained higher rate of achievement HbA_{1c} <7% without any hypoglycemia (18.9%) than NPH-group (7.1%) and Premixed-group (6.3%; $p<0.001$). Mild-to-moderate hypoglycemic events were reported at 638 events (1.9 events/patient-year) while severe hypoglycemia was reported at 10 events (3.0 event/100 patient-year).*

Conclusion: *In this observational study of real-life clinical practice in Thailand, most common newly prescribed insulin for patients having inadequate glycemic control was NPH, followed by LAA and premixed insulin. More patients on LAA achieved target HbA_{1c} without hypoglycemic events than those on NPH and premixed insulin.*

Keywords: *Hemoglobin A1c, Isophane insulin, Glycemic control, Insulin, Long-acting insulin, Management, Hypoglycemia, Thailand*

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Prevalence of diabetes in Thailand is set to increase from the level of 3.5 million in 2010 (with prevalence adjusted to adult population [20-79 years] of 7.1%) to 5.0 million by 2030 (with an adjusted prevalence of 9.8%)[1,2]. In Asian countries, including Thailand, diabetes has been associated with various microvascular and macrovascular complications, resulting in morbidity and mortality[3-5]. These two complications have been linked to the elevated HbA_{1c} levels among patients with type-2 diabetes[6]. Thailand Diabetic Registry study (2006) reported that 38.2% of patients could achieve fasting plasma glucose (FPG) control of <130 mg/dl and 30.7% could achieve HbA_{1c} <7%[7]. In the DiabCare Asia Thailand study (2007), 28.7% and 19.6% achievement rates for FPG

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<120 mg/dl (6.7 mmol/l) and HbA_{1c} <7%, respectively, were reported[8].

Earlier studies including the Diabetes Control and Complications Trial Research Group (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS), had demonstrated the importance of strict glycemic control in preventing and/or reducing the risk of complications[9,10]. The American Diabetes Association and the European Association for the Study of Diabetes (ADA/EASD) guidelines recommend achieving and maintaining HbA_{1c} at <7%[11]. Medication at the time of diagnosis with metformin in combination with lifestyle changes (medical nutrition therapy and regular exercise), and timely augmentation of the therapy with additional agents including insulin, in patients who do not meet glycemic goals by taking only oral antidiabetic drugs (OADs) were recommended.

Diabetes treatment patterns in Thai patients have been earlier described by the InterASIA in 2003 and by the Thailand Diabetes Registry in 2006[2,12]. However, these studies were cross-sectional in nature, and thus lacked follow-up data for describing effectiveness and safety of each insulin therapy. The present study was a longitudinal study to assess the treatment pattern of insulin usage in patients who initially had inadequate glycemic control in Thailand.

Material and Method

Study design

The Thai Insulin Therapy Assessment Program (TITAN) registry was a 6-month prospective, longitudinal, multicenter, observational study conducted in Thailand. Primary objective was to observe the pattern of insulin usage in patients who failed to achieve target HbA_{1c} <7%. The secondary objectives were 1) to determine the reasons for using each type of insulin, 2) to observe change in HbA_{1c} values, and 3) to observe the frequency of symptomatic hypoglycemic episodes.

The study recruited patients having type 1 or type 2 diabetes mellitus, who failed to achieve target HbA_{1c} <7% with treatment(s) taken before baseline visit, and were started on insulin or, for those who have been using insulin(s) before, switched to another insulin at the baseline visit. Pregnant and breastfeeding women were excluded from the study. Insulin treatment, whether starting or switching, and dose adjustment was at the discretion of participating physicians. The participating physicians were selected from which they were representative of physicians who handled diabetic patients and entitled to prescribe insulin, based on the specialty and the healthcare structure in the participating sites. With this regard, of 41 physicians from 41 study sites, 21 were endocrinologists, 15 were internal medicines, three were cardiologists, and the other two were nephrologists. The patients were recruited by means of consecutive enrollment, and all of them had given their consent before participating to the study.

Data collection

Data were collected from three study visits, at 0, 3, and 6-month (V1, V2, and V3). Data collected on V1 included patient demographics, physical examinations, history of diabetes, HbA_{1c}, FPG, treatment taken on the baseline visit (insulin or OAD), details of new insulin prescribed, and reason for starting or switching to a new insulin. At V2 and V3, data on HbA_{1c}, FPG, changes in the usage of insulin and OAD and their dosages, and hypoglycemic events were recorded. Effectiveness and safety among insulin classes were compared between insulin treatment groups.

This registry was conducted in accordance with the Declaration of Helsinki[13] and guideline for Good Epidemiological Practice in the United States[14]. The protocol was approved by the local Ethics Committees at each study site. All patients provided their consents by signing informed consent form.

Statistical analysis

Patient data were summarized using mean, median, and standard deviation, or using counts and percentages. Quantitative variables were compared by analysis of variance or Student's t-test or Kruskal-Wallis test, depending on data-distribution characteristic. Qualitative variables were compared using Fisher's exact probability or Chi-squared test. Achievements of HbA_{1c} among subgroups were compared by multivariate logistic regression analysis. Statistical analysis was done using 2-tailed test at a 5% level of significance, and performed by using the software package SPSS 15.0 for Windows (SPSS Inc., Chicago, IL).

