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Naturalistic Evaluation of Hypoglycemic Events in Diabetic Subjects (NEEDS STUDY)

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Abstract

Objective: Patients with type 2 diabetes mellitus (T2DM) often experience hypoglycemia and weight gain due to treatment side effects. Sulfonylurea (SU) or combined SU and metformin (SU+MET) has been frequently prescribed among the patients with longstanding disease. This study aimed to assess the glycemic goal attainment rates, hypoglycemic episodes, weight gain, and treatment compliance among T2DM patients receiving SU monotherapy or SU+MET.

Research Design and Methods: A multicenter cross-sectional, retrospective review study was conducted in 5 tertiary care hospitals, Thailand. The well-defined T2DM patients aged 30 or over in general practice were included consecutively during a 12-month period. Glycemic control, experiences of hypoglycemia, weight gain and compliance were evaluated. Glycemic goal attainment was a hemoglobinA_{1c} (HbA_{1c}) level less than 7%.

Results: Out of the 659 patients (mean age (±SD)), 65.5 (10.0) years and median duration of T2DM (IQR), 10 (5-15) years), 313 (47.5%) achieved the glycemic goal. Goal attainment was significantly lower among patients treated with SU+MET than those treated with SU alone (43.5% vs. 63.0%; Odd Ratio (OR): 0.45, 95%CI: 0.31, 0.66, p <0.001). HbA_{1c} levels were significantly lower among patients with goal attainment (6.3±0.5 vs 8.1±1.2%, p <0.001). One-third of patients reported experiencing hypoglycemia (30.7%) and weight gain (35.4%). Weight gain in the patients receiving SU+MET was lower than those receiving SU alone (33.1% vs 44.6%, p =0.015), but there was no difference for hypoglycemic events. Major events in the previous 12 months were experienced by 68 patients, most commonly congestive heart failure and ischemic heart disease. Approximately half of the patients (52.2%) reported not always taking their medication as prescribed.

Conclusions: Among T2DM patients receiving SU or SU+MET, only about half of the patients achieved glycemic goal and compliance with the treatment. Hypoglycemia and weight gain posed a more significant burden and weight gain was related to SU alone.

Strengths and limitations of this study

- The study was conducted with a Thai T2DM patient population. The patients were well-defined T2DM patients treated with Sulfonylurea (SU) monotherapy or combined SU and Metformin for at least 6 months by an endocrinologist, cardiologist, nephrologist or family practitioner.
- Glycemic goal attainment and clinical laboratory results in this study were naturalistic results. Hypoglycaemia, worry of hypoglycaemia, weight gain, fear of weight gain and compliance with medication were from the patient self-reporting. The factors related to glycemic goal attainment, hypoglycemic and weight gain were collected and presented.
- The study was carried out in tertiary care hospitals, so the results may not able to be generalized to patients of other hospital levels. The observational nature of this study does not rule out the role of residual confounding variables in observed associations. Use of the patient surveys and self-reported treatment experiences generally underestimate hypoglycemia associated with oral hypoglycemic agents.

BACKGROUND

Type 2 diabetes mellitus (T2DM) is the most common form of DM, accounting for approximately 90% of all cases diagnosed worldwide. The clinical heterogeneity of T2DM patients, in terms of characteristics such as duration of diabetes and comorbid illnesses greatly increases the challenge of providing care[1]. A longer duration of diabetes is associated with more complications and more difficulty maintaining glycemic control. The American Diabetes Association (ADA) [2] and Diabetes Association of Thailand recommends a hemoglobinA1C (HbA1c) target <7.0% for most patients and for patients with HbA1c >9%; a combination of two or more oral hypoglycemic agents and/or insulin should be considered. Sulfonylurea monotherapy (SU) or in combination with metformin (SU+MET) have been the most commonly prescribed oral antidiabetic drugs in some Asian countries [3]. In Thailand, about one-third of the patients (31%) receive antihyperglycemic agent monotherapy and 69% receive combination therapy[4]. The prescribing patterns showed that Sulfonylurea-based therapies predominate. SU was the most commonly prescribed in monotherapy (42%) and SU+MET was the most commonly prescribed in combination therapy (60.2%) [4].

Diabetes is associated with nearly double the risk of death, mainly from cardiovascular disease and increasing concerns propose that some oral hypoglycemic agents may increase the risk of cardiovascular events [5, 6]. Related studies have shown users of SU had a 43% increased risk of all-cause mortality and 70% increased risk for cardiovascular disease mortality compared with patients treated with metformin [7, 8]. More recently, monotherapy with first or second generation SU was significantly associated with a 24% to 61% increased risk for all-cause mortality and second generation SU with an 18% to 30% increased risk for congestive heart failure [9]. Patients with T2DM treated with SU are at high risk of hypoglycemia, weight gain and cardiovascular diseases. In a review of 1,418

reported cases of severe hypoglycemia, 59% of events were related to SU use [10], and in the first year of the UK Prospective Diabetes (UKPDS) study, 31% of patients treated with glibenclamide experienced hypoglycemic symptoms, which was a similar proportion to those treated with insulin [11].

Patients often gain weight due to the side effects of current therapies, particularly SU, insulin and glitazone therapies. In addition, frequent intake of food between regular meals to avoid hypoglycemic events increases the potential for significant weight gain in a population of patients who are already at increased risk from cardiovascular morbidity and mortality [12]. Due to the barrier of hypoglycemia and weight gain, therapies such as SU may not be able to lower glycemic levels sufficiently or long enough to optimally reduce micro- and macrovascular endpoints. It may be prudent to avoid SU among patients with pre-existing cardiovascular conditions as further research in this area is needed. Therefore, treatment with SU may present a particular risk for patients with pre-existing cardiovascular or renal disease. For patients in these practice settings, treatment patterns, goal attainment rates and long-term diabetes complication rates remain unknown. To address these issues, we assessed the goal attainment rates, frequency and severity of hypoglycemic episodes, weight gain experiences and treatment compliance among Thai T2DM patients who had been treated with SU monotherapy or SU and metformin combination therapy.

MATERIALS AND METHODS

Study design and setting

A multicenter, observational, retrospective and cross-sectional study was conducted in 5 tertiary care hospitals, in Thailand (i.e. Srinagarind, Phramongkutklao, Ramathibodi, King Chulalongkorn Memorial, and Siriraj hospitals). T2DM patients' clinical charts were retrospectively reviewed in order to identify potential patients. The potential patients were

invited and enrolled into the study between February 2013 and March 2015. The potential patients were screened during a 6-month study enrollment period. Eligible patients were enrolled into the study at usual physician office visits. Pre-specified medical data was extracted for the 12-month period before a patient's study enrollment date. This study was approved by the Ethics Committee of each hospital. Patients satisfying the selection criteria were enrolled in the study after providing written informed consent to participate.

Study population

The study population comprised adults diagnosed with T2DM according to ADA criteria, and 30 years of age or older, who had been treated with SU monotherapy or SU and metformin combination (SU+MET) therapy for at least six months in each by an endocrinologist, cardiologist, nephrologist or family practitioner. Patients who required daily concomitant insulin, were pregnant, T1DM or gestational diabetes, receiving oral diabetic medications other than SU or SU+MET, already participating in another clinical study, or could not complete the questionnaire, were excluded.

Sample size

We estimated the sample size by using the following formula[13]; $n = \frac{Z^2 \times P(1-P)}{d^2}$. In the Asia Pacific Real-Life Effectiveness and Care Patterns of Diabetes Management (AP RECAP-DM) Study [14], the prevalence of hypoglycemia was reported at 36% (95%: CI = 33.8% to 37.8%). Assuming a proportion of 0.36, a confidence level of 0.95 and a desired margin of error of ±3.5%, n=723 subjects were required for this study.

Study measurements

Age, gender, height, weight, duration of diabetes, age at diagnosis, smoking status, alcohol consumption, physical activity, family history, presence and type of macro and microvascular complications and co-morbid conditions were retrospectively reviewed by physicians or trained chart reviewers from the patients' medical charts and entered into

standardised data collection form. The pre-specified medical data from charts were extracted for the 12-month period before the patient enrollment date.

On the study enrollment date, all participating patients were subjected to a standard blood draw to cross-sectionally assess $HbA_{1c,}$ fasting plasma glucose (FPG), serum creatinine, total-cholesterol, LDL-cholesterol, HDL-cholesterol, triglyceride and urinary albumin levels after overnight fasting to measure fasting. However, when performing blood and urine tests on enrollment date was difficult, the results of the test could be performed within 7 days after the enrollment date. Each patient's body weight, blood pressure and waist circumference were also cross-sectionally measured and recorded. Goal-attainment was defined as a patient having an HbA_{1c} level at the date of enrollment.

The Experience of Low Blood Sugar (Hypoglycemia) Questionnaire (Supplement I) developed by the Merck Sharp & Dohme Corp. (MSD) was used to measure patients' experience of hypoglycemia during the previous 6 months prior to the enrolment. The questionnaire contains 6 items which should be answered by yes/no or by using a 5-point Likert scale. The patients' hypoglycemia symptoms experienced were then stratified by severity (from none, mild, moderate, severe, and very severe) and subsequently classified according to having experienced hypoglycemia (yes/no) and the maximum severity of hypoglycemic episodes experienced. The patient's worry of hypoglycemia were assessed by using the worry scale of Hypoglycemia Fear Survey Questionnaire (HFS II) [15]. Each item was answered using a 5-point Likert scale from being never, rarely, sometimes, often and almost always, respectively.

A questionnaire was developed by Mapi Values (Supplement II) to measure patients' experience of weight gain during the previous year. The questionnaire contained 5 items which could be answered using a 3-, 5-, or 6-point Likert scales. Fear of Weight Gain Questionnaire developed by Mapi Values was used to measure patients' fears of weight gain (Supplement

III). The questionnaire contained 3 items, which should be answered using a 5-point Likert scale ranging from never, rarely, sometimes, often, and almost always, respectively.

Self-reported compliance with medication were assessed by the Self-Report Adherence and Barriers Questionnaire [16]. The level of compliance with the medication used a 5-point Likert scale (5 items), i.e. always, usually, sometimes, rarely and never taken as prescribed.

Statistical analysis

All comparisons were evaluated statistically using chi-square test, Fisher exact test, t-test, rank-sum test, or F-test as appropriate. The odds ratio (OR) (95% confidence interval, 95%CI) of glycemic goal attainment, occurrence of hypoglycemia and weight gain were predicted using a logistic-regression model. All data analyses were performed using STATA release 14.1 (StatCorp, College Station, TX). *P*-value less than 0.05 was considered statistically significant, unless otherwise specified.

RESULTS

Participants and demographics

From 718 patients screened, 659 patients were eligible for study analysis. The participant flow is shown in **Figure 1**. One half (50.7%) were female and mean age (±SD) was 65.5 (±10.0) years. Median duration (IQR) since diagnosis of T2DM was 10 (5-15) years; 321 (48.8%) patients reported that a first degree relative had been diagnosed with T2DM (**Table 1**). The number of patients treated by an endocrinologist, cardiologist, nephrologist and family practice physician comprised 304 (46.1%), 172 (26.1%), 119 (18.1%) and 64 (9.7%), respectively.

A majority of patients (79.1%) had been treated with a combination of SU and metformin and the others with SU alone (20.9%). The proportion of patients treated with SU

alone was highest (41.2%) among those treated in a nephrology clinic and lowest among those treated in an endocrinology clinic (12.5%).

Concomitant medications used in the previous six months are shown in **Table 1**. The majority of patients (84.3%) received anti-hypertensive medications in the six months enrollment. These included angiotensin II receptor blockers (ARBs), angiotensin-converting enzyme (ACE) inhibitors, calcium agonists, beta-blockers and various others. A similarly large proportion of patients (549, 83.3%) were receiving lipid lowering medications. These were mostly statins (77.0%) and fibrate (8%). None of the patients were recorded as having received weight-reducing medication during the six months before enrollment.

Goal attainment and related factors

Goal attainment (HbA_{1c} level <7%) was achieved in 313 (47.5%), overall. The level of HbA_{1c} (6.3±0.5 vs. 8.1±1.2 %, p <0.001) and fasting plasma glucose (125.4±29.8 vs. 160.2±46.8, p <0.001) were significantly lower among patients with goal attainment than patients without. Goal attainment was significantly lower among patients treated with the combination of SU and metformin than among those treated with SU alone (43.5% vs. 63.0%; Odd Ratio (OR): 0.45, 95%CI: 0.31 to 0.66, $p < 0.001$). The other demographic and laboratory variables did not differ significantly between patients with and without goal attainment (**Table 2**).

Hypoglycemia and related factors

Overall, 202 patients (30.7%) reported experiencing at least one hypoglycemic event in the previous six months. Mild hypoglycemia episodes (27.8%) were more frequently experienced than more severe episodes. Among all patients, the maximum severity of hypoglycemia ranged from mild (n=119, 18.1%) to moderate (n= 67, 10.2%) and severe or very severe (n=15, 2.3%). No significant difference was observed in the proportion experiencing hypoglycemia or in the maximum hypoglycemia severity between treatment with

SU alone and treatment with SU and metformin (**Table 3**).