Sample size calculation

The sample size was calculated to be 674 considering that 60% of patients did not achieve target HbA_{1c}[15], with type 1 error (α) of 5%, CI of 1.96, and an error margin of ± 0.037. Considering the estimated dropout rate of 19%, we planned to recruit 800 patients, in 40 centers nationwide over 12-month period.

Results

Patients

Between July 2008 and February 2010, 751 diabetic patients were recruited from 41 centers. Of these, 729 (97.1%) patients had type 2 diabetes mellitus. The 6-month dropout rate was 6.3%. Majority of patients (78.3%) continued the same insulin they were prescribed at V1 throughout the study period, without crossing-over to other insulin. Patients who did so were stratified into three subgroups, 1) the NPH group (NPH-gr): intermediate acting neutral protamine Hagedorn (NPH) insulin, regardless whether its use was intentionally for a basal replacement or not (n = 211), 2) the long-acting insulin analogue (LAA) group (LAA-gr): long-acting insulin glargine or detemir (n = 201), and 3) the premixed insulin group (Premixed-gr): any short or intermediate insulin mixture, regardless of its formulation (i.e. insulin ratio) or being an insulin analogue (n = 176). The baseline patient characteristics of total as well as subgroup of patients were presented in Table 1. The mean age (SD) of patients was 57.0 (12.8) years and 34.8% of patients were male. Some of the baseline characteristics were imbalanced across the three subgroups, i.e. age, duration of diabetes, which were higher in LAA-gr as compared to NPH-gr, and Premixed-gr, and HbA_{1c}, which was highest in the Premixed-gr.

Overall anti-diabetic treatment

Before enrollment, 426 patients (56.7%) were insulin naïve. According to the study protocol, these patients were considered on the transition to insulin initiation. With this regard, the majority of them (59.6%) had been receiving two OAD items before the transition, while the others 23.7%, 12.7%, and 2.8% had the OAD with three, one, and four items, respectively. Sulfonylurea was the most common used OAD (93.8%), followed by metformin (81.5%) and thiazolidinedione (24.2%). At enrollment, about a half of the insulin naïve patients started with NPH insulin (50.5%), followed by LAA (35.0%), and premixed insulin (14.1%). Paths of insulin usage and 6-month continuation rates of the insulin patients received at V1 were shown in Table 2. The continuation rate was highest for patients starting with LAA (85.2%).

Among 325 patients who had been receiving at least one insulin before the enrollment, the most common insulin previously received was NPH (154 patients, 47.4%), followed by premixed insulin (39.1%) and LAA (12.3%), respectively. Subsequent paths of new insulin usages and their 6-month continuations (adhered to the insulin patients received at V1) were shown in Table 2. The 6-month continuation rates for the individual insulin that patients received at V1 varied between 67.3% and 100%.

Insulin treatments among the insulin subgroups

The data on insulin treatment in subgroup patients were presented in Table 3. Majority of insulin prescribed to the LAA-gr were glargine (93.5% at V1), while in the Premixed-gr, the majority (83.0% at V1) was 70%NPH/30%-regular insulin. Median dosage

Table 1. Baseline characteristics in total and subgroup patients

Characteristics	Total (n = 751)	By group stratifications (n = 588)			
		NPH-group (n = 211)	LAA-group (n = 201)	Premixed-group (n = 176)	*p*-value*
Male, n (%)	261 (34.8)	52 (24.6)	73 (36.3)	70 (39.8)	0.004[a]
Age (SD) (years)	57.0 (12.8)	54.2 (12.6)	61.6 (11.8)	54.7 (12.7)	<0.0001
Waist circumference (SD) (cm)					
Male	92.0 (12.2)	91.7 (10.7)	91.6 (10.1)	93.0 (12.8)	0.728
Female	90.5 (11.9)	89.8 (11.7)	91.5 (11.7)	90.3 (11.7)	0.467
BMI (SD) (kg/m^2)	26.2 (5.0)	26.2 (4.8)	26.4 (4.6)	26.3 (5.1)	0.9
Duration of diabetes (median, IQR) (year)	8.8 (4.6, 13.4)	7.5 (4.2, 10.9)	10.2 (6.3, 14.8)	8.2 (4.6, 13.4)	0.0001[b]
HbA_{1c} (SD) (%)	10.0 (1.9)	9.9 (1.8)	9.9 (1.9)	10.4 (1.9)	0.006
FPG (SD) (mg/dl)	211.5 (78.8)	208.3 (68.5)	207.8 (68.9)	211.8 (98.4)	0.868

NPH = neutral protamine Hagedorn; LAA = long-acting insulin analogues; Premixed = premixed insulin; BMI = body mass index; FPG = fasting plasma glucose

All values are mean (SD), unless otherwise specified

* Calculated by ANOVA, [a] Chi-square, [b] Kruskal-Wallis test

Table 2. Treatment paths in total patients during 6-month study period (n = 751)