Demographic and health-behaviour variables mostly did not differ significantly between patients experiencing and those not experiencing hypoglycemia. However, the patients having hypoglycemic episodes were slightly younger (63.9±10.6 vs. 66.2±9.6 years, p=0.008), reported higher frequencies of taking a low sugar diet (57.7% vs. 47.6%, OR: 1.61, 95%CI 1.06, 2.44, p=0.018) and were more likely to regularly check their finger-stick blood glucose (22.3% vs. 15.1%, OR; 1.50; 95%CI 1.08 to 2.10, p=0.033). Laboratory results and clinical measurements on the date of enrollment showed no significant differences between the hypoglycemia groups with the exception of a slightly lower waist circumference among those experiencing hypoglycemia (**Table 4**). Worry about hypoglycemia score (ranged from 0 to 4) was progressively greater among patients who experienced greater severity of hypoglycemia (mean (95%CI), 0.28 (0.08, 0.32), 0.48 (0.37, 0.59), 0.79 (0.64, 0.93), and 1.05 (0.75, 1.36); p-value <0.001, for no hypoglycemia, mild, moderate, and severe/very severe hypoglycemia experienced, respectively).

Weight gain and related factors

Weight gain in the previous 12 months was reported among 223 patients (35.4%), with no significant differences among clinic settings, but a lower proportion among those receiving SU and metformin compared with those receiving SU alone (33.1% vs. 44.6%, respectively; OR: 0.61, 95%CI: 0.41 to 0.91, p =0.015). The other demographic and laboratory variables did not differ significantly between patients experiencing and not experiencing weight gain except for significantly higher systolic blood pressure was found among patients experiencing weight gain (137.7±17.7 vs. 133.9±16.5 mmHg, p = 0.007) (**Table 5**). Fear of weight gain score (ranges 0–4) was greater among patients experiencing weight gain (mean (95%CI): 1.08 (0.97, 1.18) vs. 0.40 (0.28, 0.44), p < 0.001).

Major events and vascular complications

Major events in the previous 12 months were experienced by 68 patients (10.4%), most commonly congestive heart failure (27.9%) and ischemic heart disease (11.8%). Of these, 28 were hospitalised due to the event. Length of hospital stay ranged from less than 1 day to 43 days, with a mean among those hospitalised patients of 6.9 days. Macro and/or micro vascular complications were experienced by 137 patients (20.8%), mostly commonly ischemic heart disease (56.9%), renal failure (13.1%) and stroke (12.4%). For obvious reasons, ischemic heart disease, congestive heart failure and myocardial infarction patients were mostly treated in a cardiology clinic and renal failure patients in a nephrology clinic. Renal failure was more common among patients treated with SU alone (7.3%) than among those treated with SU and metformin (1.5%).

Compliance with medications

Compliance with medication reported on the 5-level Likert score was collapsed in two categories: always taking the medication exactly as prescribed and less than always. Slightly more than one half of patients (52.2%) reported not always taking their medication as prescribed. Compared with those reporting that they always took their medication as prescribed, those with lower compliance reported a higher percentage of being bothered by side effects (31 (9.1%) vs. 14 (4.5%), p=0.013) and/or having problems with filling their prescription all or most of the time (31 (9.1%) vs. 13 (4.2%), p=0.021). Neither reported experience of hypoglycemia, recorded weight gain, nor treatment type, differed significantly between the two compliance groups.

Table 1. Demographic characteristics of patients receiving SU or SU plus metformin over the previous 6 months (N=659)

Variable	N=659
Female, n (%)	330 (50.7)
Hypoglycemic agents, n (%)	
Sulfonylurea (SU)	138 (20.9)
Combination of SU and metformin	521 (79.1)
Age (years)	65.5 ± 10.0
Body weight (kg)	66.1 ± 13.3
Height (cm)	160.4 ± 8.7
Occupation, n (%)	
Employed	187 (28.5)
Retired	217 (33.1)
Homemaker	164 (25.0)
Disabled	14 (2.1)
Other	73 (11.1)
Median duration of DM (years), median (IQR)	10 (5, 15)
Low sugar diet, n (%)	330 (50.7)
Low calorie diet, n (%)	305 (47.0)
No regular physical activity, n (%)	220 (33.5)
Regular fingerstick glucose monitoring, n (%)	114 (17.3)
Alcohol consumption, n (%)	165 (25.1)
Smoking status	
Current or former smoker	228 (33.5)
Current only	41 (6.2)
Family history: DM in 1st degree relatives, n=565	321 (56.8)
Taking anti-hypertensive agents	556 (84.3)
Beta-blockers	233 (35.6)
ACEIs	192 (29.5)
ARBs	203 (31.2)
Calcium antagonists	241 (37.0)
Others	160 (26.5)
Taking lipid-lowering medications	549 (83.3)
Statins	503 (77.0)
Fibrate	52 (8.0)
Niacin	2 (0.3)
Ezetimibe	22 (3.4)
Others	4 (0.7)

All values are expressed as mean ± SD or number and percentage.
Abbreviations: ACEIs, angiotensin converting enzyme inhibitors; ARBs, angiotensin II receptor blockers (ARBs);

Table 2. Goal attainment (HbA1c <7% on the date of enrollment) by patients' demographics, medical history, laboratory and clinical measurements.

Variable	Number (%) or mean (SD) Goal not attained (N=345)	Goal attained (N=313)	*P value
Patient's demographics and medical history			
Female	184 (54.1)	146 (47.1)	0.084
Age (years)	64.9±10.3	66.2±9.9	0.105
Duration of DM (years), median (IQR)	11.4 ±7.1	10.5±6.8	0.087
Low sugar diet	166 (49.0)	163 (56.4)	0.389
Low calorie diet	153 (45.4)	151 (48.6)	0.432
No regular physical activity	106 (30.8)	113 (36.3)	0.137
Regular fingerstick glucose monitoring	64 (18.6)	50 (16.0)	0.410
Alcohol consumption	82 (23.8)	82 (26.3)	0.365
Smoking status	112 (32.5)	116 (37.1)	0.220
Family history: DM in 1st degree relatives	161 (54.8)	159 (58.9)	0.350
Any comorbid macro and vascular conditions	69 (20.1)	68 (21.7)	0.632
Any major events	40 (11.7)	28 (9.0)	0.305
Hypoglycemic agents			
Sulfonylurea (SU)	51 (14.8)	87 (27.8)	<0.001**
Combination of SU and metformin	294 (85.2)	226 (72.2)	
Laboratory at enrollment			
HbA_{1C} (%)	8.10±1.21	6.32±0.48	<0.001**
FPG (mg/dL)	160.2±46.8	125.4±29.8	<0.001**
Serum creatinine (mg/dL)	1.23±1.05	1.28±1.00	0.653
LDL-cholesterol (mg/dL)	101.1±33.9	94.0±32.5	0.050
Triglycerides (mf/dL)	154.9±86.1	141.0±82.3	0.149
Urine albumin (mg/gCr)	91.0±187.1	90.7±342.2	0.996
Clinical measurements at enrollment			
Body weight (kg)	66.1±13.2	66.1±13.3	0.991
Weight gain in previous 12 months	1.40±0.91	1.65±1.58	0.137
Waist circumference (cm)	92.0±10.5	91.8±10.7	0.844
Systolic blood pressure (mmHg)	136.2±18.2	133.7±16.2	0.064
Diastolic blood pressure (mmHg)	74.4±10.0	73.9±10.3	0.509

* Chi-square test or Rank-sum test as appropriate for categorical variables and Independent t-test or Wilcoxon Rank Sum test as appropriate for continuous variables.

***p*-value < 0.05

Abbreviations: DM, Diabetes Mellitus; FPG, fasting plasma glucose; $HbA_{1C,}$ Hemoglobin A_{1C}; HDL, high density lipoprotein; LDL, low density lipoprotein1c

Table 3. Experience of hypoglycemic episodes in the previous 6 months and weight gain in the previous 12 months by treatment type. (N=659)

	Number (%)		*p*-value
	SU (N=138)	SU and metformin (N=521)	
Experience of hypoglycemic episodes in the previous 6 months, n (%)			
No hypoglycemia	93 (67.4)	364 (69.9)	0.604*
Hypoglycemia	45 (32.6)	157 (30.1)	
Maximum severity of hypoglycemic episodes experienced[a]			
No hypoglycemia	93 (67.4)	364 (69.9)	0.656#
Mild	29 (21.0)	90 (17.3)	
Moderate	13 (9.4)	54 (10.4)	
Severe/Very severe	3 (2.2)	12 (2.3)	
Hypoglycemic episodes experience by each severity level, n (%)			
Mild	41 (29.7)	141 (27.1)	
Moderate	15 (10.9)	61 (11.7)	
Severe	2 (1.5)	9 (1.7)	
Very severe	2 (1.5)	3 (0.6)	
Frequency of hypoglycemic episodes for each severity level[a]			
Mild hypoglycemic episodes			
1-2 times over the last 6 months	24 (17.4)	93 (17.9)	
3-6 times over the last 6 months	10 (7.3)	30 (5.8)	
more than once per month	5 (3.6)	12 (2.3)	
more than once per week	2 (1.5)	6 (1.2)	
Moderate hypoglycemic episodes			
1-2 times over the last 6 months	10 (7.3)	44 (8.5)	
3-6 times over the last 6 months	1 (0.7)	9 (1.7)	
more than once per month	4 (2.9)	6 (1.2)	
more than once per week	0	2 (0.4)	
Severe hypoglycemic episodes			
1-2 times over the last 6 months	1 (0.7)	4 (0.8)	
3-6 times over the last 6 months	1 (0.7)	1 (0.2)	
more than once per month	0	4 (0.8)	
Very severe hypoglycemic episodes			
1-2 times over the last 6 months	1 (0.7)	1 (0.2)	
3-6 times over the last 6 months	0	1 (0.2)	

*Chi-square or Fisher exact test as appropriate.
#Likelihood ratio test from proportional logit model.
[a] Numbers may not sum to totals owing to missing data.

Table 4. Clinical factors between patient with and without hypoglycemia in previous 6 months

Variable	Number (%) or mean (SD) No hypoglycemia (N=457)	Number (%) or mean (SD) Hypoglycemia (N=202)	*p-value
Patient's demographics and medical history			
Female	221 (49.2)	109 (54.0)	0.272
Age (years)	66.2±9.6	63.9±10.6	0.008**
Duration of DM (years)	10.9±7.1	11.1±6.7	0.738
Low sugar diet	214 (47.6)	116 (57.7)	0.018**
Low calorie diet	203 (45.2)	102 (51.0)	0.174
No regular physical activity	144(31.7)	76 (27.6)	0.152
Regular fingerstick glucose monitoring	69 (15.1)	45 (22.3)	0.033**
Alcohol consumption	117 (25.6)	48 (24.0)	0.502
Smoking status	163 (35.7)	65 (32.1)	0.558
Family history: DM in 1st degree relatives	219 (55.7)	102 (59.3)	0.461
Any comorbid macro and vascular conditions	99 (55.7)	38 (18.8)	0.407
Any major events	50 (21.8)	18 (9.0)	0.490
Hypoglycemic agents			
Sulfonylurea (SU)	93 (20.3)	45 (22.2)	0.604
Combination of SU and metformin	364 (79.7)	157 (77.7)	
Laboratory at enrollment			
HbA1c (%)	7.29±1.28	7.17±1.31	0.247
FPG (mg/dL)	145.6±44.6	139.4±39.7	0.085
Serum creatinine (mg/dL)	1.26±1.08	1.23±0.89	0.767
LDL-cholesterol (mg/dL)	97.7±33.9	98.1±32.4	0.912
Triglycerides (mf/dL)	150.4±88.0	143.4±75.5	0.507
Urine albumin (mg/gCr)	68.3±169.1	125.2±398.1	0.456
Clinical measurements at enrollment			
Body weight (kg)	66.5±12.9	65.2±14.1	0.239
Weight gain in previous 12 months	1.43±1.11	1.74±1.60	0.101
Waist circumference (cm)	92.4±10.1	91.0±11.7	0.119
Systolic blood pressure (mmHg)	135.7±17.1	133.5±17.6	0.128
Diastolic blood pressure (mmHg)	74.5±10.2	73.4±9.8	0.186

* Chi-square test or Rank-sum test as appropriate for categorical variables and Independent t-test or Wilcoxon Rank Sum test as appropriate for continuous variables.

**p-value < 0.05

Abbreviations: DM, Diabetes Mellitus; FPG, fasting plasma glucose; $HbA_{1C,}$ Hemoglobin A_{1C}; HDL, high density lipoprotein; LDL, low density lipoprotein1c

Table 5. Clinical factors between patient with and without weight gain in previous 12 months

Variable	Number (%) or mean (SD)		*p-value
	No weight gained (N=406)	Weight gained (N=223)	
Patient's demographics and medical history			
Female (N, %)	207 (51.9)	112 (50.4)	0.738
Age (years)	65.3±10.0	65.8±9.6	0.558
Duration of DM (years)	10.7±6.8	11.6±7.5	0.159
Low sugar diet	212 (52.7)	104 (47.5)	0.240
Low calorie diet	300 (50.0)	95 (43.4)	0.130
No regular physical activity	147 (36.3)	65 (29.4)	0.093
Regular fingerstick glucose monitoring	64 (15.8)	47 (21.1)	0.102
Alcohol consumption	103 (25.5)	55 (24.7)	0.773
Smoking status	137 (33.7)	55 (24.7)	0.930
Family history: DM in 1st degree relatives	203 (57.8)	84 (55.6)	0.649
Any comorbid macro and vascular conditions	70 (17.3)	52 (23.3)	0.074
Any major events	44 (10.9)	20 (9.0)	0.494
Hypoglycemic agents			
Sulfonylurea (SU)	72 (17.7)	58 (26.0)	0.015**
Combination of SU and metformin	334 (82.3)	165 (74.0)	
Laboratory at enrollment			
HbA_{1C} (%)	7.26±1.31	7.17±1.06	0.397
FPG (mg/dL)	143.7±44.0	141.8±40.4	0.600
Serum creatinine (mg/dL)	1.28±1.17	1.14±0.50	0.240
LDL-cholesterol (mg/dL)	96.4±33.3	100.8±31.8	0.244
Triglycerides (mf/dL)	145.0±78.4	158.6±98.8	0.297
Urine albumin (mg/gCr)	117.8±350.3	55.3±147.6	0.400
Clinical measurements at enrollment			
Body weight (kg)	65.4±13.2	667.3±13.7	0.103
Weight gain in previous 12 months (kg)	-	1.52±1.28	-
Waist circumference (cm)	91.4±9.7	92.8±11.4	0.093
Systolic blood pressure (mmHg)	133.9±16.5	137.7±17.7	0.007**
Diastolic blood pressure (mmHg)	74.2±10.1	74.5±10.2	0.708