Path of insulin use among patients who were insulin naïve prior to enrollment visit				
	Insulin initiation	At enrolment* n (%)	At 6 months n	Continuation rate** (%)
Insulin naïve (n = 426)	NPH	215 (50.5)	168	78.1
	LAA	149 (35.0)	127	85.2
	Premixed	60 (14.1)	48	80.0
	Insulin combination+	2 (0.4)	NA	NA
Path of insulin use among patients who experienced one or more insulin before enrollment				
Insulin before enrollment	Insulin newly prescribed	At enrolment* n (%)	At 6 months n	Continuation rate* (%)
NPH (n = 154)	NPH	5 (3.2)	5	100.0
	LAA	37 (24.0)	35	94.6
	Premixed	109 (70.8)	96	88.1
LAA (n = 40)	NPH	12 (30.0)	10	83.3
	LAA	4 (10.0)	4	100.0
	Premixed	10 (25.0)	8	80.0
	Insulin combination+	14 (35.0)	NA	NA
Premixed (n = 127)	NPH	37 (29.1)	28	75.7
	LAA	49 (38.6)	33	67.3
	Premixed	26 (20.5)	23	88.5
	Insulin combination+	15 (11.8)	NA	NA
Insulin combination+ (n = 4)	LAA		2 (50.0)	
	Premixed		1 (25.0)	

NA = not applicable

* Percentages in parenthesis were calculated from dividing number of subjects at enrollment visit by number of subjects allocated to each categorized path in beginning (numbers shown in left-most column), and multiplying with 100

** Continuation rates of each path were calculated from dividing number of subjects at 6-month visit by number of subjects at enrollment visit, within each path, and multiplying with 100

+ Insulin combination; patients were treated with short-acting insulin or any combination among NPH, LAA and Premixed

were highest in the Premixed-gr (up to 38 units/day at V3), meanwhile the dosage increment was highest carried out in the LAA-gr, of which the median dose was increased from 12 units/day at V1 to 20 units/day at V3. Subgroup with the lowest use of OAD combination was the Premixed-gr (varied between 67.0%- 74.4% over time).

Effectiveness of insulin treatments in total and in insulin subgroups

Glycemic control

Table 3 showed data on glycemic controls in total and in subgroup patients. The mean FPG level in total patients decreased from 221.5 mg/dl at V1 to 155.3 mg/dl at V3 (6-month FPG reduction of -56.2 mg/dl, $p = 0.001$). By subgroups, the 6-month FPG reductions were -62.9 mg/dl for LAA-gr, -56.4 mg/l for NPH-gr and -42.8 mg/l for Premixed-gr ($p = 0.031$ for LAA-gr versus Premixed-gr). For the HbA_{1c} values, mean HbA_{1c} were also significantly decreased from V1 to V3 (-1.4%; decreased from 10.1% at V1 to 8.7%, $p = 0.008$). Comparing among subgroups, proportion of patients who attained HbA_{1c} <7% at 6 months was higher in the LAA-gr (21.9%) than in Premixed-gr (8.0%) and NPH-gr (7.6%) ($p<0.001$, Table 3). In a multivariate analysis adjusted for age, duration of diabetes, sex, systolic blood pressure, and body mass index, including HbA_{1c} at baseline, assignment to LAA-gr was a factor associated with HbA_{1c} <7% achievement at 6 months, as compared to those who were assigned to NPH-gr (odd ratio 3.2, 95% confidence interval 1.69, 6.06) (Table 4).

A well-controlled FPG does not always reflect a good quality of glycemic control. With this regard, 161 patients who already had achieved a well-controlled FPG of less than 110 mg/dl at six-month were analyzed for frequency of residual uncontrolled

Table 3. Insulin treatment, glycemic control, and hypoglycaemia

	Subgroup	At enrolment	3 months (V2)	6 months (V3)
Insulin treatment				
Number of subjects using specified molecule	NPH-group	n = 211 for entire NPH-group		
	LAA-group	n = 201 for entire LAA-group		
	Glargine	188	185	186
	Detemir	13	16	15
	Premixed-group	n = 176 for entire Premixed-group		
	75/25 lispro[a]	1	3	3
	75/25 aspart[b]	29	27	27
	70/30[c]	146	146	146
Median dose (IQR) (unit/day)	NPH- group	10 (6, 10)	12 (10, 18)	14 (10, 20)
	LAA- group	12 (10, 20)	18 (10, 26)	20 (12, 28)
	Premixed-group	32 (22, 50)	36 (26, 50)	38 (26, 54)
OAD combination, n (%)	NPH-group	189 (89.6)	189 (89.6)	190 (90.0)
	LAA-group	167 (83.1)	173 (86.1)	171 (85.1)
	Premixed-group	118 (67.0)	129 (73.3)	131 (74.4)
Glycemic control				
Mean FPG (SD) (mg/dl)	NPH-group	208.3 (68.5)	167.2 (64.6)	151.9 (61.1)*
	LAA-group	207.8 (68.9)	159.0 (59.2)	144.9 (53.7)*
	Premixed-group	211.8 (98.4)	170.9 (69.0)	169.0 (78.6)*
	Entire study cohort[f]	211.5 (78.8)	166.2 (66.4)	155.3 (65.1)
Number of subjects with FPG <110 mg/dl (%)	NPH-group	8 (3.8)	31 (14.7)	53 (25.1)
	LAA-group	10 (5.0)	30 (14.9)	53 (26.4)
	Premixed-group	22 (12.5)	29 (16.5)	32 (18.2)
	Entire study cohort[f]	47 (6.3)	109 (14.5)	161 (21.4)
Mean HbA_{1c} (SD) (unit in %)	NPH-group	9.9 (1.8)*	9.0 (1.9)	8.7 (1.6)
	LAA-group	9.9 (1.9)*	8.9 (1.9)	8.5 (1.7)
	Premixed-group	10.4 (1.9)*	9.3 (1.9)	9.0 (1.9)
	Entire study cohort[f]	10.1 (1.9)	9.1 (2.0)	8.7 (1.8)
Number of subject with HbA_{1c} <7% (%)	NPH-group	-	18 (8.5)	16 (7.6)*
	LAA-group	-	13 (6.5)	44 (21.9)*
	Premixed-group	-	9 (5.1)	14 (8.0)*
	Entire study cohort[f]	-	48 (6.4)	96 (12.8)
6-month hypoglycemia				
Number of mild-to-moderate events[d]	NPH-group	291 (2.9 per person-year)		
	LAA-group	140 (1.5 per person-year)		
	Premixed-group	90 (1.1 per person-year)		
	Entire study cohort[f]	638 (1.9 per person-year)		
Number of severe events[e]	NPH-group	1 (1.0 per 100 person-years)		
	LAA-group	2 (2.1 per 100 person-years)		
	Premixed-group	6 (7.2 per 100 person-years)		
	Entire study cohort[f]	10 (3.0 per 100 person-years)		