* Chi-square test or Rank-sum test as appropriate for categorical variables and Independent t-test or Wilcoxon Rank Sum test as appropriate for continuous variables.
**p-value < 0.05
Abbreviations: DM, Diabetes Mellitus; FPG, fasting plasma glucose; $HbA_{1C,}$ Hemoglobin A_{1C}; HDL, high density lipoprotein; LDL, low density lipoprotein

Goal attainment and related factors

Goal attainment (HbA_{1c} level <7%) was achieved in 313 (47.5%), overall. The level of HbA_{1c} (6.3±0.5 vs. 8.1±1.2 %, p <0.001) and fasting plasma glucose (125.4±29.8 vs. 160.2±46.8, p <0.001) were significantly lower among patients with goal attainment than

patients without. Goal attainment was significantly lower among patients treated with the combination of SU and metformin than among those treated with SU alone (43.5% vs. 63.0%; Odd Ratio (OR): 0.45, 95%CI: 0.31 to 0.66, $p < 0.001$). The other demographic and laboratory variables did not differ significantly between patients with and without goal attainment (**Table 2**).

Hypoglycemia and related factors

Overall, 202 patients (30.7%) reported experiencing at least one hypoglycemic event in the previous six months. Mild hypoglycemia episodes (27.8%) were more frequently experienced than more severe episodes. Among all patients, the maximum severity of hypoglycemia ranged from mild (n=119, 18.1%) to moderate (n= 67, 10.2%) and severe or very severe (n=15, 2.3%). No significant difference was observed in the proportion experiencing hypoglycemia or in the maximum hypoglycemia severity between treatment with SU alone and treatment with SU and metformin (**Table 3**).

Demographic and health-behavior variables mostly did not differ significantly between patients experiencing and those not experiencing hypoglycemia. However, the patients having hypoglycemic episodes were slightly younger (63.9±10.6 vs. 66.2±9.6 years, p=0.008), reported higher frequencies of taking a low sugar diet (57.7% vs. 47.6%, OR: 1.61, 95%CI 1.06, 2.44, p=0.018) and were more likely to regularly check their finger-stick blood glucose (22.3% vs. 15.1%, OR; 1.50; 95%CI 1.08 to 2.10, p=0.033). Laboratory results and clinical measurements on the date of enrollment showed no significant differences between the hypoglycemia groups with the exception of a slightly lower waist circumference among those experiencing hypoglycemia (**Table 4**). Worry about hypoglycemia score (ranged from 0 to 4) was progressively greater among patients who experienced greater severity of hypoglycemia (mean (95%CI), 0.28 (0.08, 0.32), 0.48 (0.37, 0.59), 0.79 (0.64, 0.93), and 1.05 (0.75, 1.36); p-

value <0.001, for no hypoglycemia, mild, moderate, and severe/very severe hypoglycemia experienced, respectively).

Weight gain and related factors

Weight gain in the previous 12 months was reported among 223 patients (35.4%), with no significant differences among clinic settings, but a lower proportion among those receiving SU and metformin compared with those receiving SU alone (33.1% vs. 44.6%, respectively; OR: 0.61, 95%CI: 0.41 to 0.91, p =0.015). The other demographic and laboratory variables did not differ significantly between patients experiencing and not experiencing weight gain except for significantly higher systolic blood pressure was found among patients experiencing weight gain (137.7±17.7 vs. 133.9±16.5 mmHg, p = 0.007) (**Table 5**). Fear of weight gain score (ranges 0–4) was greater among patients experiencing weight gain (mean (95%CI): 1.08 (0.97, 1.18) vs. 0.40 (0.28, 0.44), $p < 0.001$).

Major events and vascular complications

Major events in the previous 12 months were experienced by 68 patients (10.4%), most commonly congestive heart failure (27.9%) and ischemic heart disease (11.8%). Of these, 28 were hospitalised due to the event. Length of hospital stay ranged from less than 1 day to 43 days, with a mean among those hospitalised patients of 6.9 days. Macro and/or micro vascular complications were experienced by 137 patients (20.8%), mostly commonly ischemic heart disease (56.9%), renal failure (13.1%) and stroke (12.4%). For obvious reasons, ischemic heart disease, congestive heart failure and myocardial infarction patients were mostly treated in a cardiology clinic and renal failure patients in a nephrology clinic. Renal failure was more common among patients treated with SU alone (7.3%) than among those treated with SU and metformin (1.5%).

Compliance with medications

Compliance with medication reported on the 5-level Likert score was collapsed in two categories: always taking the medication exactly as prescribed and less than always. Slightly more than one half of patients (52.2%) reported not always taking their medication as prescribed. Compared with those reporting that they always took their medication as prescribed, those with lower compliance reported a higher percentage of being bothered by side effects (31 (9.1%) vs. 14 (4.5%), p=0.013) and/or having problems with filling their prescription all or most of the time (31 (9.1%) vs. 13 (4.2%), p=0.021). Neither reported experience of hypoglycemia, recorded weight gain, nor treatment type, differed significantly between the two compliance groups.

DISSCUSSION

The present study indicated that SU or a combination of SU and metformin were important tools in attaining glycemic control <7% among advanced T2DM patients. The burden of hypoglycemia and weight gain was high in T2DM patients up to ten years after diabetes diagnosis, and a majority of surveyed patients reported mild symptoms of hypoglycemia. Initiation of treatment with SU alone was followed by a change in average weight-gain. Overall, the findings support recommendations to adopt a patient-centered approach in selecting T2DM interventions and for setting glycemic goals that minimise the risk of hypoglycemia and weight gain.

Overall, 47.5% of patients had HbA1c values less than 7%. The quality of the glycemic control in our study may seem relatively high with SU plus metformin or sulfonylurea alone when compared with the UKPDS intervention group. In our study, the average HbA1c after median follow-up ten years was approximately 7.1 to 7.2% and the reference range of HbA_{1c} was 7.2 to 7.4 % in UKPDS study after six years [17]. The high

average age (65 years) and approximately 50% of compliance scores in the present study in comparison with UKPDS may primarily be ascribed to similar glycemic control and goal attainment with HbA1c level <7%.

Patients with increased numbers of hypoglycemia events are at risk for long term complications and mortality [18, 19], and hypoglycemia remains a major limiting factor in treating patients with T2DM, with an estimated prevalence of 12% to 30% depending on treatment [20-22]. Among the various antidiabetic medications available for T2DM, SU was more likely to be associated with hypoglycemia than non-SU antidiabetic medications [23]. Our study confirmed that patients taking SU with their antidiabetic medications had a high incidence of symptomatic hypoglycemia (30%). However, the actual rate of hypoglycemia may vary from that reported herein due to the study design, study population, differences in diabetes education and social status, that may have affected attitudes toward participating in the medical care. In the present study, patients with T2DM having advanced age and Thai ethnicity, one third of retired status and average baseline HbA_{1c} at 7.1 to 7.2% were more likely to have a high incidence of hypoglycemia. Moreover, the report of hypoglycemic incidence, using a medical survey, might have underestimated the prevalence of hypoglycemia among these patients.

In our sub-analysis, the greater number of hypoglycemia events observed which involved a low dietary sugar intake and regular fingerstick glucose monitoring, may possibly be due to relatively aggressive glycemic control monitoring. The increased hypoglycemia events observed in this setting was assumed to be due to implementing more stringent goals for metabolic control. In addition, our observational study did not rule out the role of other confounding variables influencing the positive associated outcomes.

In the present study, physicians largely followed the recommendations given to patients with T2DM, supplying metformin to the most obese patients and SU to patients with

lower bodyweight. Similar to related studies [24, 25], we observed a higher incidence of weight gain in the group with only SU treatment, and body weight did not change following treatment with a combination of metformin and SU. Therefore, for patients with T2DM, whose disease cannot be controlled by SU, biguanides might be an appropriate choice depending on whether the patient is overweight and the severity of symptoms.

Macro- or microvascular complications were present among 20.8% of the patients. Related studies have shown that hypoglycemia increased the risk of cardiovascular diseases possibly because of reduced coronary blood flow in the heart and major metabolic stress leading to cardiac arrhythmia [26, 27]. However, none of the T2DM patients in our study were observed to have cardiovascular symptoms during a hypoglycemia attack.

The study had some limitations. By design, this cross-sectional survey and retrospective cohort study used a convenient sample of patients. The study sample was limited to patients in tertiary care hospitals, so the results may not able to be generalized to patients of primary or secondary care hospitals. The observational nature of this study does not rule out the role of residual confounding variables in observed associations. In addition, hospitals' medical records, patient surveys and self-reported treatment experience generally underestimate hypoglycemia associated with oral hypoglycemic agents.

CONCLUSIONS

The major findings among the patients with Thai T2DM patients receiving SU or SU+MET, was that only about half of the patients achieved glycemic goal and compliance to the treatment. Hypoglycemia and weight gain were an important significant burden. Patients with a pronounced weight gain were often treated with SU monotherapy. The fear and worry about hypoglycemia and weight gain were higher among the patients who experienced hypoglycemic events and weight gain. Therefore, clinicians should also investigate information about patient's past experience on treatment side effects and treatment

compliance combining with the effectiveness of the antidiabetic drugs to find out the root cause when target goals are not met in diabetes care.

Figure legends

Figure 1. Participant flow

Supplementary materials

Supplement I: Experience of Low Blood Sugar (Hypoglycemia) Questionnaire

Supplement II: Experience of Weight Gain Questionnaire

Supplement III: Fear of Weight Gain Questionnaire

Abbreviations

ADA, American Diabetes Association; HbA_{1c}, $HemoglobinA_{1C}$; MET, Metformin; OR, odd ratio; T2DM, Type 2 diabetes mellitus; SU, Sulfonylurea; 95%CI, 95% confidence interval.

Availability of data and materials

Other statistical analysis results to support the findings of this study are available for one year after publication from the corresponding author by email upon reasonable request. Individual patient data and materials not provided as supplements will not be shared.

Contributors

BS, TP, BO, SS, YB and WN collected the data, drafted the article, reviewed the literature and revised it critically equally. BS and WN provided valuable input in study design, data collection and literature review. All authors read and approved the manuscript and met the criteria for authorship.

Competing interests

The authors declare that they have no competing interests. Although, MSD (Thailand) Ltd supported for the study funding but the study was conducted and the study results were interpreted without the influence of the pharmaceutical company.

Funding

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Consent for publication

Publication consent is not applicable.

Ethics approval and consent to participate

This study was approved by the Human Research Ethics Committee of each hospital. (Royal Thai Army Medical Department IRB. Ref No: P039h/55, KKU EC. Ref No: HE551257, Ramathibodi Hospital EC. Ref No: 11-55-24, Faculty of Medicine, Chulalongkorn University, IRB Ref No: 412/55, Siriraj Hospital Ref No: 636/2555(EC4))

Patient and Public Involvement

Neither patients nor public were involved in study planning, design, management, evaluation or interpretation.

Significance of this study

What is already known about this subject?

Sulfonylurea (SU) or combined SU and metformin (SU+MET) are commonly prescribed to Thai T2DM patient. Hypoglycemia or other adverse effects of treatment (i.e., polypharmacy) are a cause of failure to achieve HbA_{1c} goal per ADA recommendation.

What are the new findings?

- More than half of Thai T2DM patients treated with SU monotherapy or SU+MET could not achieve the glycemic goal attainment.
- One half of the patients reported not always taking their medication as prescribed.
- Goal attainment was significantly lower among the patients treated with the combination.
- Feelings of fear or worry about the treatment effects significantly increased in the patients experiencing side effects.

How might these results change the focus of research or clinical practice?

Our results suggest that glycemic goal failure in T2DM patients treated with SU-based therapy may not only be caused from the limitation of medications due to side effects, but non-compliance to the treatment may be a part of failure. The non-compliance may be a result from fear and worry about treatment side effects that the clinician should monitor. Research to identify the root cause of non-compliance and relationship with the failure of glycemic control should be conducted.