[a] 25% lispro/75% lispro protamine, [b] 25% aspart/75% aspart protamine, [c] 30% RI/70% NPH

[d] Symptomatic but not need the external assistance, with or without blood glucose level of <70 mg/dL or with/without blood sugar measurement

[e] Required assistance from another person as a result of hypoglycemia, regardless with/without blood sugar measurement, but the recovery attributable to restoration of blood glucose to normal

[f] Projected to entire 751 study population for which summation of subject numbers from 3 subgroups did not fully cover

* $p<0.01$, compared across 3 insulin groups at the visit

Table 4. Multivariate analysis for achievement of HbA_{1c} <7% at the 6-month visit

	Adjusted OR[a]	95% CI		*p*-value
		Lower	Upper	
NPH	1.00			
LAA	3.20[b]	1.69	6.06	<0.001
Premixed	1.24[b]	0.58	2.66	0.575
HbA_{1c} at baseline (%)	0.84	0.72	0.99	0.032
Age (years)	1.04	1.01	1.06	0.006
Duration of DM (years)	0.95	0.90	0.99	0.015

DM = diabetes mellitus; BP = blood pressure
[a] Adjusted for HbA_{1c} at baseline, age, duration of DM, sex, systolic BP, and BMI
[b] Relative with NPH

HbA_{1c}. At the goal of HbA_{1c} <7%, 72.0% (116 patients) did not meet this goal. When considering by insulin subgroups, 64.2% of 53 patients in LAA-gr who were already at a well-controlled FPG remained unmet in the HbA_{1c} target, meanwhile 73.6% out of 53 patients from NPH-gr, and 84.4% out of 32 patients from Premixed-gr still did not meet this demand. Although these residual unmet HbA_{1c} controls tended to be lesser in the LAA-gr, the difference was not statistically significant ($p = 0.17$).

Tolerability of insulin treatments

One hundred twenty three patients (16.4% by total) experienced at least one hypoglycemic episode during 6-month study period. The proportions of patients under this consideration were similar across subgroups (Premixed-gr: 17.6%, LAA-gr: 13.4%, and NPH-gr: 12.8%; $p = 0.357$). When considering on the number of events, 638 mild-to-moderate hypoglycemic events (equivalent to 1.9 events/person-year) and 10 severe hypoglycemic events (0.03 events/person-year) were reported. Incidence rate by subgroups were shown in Table 3. Weight gains were noted at 6-month in all groups. However, the gains were not significantly different across the subgroups (ranging 0.8-1.2 kg).

Glycemic control without hypoglycemia

Proportion of patients who achieved HbA_{1c} <7% without any hypoglycemic events during six months was higher in LAA-gr (18.9%), as compared with NPH-gr (7.1%) and Premixed-gr (6.3%) (p<0.001). However, at cut-off HbA_{1c} <6.5%, proportions of patients attaining this target was similar across subgroups (Fig. 1).

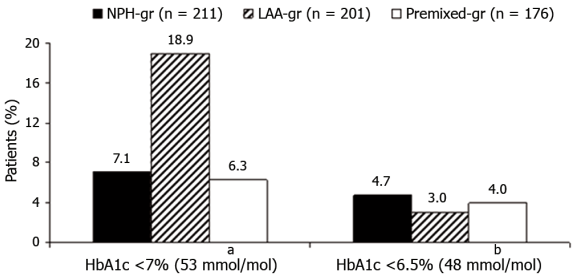

Fig. 1 Patients attaining target HbA_{1c} without any hypoglycemic events at the 6-month visit.
[a] p<0.001, [b] $p = 0.655$

Reasons for using each type of insulin

Among insulin-naïve patients, the lack of efficacy of current treatment (52.8%) was the most common reason for starting insulin, followed by poor glycemic control (14.3%), poor diet control (11.5%), and poor compliance (7.5%). As well as the insulin naïve patients, the most common reason for switching to other insulin among patients previously treated with insulin was the lack of efficacy of current treatment (80.3%). However, second most common reason was not the same across subgroups. In patients formerly used NPH, the second most common reason was hypoglycemia (11 out of 146 patients) and for those who formerly used LAA and who formerly used premixed insulin, the second most common reason was patients' dissatisfaction (5 out of 22 patients) and hypoglycemia (20 out of 146 patients), respectively. The data on reasons for starting with or switching to new insulin were shown in Supplementary Table 1.

Discussion

In this real-world study on insulin treatments, many aspects of result can be discussed as following:

Firstly, there was a substantial number of insulin naïve patients at the enrollment (426 patients, 56.7%), and thus obtainable data would reflect insulin managements at the circumstance when physicians started insulin treatment to their patients. With this regard, NPH insulin accounted for about half (50.5%) of insulin initiation. Assuming that the NPH insulin was intentionally used for basal insulin replacement purpose, as to the LAA does, the overall basal insulin replacement strategy (basal strategy) would be up to 85.5%, and thus reflecting higher popularity of basal than the premixed strategy among Thai physicians in

Supplementary Table 1. Summary of reasons for starting or switching to new insulin treatment at enrollment (all values are n (%))

Reasons for using new insulin	Insulin-naive patients				Prior insulin users					
	With any insulin (n = 426)	With NPH insulin (n = 215)	With LAA (n = 149)	With premix insulin (n = 60)	Formerly used NPH insulin and changed to		Formerly used LAA and changed to		Formerly used premix insulin and changed to	
					LAA (n = 37)	Premix insulin (n = 109)	NPH insulin (n = 12)	Premix insulin (n = 10)	NPH insulin (n = 37)	LAA (n = 48)
Poor glycemic control	61 (14.3)	27 (12.6)	25 (16.8)	9 (15.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.1)
Side effect	1 (0.2)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Unsuitable for OAD	13 (3.1)	3 (1.4)	3 (2.0)	7 (11.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (10.0)	0 (0.0)	0 (0.0)
Poor diet control	49 (11.5)	20 (9.3)	18 (12.1)	11 (18.3)	0 (0.0)	2 (1.8)	1 (8.3)	0 (0.0)	0 (0.0)	2 (4.2)
Diabetic complications	13 (3.1)	8 (3.7)	2 (1.3)	2 (3.3)	0 (0.0)	2 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.1)
Patient dissatisfaction	2 (0.5)	1 (0.5)	1 (0.7)	0 (0.0)	4 (10.8)	0 (0.0)	4 (33.3)	1 (10.0)	1 (2.7)	2 (4.2)
Allergy	1 (0.2)	2 (0.9)	2 (1.3)	3 (5.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hypoglycemia	7 (1.6)	2 (0.9)	2 (1.3)	3 (5.0)	7 (18.9)	4 (3.7)	0 (0.0)	1 (10.0)	9 (24.3)	11 (22.9)
Poor compliance	32 (7.5)	8 (3.7)	11 (7.4)	13 (21.7)	5 (13.5)	0 (0.0)	1 (8.3)	0 (0.0)	3 (8.1)	11 (22.9)
Weight gain	1 (0.2)	1 (0.5)	0 (0.0)	0 (0.0)	1 (2.7)	0 (0.0)	1 (8.3)	0 (0.0)	1 (2.7)	1 (2.1)
Lack of efficacy of current treatment	225 (52.8)	134 (62.3)	74 (49.7)	16 (26.7)	28 (75.7)	105 (96.3)	7 (58.3)	7 (70.0)	32 (86.5)	29 (60.4)

OAD = oral antidiabetic drug

these circumstances. High adoption level of the Thai physicians to guidelines at the time (e.g. the Thai guideline for diabetes management 2008[16], which suggested basal insulin before premixed insulin in stepwise management of T2DM) or otherwise, fewer injection frequency and simplicity of titration of the basal insulin[17] were among the possible reasons underpinning the popularity of basal strategy.

Secondly, the study had observed insulin usages for a period of 6-month. Although a variety of insulin patterns over the study period were observed, only some patterns were shared in common, as shown in Table 2. This variety reflected real-world appropriateness of treatment for individual patient i.e. patients who had poor glycemic control, undesirable effects, patients' satisfaction and acceptance, etc.

Thirdly, subgroup stratification was applied to compare treatment effectiveness and safety among the insulin classes. As a result, proportion of patients who achieved HbA_{1c} <7% was significantly higher in LAA-gr than NPH-gr and Premixed-gr (Table 4). According to internal evidence of the study, it was likely that higher incremental dose over 6 months of the LAA-gr (median 8 units vs. 4 units of NPH-gr and 6 units of Premixed-gr, Table 3) might contribute to this higher achievement.

It should be noted from current study that a remarkable number of patients (87.2%) were still unmet for the HbA_{1c} target of less than 7% at 6-month despite having had insulin treatment. Factors known to influence a successive glycemic control in insulin users were treatment adherence[18] and injection omission[19], for instance. However, these two factors depended on patients and were not assessed in the present study. Nevertheless, small amount of insulin dosage increment (4 to 8 units over 6 months) seems to be an obvious issue for further study. Moreover, another reason for the unmet target HbA_{1c} might be attributable to the inadequacy in postprandial control of plasma glucose. Among patients who achieved FPG control (less than 110 mg/dl), 72% of them still had HbA_{1c} over 7.0%. The latter finding called for attention on monitoring and management of postprandial plasma glucose.