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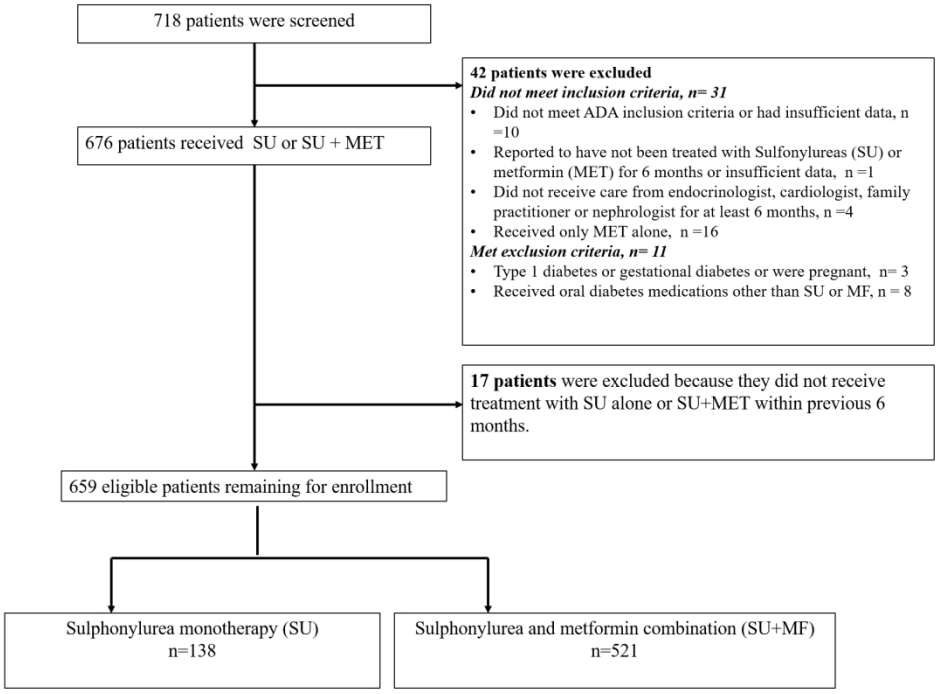

Figure 1. Participant flow

340x253mm (150 x 150 DPI)

SUPPLEMENT I

Naturalistic Evaluation of Hypoglycemic Events in Diabetic Subjects (NEEDS study)

Experience of Low Blood Sugar (Hypoglycemia)

Below is a list of symptoms you might experience when you have an episode (incident) of hypoglycemia (low blood sugar). Before answering the questions please read the list of symptoms carefully.

Some symptoms of **low blood sugar** (hypoglycemia) are:

- sweating
- shakiness
- dizziness
- hunger
- headache
- pale skin color
- confusion/feeling disoriented
- clumsy or jerky movements
- sudden moodiness or behavior changes
- tingling sensations around the mouth
- difficulty concentrating
- blood sugar is ≤ 70 mg/dL

1. Have you ever felt symptoms of low blood sugar (as described in the box above) in the last 6 months?

☐1 Yes
☐0 No (If no, go to questionnaire HFS)

If **YES**, please tick the box that best describes how severe and how often the symptoms of low blood sugar have been during the last 6 months.

2a. During the last 6 months, did you experience **MILD** symptoms of low blood sugar defined as *Little or no interruption of your activities, and you didn't feel you needed assistance to manage your episode(s) of low blood sugar or symptoms*?

☐1 Yes
☐0 No

2b. How often have you experienced **MILD** symptoms of low blood sugar?

☐0 I did not experience MILD symptoms of low blood sugar
☐1 1 to 2 times over the last 6 months
☐2 3 to 6 times over the last 6 months
☐3 more than once per month
☐4 more than once per week
☐5 everyday

3a. During the last 6 months, did you experience **MODERATE** symptoms of low blood sugar defined as *Some interruption of your activities, but didn't feel you needed assistance to manage your episode (s) of low blood sugar or symptoms*?

☐1 Yes
☐0 No

3b. How often have you experienced **MODERATE** symptoms of low blood sugar?

☐0 I did not experience MODERATE symptoms
☐1 1 to 2 times over the last 6 months
☐2 3 to 6 times over the last 6 months
☐3 more than once per month
☐4 more than once per week
☐5 everyday

4a. During the last 6 months, did you experience **SEVERE** symptoms of low blood sugar defined as *Felt that you needed the assistance of others to manage your episode(s) of low blood sugar or symptoms (for example, to bring you food or drink*)?

SUPPLEMENT I

Naturalistic Evaluation of Hypoglycemic Events in Diabetic Subjects (NEEDS study)

☐1 Yes
☐0 No

4b. How often have you experienced **SEVERE** symptoms of low blood sugar?

☐0 I did not experience SEVERE symptoms
☐1 1 to 2 times over the last 6 months
☐2 3 to 6 times over the last 6 months
☐3 more than once per month
☐4 more than once per week
☐5 everyday

5a. During the last 6 months, did you experience **VERY SEVERE** symptoms of low blood sugar defined as *Needed medical attention (for example, called an ambulance, visited an emergency room or hospital, or saw a doctor or nurse*)?

☐1 Yes
☐0 No

5b. How many times have you experienced **VERY SEVERE** symptoms of low blood sugar?

|__|__| times during the last 6 months

6. Overall, how much were you bothered by your symptoms of your low blood sugar during the last 6 months?

☐0 Not concerned (I did not have low blood sugar symptoms during the last 6 months)
☐1 Not at all
☐2 A little bit
☐3 Somewhat
☐4 Very
☐5 Extremely

SUPPLEMENT II

Naturalistic Evaluation of Hypoglycemic Events in Diabetic Subjects (NEEDS study)

Experience of Weight Gain

The following questions ask about weight gain. Please answer every question by *ticking the box* that best represents your opinion. There are no right or wrong answers.

1. During the last year, have you experienced a weight gain without meaning to?

- ☐1 Yes
- ☐2 No I lost weight
- ☐3 No my weight was stable

2. During the last year, how much weight did you gain?

- ☐1 Less than 5 Kilos
- ☐2 Between 5 and 9 kilos
- ☐3 Between 10 and 15 kilos
- ☐4 More than 15 kilos

3. How severe was your weight gain during the last year?

- ☐1 Very mild
- ☐2 Mild
- ☐3 Moderate
- ☐4 Severe
- ☐5 Very severe

4. How much were you bothered by your weight gain during the last year?

- ☐1 Not at all
- ☐2 A little bit
- ☐3 Somewhat
- ☐4 Very
- ☐5 Extremely

5. During the last year, was it difficult for you to maintain your weight?

- ☐1 Not at all
- ☐2 A little bit
- ☐3 Somewhat
- ☐4 Very
- ☐5 Extremely

SUPPLEMENT III
Naturalistic Evaluation of Hypoglycemic Events in Diabetic Subjects (NEEDS study)

Fear of Weight Gain

Please check the box that best describes how often you worry about each of the following items.