The ADA/EASD guidelines highlight the need for early addition of insulin therapy in patients that are not meeting their glycemic goals[20]. According to these guidelines, basal insulin (intermediate- or long-acting insulin) should be used to initiate insulin therapy in patients inadequately controlled on OAD(s). Among basal insulin, LAAs, when compared to NPH insulin,

have been associated with lower overall and nocturnal hypoglycemia due to relative peak-less time-action curves[21]. Switching to LAAs from previously used premixed insulin regimen in patients having inadequate glycemic control, had shown significant improvement in glycemic control with a low incidence of hypoglycemia, along with increased feasibility and convenience[22-24]. Similarly, use of LAAs in patients inadequately controlled on NPH insulin, had also shown to improve glycemic control as well as quality of life, without increasing hypoglycemia[25-27]. Earlier studies have reported ease in titrating doses of LAAs, which also facilitates patient-directed titration[28], as well as low incidence of hypoglycemia[21,29]. Our study re-iterated earlier findings with the LAA-gr showing higher continuation rate, lower FPG levels, and more number of patients achieving target HbA_{1c} without any hypoglycemic event during six months. Additionally, the high increase in dosage of LAAs in our study could be attributed to the physicians' perception of low hypoglycemic rate associated with LAAs.

In conclusion, in the present observational study of clinical practice on insulin usage pattern in patients who had inadequate glycemic control in Thailand, NPH insulin was the most common insulin initiated to insulin-naïve patients, and was also the most common insulin previously used in insulin-experienced patients. However, regard to effectiveness/safety observation, the LAA treatment demonstrated a better advantage in diabetic control as having higher success rate of achieving HbA_{1c} target without clinically significant hypoglycemia risk as compared to other insulin regimens.

Strengths and limitations

The results of the present observational study conducted in Thailand reflect the real-life clinical management of diabetic patients with inadequate glycemic control and provide important information on effectiveness and hypoglycemic events with insulin treatment in large heterogeneous populations. Since the study was non-randomized in nature, a number of limitations and biases would be present. These included the selection bias for newly prescribed insulin were noted per the physicians' perception which depended on various reasons, and as such, causality-relationship between treatments and outcomes should be carefully interpreted. Since the measurements of HbA_{1c}, FPG, and other clinical measurements were performed in different laboratories/hospitals, there might be inter-laboratory variations.

What is already known on this topic?

Treatment with insulin has been well adopted into several guidelines as an advanced step of blood glucose control in type 2 diabetes mellitus (DM), as well as the main therapy for the type 1 DM. Insulin management plays a critical role in blood glucose control. However, in real-life practice, the insulin management is highly complex, as it requires a holistic consideration for the treatment individually depends on the context of each patient and each country. As such, understanding insulin management pattern is an important step of knowledge accumulation paving the way to improve the glycemic control in Thai patients. Although diabetic treatment patterns have been explored before in some other studies, they were cross-sectional in nature, and thus lacking information related to the longitudinal outcomes. In current study, the insulin management patterns were studied in a prospective manner, of which the findings would serve additional knowledge to the medical society.

What this study adds?

This study reflects real-life insulin usage patterns in Thai diabetic patients, which include insulin types, frequency of oral hypoglycemic agent co-administrations, patient's characteristics respond to insulin, and dosage patterns, etc. With its longitudinal design, the study has assessed the glycemic control outcomes, including hypoglycemia, for which the data were globally analyzed or analyzed by subgroups according to the types of insulin.

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Potential conflicts of interest

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References

1. Shaw JE, Sicree RA, Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. Diabetes Res Clin Pract 2010; 87: 4-14.
2. Aekplakorn W, Stolk RP, Neal B, Suriyawongpaisal P, Chongsuvivatwong V, Cheepudomwit S, et al. The prevalence and management of diabetes in Thai adults: the international collaborative study of cardiovascular disease in Asia. Diabetes Care 2003; 26: 2758-63.
3. Nitiyanant W, Tandhanand S, Mahtab H, Zhu XX, Pan CY, Raheja BS, et al. The Diabcare-Asia 1998 study--outcomes on control and complications in type 1 and type 2 diabetic patients. Curr Med Res Opin 2002; 18: 317-27.
4. Sriwijitkamol A, Moungngern Y, Vannaseang S. Assessment and prevalences of diabetic complications in 722 Thai type 2 diabetes patients. J Med Assoc Thai 2011; 94 (Suppl 1): S168-74.
5. Pratipanawatr T, Rawdaree P, Chetthakul T, Bunnag P, Ngarmukos C, Benjasuratwong Y, et al. Thailand Diabetic Registry cohort: predicting death in Thai diabetic patients and causes of death. J Med Assoc Thai 2010; 93 (Suppl 3): S12-20.
6. Gerich JE. The importance of tight glycemic control. Am J Med 2005; 118 (Suppl 9A): 7S-11S.
7. Rawdaree P, Ngarmukos C, Deerochanawong C, Suwanwalaikorn S, Chetthakul T, Krittiyawong S, et al. Thailand diabetes registry (TDR) project: clinical status and long term vascular complications in diabetic patients. J Med Assoc Thai 2006; 89 (Suppl 1): S1-9.
8. Nitiyanant W, Chetthakul T, Sang-A-kad P, Therakiatkumjorn C, Kunsuikmengrai K, Yeo JP. A survey study on diabetes management and complication status in primary care setting in Thailand. J Med Assoc Thai 2007; 90: 65-71.
9. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993; 329: 977-86.
10. Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ 2000; 321: 405-12.
11. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al. Management of hyperglycaemia in type 2 diabetes: a patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia 2012; 55: 1577-96.
12. Kosachunhanun N, Benjasuratwong Y, Mongkolsomlit S, Rawdaree P, Plengvidhya N, Leelawatana R, et al. Thailand diabetes registry project: glycemic control in Thai type 2 diabetes and its relation to hypoglycemic agent usage. J Med Assoc Thai 2006; 89 (Suppl 1): S66-71.

13. World Medical Association Declaration of Helsinki ethical principles for medical research involving human subjects [Internet]. 2008 [cited 2013 Mar 6]. Available from: http://www.wma.net/en/30publications/10policies/b3/17c.pdf
14. International Society for Pharmocoepidemiology. Guidelines for good epidemiology practices for drug, devise, and vaccine research in the United States [Internet]. 2007 [cited 2013 Feb 19]. Available from: https://www.pharmacoepi.org/resources/guidelines_08027.cfm
15. Ringborg A, Cropet C, Jonsson B, Gagliardino JJ, Ramachandran A, Lindgren P. Resource use associated with type 2 diabetes in Asia, Latin America, the Middle East and Africa: results from the International Diabetes Management Practices Study (IDMPS). Int J Clin Pract 2009; 63: 997-1007.
16. Diabetes Association of Thailand. Thai guideline for the diabetes management [Internet]. 2008 [cited 2014 Oct 7]. Avialable from: http://drug.pharmhcu.com/guideline/diabetes.pdf
17. Vaag A, Lund SS. Insulin initiation in patients with type 2 diabetes mellitus: treatment guidelines, clinical evidence and patterns of use of basal vs premixed insulin analogues. Eur J Endocrinol 2012; 166: 159-70.
18. Cramer JA, Pugh MJ. The influence of insulin use on glycemic control: How well do adults follow prescriptions for insulin? Diabetes Care 2005; 28: 78-83.
19. Peyrot M, Rubin RR, Kruger DF, Travis LB. Correlates of insulin injection omission. Diabetes Care 2010; 33: 240-5.
20. Nathan DM, Buse JB, Davidson MB, Ferrannini E, Holman RR, Sherwin R, et al. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2009; 32: 193-203.
21. Horvath K, Jeitler K, Berghold A, Ebrahim SH, Gratzer TW, Plank J, et al. Long-acting insulin analogues versus NPH insulin (human isophane insulin) for type 2 diabetes mellitus. Cochrane Database Syst Rev 2007; (2): CD005613.
22. Sharplin P, Gordon J, Peters JR, Tetlow AP, Longman AJ, McEwan P. Switching from premixed insulin to glargine-based insulin regimen improves glycaemic control in patients with type 1 or type 2 diabetes: a retrospective primary-care-based analysis. Cardiovasc Diabetol 2009; 8: 9.
23. Gomez-Peralta F, Carraminana-Barrera F, Felix-Redondo FJ, Fraile-Gomez J. Glycaemic control in patients with type 2 diabetes switching from premixed insulin to long-acting basal insulin analogue plus oral antidiabetic drugs: an observational study. Int J Clin Pract 2012; 66: 959-68.
24. Yang W, Lv X, Li Q, Jia W, Tian H. A prospective study to optimize insulin treatment by switching to insulin glargine in type 2 diabetic patients previously uncontrolled on premixed insulin: the optimization study. Curr Med Res Opin 2012; 28: 533-41.
25. Sharplin P, Gordon J, Peters JR, Tetlow AP, Longman AJ, McEwan P. Improved glycaemic control by switching from insulin NPH to insulin glargine: a retrospective observational study. Cardiovasc Diabetol 2009; 8: 3.
26. Kanazawa Y, Igarashi Y, Komiya K, Sakurai Y, Shimizu T, Fujitani Y, et al. Long-term efficacy of insulin glargine after switching from NPH insulin as intensive replacement of basal insulin in Japanese diabetes mellitus. Comparison of efficacy between type 1 and type 2 diabetes (JUN-LAN Study 1.2). Endocr J 2007; 54: 975-83.
27. Oishi M, Abe N, Yokoyama H, Kuribayashi N, Tomonaga O, Matoba K, et al. Observational 6-month open-label study of Japanese type 2 diabetes patients switching from NPH insulin to insulin detemir in basal-bolus regimen: 23rd article of the Japan Diabetes Clinical Data Management Study Group (JDDM23). J Int Med Res 2012; 40: 787-97.
28. Blonde L, Merilainen M, Karwe V, Raskin P. Patient-directed titration for achieving glycaemic goals using a once-daily basal insulin analogue: an assessment of two different fasting plasma glucose targets - the TITRATE study. Diabetes Obes Metab 2009; 11: 623-31.
29. Warren E, Weatherley-Jones E, Chilcott J, Beverley C. Systematic review and economic evaluation of a long-acting insulin analogue, insulin glargine. Health Technol Assess 2004; 8: iii, 1-57.

การศึกษาเชิงสังเกตสหสถาบันแบบไปข้างหน้า เพื่อศึกษารูปแบบการรักษาด้วยอินซูลินในผู้ป่วยเบาหวานในประเทศไทย: ผลการศึกษาจากโครงการ TITAN

เพชร รอดอารีย์, วีระศักดิ์ ศรินนภากร, สมชาย พัฒนอางกุล, วีรพันธุ์ โชวิฑูรกิจ, พจน์ ตันนิรันดร, ธวัชชัย พีรพัฒน์ดิษฐ์

วัตถุประสงค์: *เพื่อศึกษารูปแบบการรักษา ประสิทธิภาพ และความปลอดภัยของผู้ป่วยเบาหวานที่เริ่มใช้อินซูลินในการรักษาในประเทศไทย*

วัสดุและวิธีการ: *การศึกษาเป็นแบบเชิงสังเกตไปข้างหน้า สหสถาบัน โดยคัดเลือกผู้เข้าร่วมโครงการที่เป็นเบาหวานชนิดที่ 1 หรือชนิดที่ 2 ที่ไม่สามารถควบคุมระดับฮีโมโกลบินเอวันซี (HbA1c) ให้ได้น้อยกว่า 7% ที่แพทย์พิจารณาให้ใช้อินซูลินหรือเปลี่ยนชนิดของอินซูลินในการรักษา ผู้เข้าร่วมโครงการศึกษาทุกรายจะได้รับรายละเอียดของโครงการ และลงชื่อยินยอมเข้าร่วมโครงการโดยสมัครใจ ข้อมูลพื้นฐาน รูปแบบการใช้อินซูลิน ระดับ HbA1c ระดับน้ำตาลในน้ำเลือดขณะอดอาหาร (FPG) และภาวะระดับน้ำตาลต่ำในเลือด จะทำการเก็บในวันที่ผู้ป่วยเข้าร่วมโครงการศึกษา ที่ 3 เดือน และ 6 เดือน ตามลำดับ*

ผลการศึกษา: *ระหว่างเดือนกรกฎาคม พ.ศ. 2551 ถึง กุมภาพันธ์ พ.ศ. 2553 มีผู้ป่วยที่ถูกคัดเลือกเข้าในโครงการศึกษาทั้งหมด 751 ราย อายุเฉลี่ย 57 ปี (ค่าเบี่ยงเบนมาตรฐาน 12.8 ปี) ค่าดัชนีมวลกาย 26.1 (ค่าเบี่ยงเบนมาตรฐาน 5.0) กก./ตร.ม. ในวันที่เริ่มโครงการ มีผู้ป่วยที่ใช้อินซูลิน NPH 269 ราย (ร้อยละ 35.8) อินซูลิน long-acting insulin analogue (LAA) 241 ราย (ร้อยละ 32.1) อินซูลิน premixed 206 ราย (ร้อยละ 27.4) และการใช้อินซูลินแบบผสมผสาน 35 ราย (ร้อยละ 5.7) เมื่อสิ้นสุดโครงการศึกษาที่ 6 เดือน พบว่าผู้ป่วยในโครงการทั้งหมดมีระดับ HbA1c และ FPG ลดลงอย่างมีนัยสำคัญทางสถิติ (1.4% และ 56.2 มก./มล. ตามลำดับ มีค่า $p<0.01$) เมื่อแบ่งผู้ป่วยเป็น 3 กลุ่ม ตามชนิดของอินซูลินที่ผู้ป่วยได้รับโดยต่อเนื่องตลอดการศึกษาจำนวนทั้งสิ้น 588 ราย (1) กลุ่ม NPH (NPH-group) จำนวน 211 ราย (2) กลุ่ม LAA (LLL-group) จำนวน 201 ราย และ (3) กลุ่ม premixed (Premixed-group) จำนวน 176 ราย พบว่าผู้ป่วยในกลุ่ม LAA-group มีอัตราส่วนผู้ป่วยที่สามารถควบคุมระดับ HbA1c ที่ <7% โดยไม่มีประสบการณ์น้ำตาลในเลือดต่ำ ร้อยละ 18.9 ซึ่งมากกว่าในกลุ่ม NPH-group (ร้อยละ 7.1) และกลุ่ม Premixed-group (ร้อยละ 6.3); $p<0.001$ ภาวะระดับน้ำตาลในเลือดต่ำเล็กน้อยถึงปานกลางถูกรายงาน 638 ครั้ง (1.9 ครั้ง/ปี-ผู้ป่วย) ในขณะที่ภาวะระดับน้ำตาลต่ำรุนแรงถูกรายงาน 10 ครั้ง (0.03 ครั้ง/ปี-ผู้ป่วย)*

สรุป: *การศึกษาเชิงสังเกตในการทำเวชปฏิบัตินี้พบว่าอินซูลินที่แพทย์สั่งใช้ในการรักษาผู้ป่วยที่ไม่สามารถควบคุมระดับน้ำตาลได้ บ่อยที่สุดคือ อินซูลิน NPH อินซูลิน LAA และ อินซูลิน premixed ตามลำดับ ผู้ป่วยที่ได้รับ LAA สามารถควบคุมระดับ HbA1c ตามเป้าหมายโดยไม่มีภาวะระดับน้ำตาลต่ำในเลือดได้มากกว่าผู้ป่วยที่ใช้อินซูลิน NPH และ อินซูลิน premixed*