	Never	Rarely	Sometimes	Often	Almost Always
1. I worry about gaining weight	☐0	☐1	☐3	☐3	☐4
2. I worry that my diabetic treatment makes me gain weight	☐0	☐1	☐3	☐3	☐4
3. I worry about not being able to stabilise my weight	☐0	☐1	☐3	☐3	☐4

Naturalistic Evaluation of Hypoglycemic Events in Diabetic Subjects (NEEDS STUDY) -

STROBE Statement—checklist of items that should be included in reports of observational studies

	CHECK	Item No	Recommendation
Title and abstract	YES	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract on PAGE 2 - Research Design and Methods: Multicenter cross-sectional, retrospective review study
	YES		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found on PAGE 2 – Abstract
	Introduction		
Background/rationale	YES	2	Explain the scientific background and rationale for the investigation being reported on PAGE 4- Background
Objectives	YES	3	State specific objectives, including any prespecified hypotheses On Page 5 – Line 35 "To address these issues, we assessed the goal attainment rates ……."
	Methods		
Study design	YES	4	Present key elements of study design early in the paper On Page 5 – Line 51 "A multicenter, observational, retrospective and cross-sectional study was conducted ……"
Setting	YES	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection On Page 5-6 – From "5 tertiary care hospitals ……." To " …….Mar 2015"
Participants	YES	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants On Page 6 –Study population
			(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	YES	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable On Page 6 –Study measurements Section
Data sources/	YES	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability

Naturalistic Evaluation of Hypoglycemic Events in Diabetic Subjects (NEEDS STUDY) -

measurement			of assessment methods if there is more than one group On Page 6 –Study measurements Section
Bias	NO	9	Describe any efforts to address potential sources of bias
Study size	YES	10	Explain how the study size was arrived at On Page 6 –Sample Size Section
Quantitative variables	Not related	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	YES	12	(*a*) Describe all statistical methods, On Page 8–Statistical Analysis Section including those used to control for confounding - **No multivariate analysis in this study**
	NO		(*b*) Describe any methods used to examine subgroups and interactions- **No subgroup analysis**
	NO		(*c*) Explain how missing data were addressed
	NO		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
			(*e*) Describe any sensitivity analyses

Results

Participants	13*	YES	(a) **Report numbers of individuals at each stage of study**—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed On Page 8 : "From 718 patients screened ……." and Figure 1 Participant flow
		YES	(b) Give reasons for non-participation at each stage The reasons are in Figure 1 Participant flow
		YES	(c) Consider use of a flow diagram Figure 1 Participant flow
Descriptive data	14*	YES	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders On page 8 Participants and demographic Section and Table 1.
		YES	(b) Indicate number of participants with missing data for each variable of interest Table 1-5 clearly provided number of participants.

Naturalistic Evaluation of Hypoglycemic Events in Diabetic Subjects (NEEDS STUDY) -

		Not related	(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	Not related	*Cohort study*—Report numbers of outcome events or summary measures over time
		Not related	*Case-control study*—Report numbers in each exposure category, or summary measures of exposure
		YES	*Cross-sectional study*—Report numbers of outcome events or summary measures Table 1-5 clearly provided number of participants.
Main results	16	YES	(*a*) Give **unadjusted estimates** Table 1-5 clearly provided unadjusted estimates Table 1-5 and Result Section (Page 9-11). For continuous variable, we provide standard deviation. For ratio, we clearly provide the number that can use for 95% CI estimation. All Odd ratios (OR) in Results section were provided along with 95% CI. and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included - - **No multivariate analysis in this study**
		NO	(*b*) Report category boundaries when continuous variables were categorized
		Not related	(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Not related	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion			
Key results	18	YES	Summarise key results with reference to study objectives Page 19 line 49, paragraph "Overall, 47.5% of patients had HbA1c values less than 7%. ……."
Limitations	19	YES	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias Page 21 line 26, paragraph "The study had some limitations……."
Interpretation	20	YES	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence Page 21 CONCLUSIONS Section
Generalisability	21	YES	Discuss the generalisability (external validity) of the study results Page 21 Line 30. " The study sample was limited to patients in tertiary care hospitals, so the results may not able to be generalized…"

Naturalistic Evaluation of Hypoglycemic Events in Diabetic Subjects (NEEDS STUDY) -

Other information			
Funding	22	YES	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based Page 22-23, Funding Section.

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Real-world Evaluation of Glycemic Control and Hypoglycemic Events among Type 2 Diabetes Mellitus: A Multicenter, Cross-sectional Study in Thailand (REEDS Study)

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Real-world Evaluation of Glycemic Control and Hypoglycemic Events among Type 2 Diabetes Mellitus: a Multicenter, Cross-sectional Study in Thailand (REEDS Study)

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Abstract

Objective: Patients with type 2 diabetes mellitus (T2DM) often experience hypoglycemia and weight gain due to treatment side effects. Sulfonylurea (SU) or combined SU and metformin (SU+MET) has been frequently prescribed among the patients with longstanding disease. This study aimed to assess the glycemic goal attainment rates, hypoglycemic episodes, weight gain, and treatment compliance among T2DM patients receiving SU monotherapy or SU+MET.

Research Design and Methods: A multicenter cross-sectional, retrospective review study was conducted in 5 tertiary care hospitals, Thailand. The well-defined T2DM patients aged 30 or over in general practice were included consecutively during a 12-month period. Glycemic control, experiences of hypoglycemia, weight gain and compliance were evaluated. Glycemic goal attainment was a hemoglobinA_{1c} (HbA_{1c}) level less than 7%.

Results: Out of the 659 patients (mean age (±SD)), 65.5 (10.0) years and median duration of T2DM (IQR), 10 (5-15) years), 313 (47.5%) achieved the glycemic goal. Goal attainment was significantly lower among patients treated with SU+MET than those treated with SU alone (43.5% vs. 63.0%; Odd Ratio (OR): 0.45, 95%CI: 0.31, 0.66, p <0.001). HbA_{1c} levels were significantly lower among patients with goal attainment (6.3±0.5 vs 8.1±1.2%, p <0.001). One-third of patients reported experiencing hypoglycemia (30.7%) and weight gain (35.4%). Weight gain in the patients receiving SU+MET was lower than those receiving SU alone (33.1% vs 44.6%, p =0.015), but there was no difference for hypoglycemic events. Major events in the previous 12 months were experienced by 68 patients, most commonly congestive heart failure and ischemic heart disease. Approximately half of the patients (52.2%) reported not always taking their medication as prescribed.

Conclusions: Among T2DM patients receiving SU or SU+MET, only about half of the patients achieved glycemic goal and compliance with the treatment. Hypoglycemia and weight gain posed a more significant burden and weight gain was related to SU alone.

Strengths and limitations of this study

- Glycemic goal attainment and clinical laboratory results in this study were naturalistic results from the Thai T2DM patients treated with Sulfonylurea (SU) monotherapy or combined SU and Metformin.
- Self-reported hypoglycaemia, worry of hypoglycaemia, weight gain, fear of weight gain and compliance with medication were collected and reported along with the related factors.
- The study was carried out in tertiary care hospitals, so the results may not able to be generalized to patients of other hospital levels.
- The observational nature of this study does not rule out the role of residual confounding variables in observed associations.
- Use of the patient surveys and self-reported treatment experiences generally underestimate hypoglycemia associated with oral hypoglycemic agents.

BACKGROUND

Type 2 diabetes mellitus (T2DM) is the most common form of DM, accounting for approximately 90% of all cases diagnosed worldwide. The clinical heterogeneity of T2DM patients, in terms of characteristics such as duration of diabetes and comorbid illnesses greatly increases the challenge of providing care[1]. A longer duration of diabetes is associated with more complications and more difficulty maintaining glycemic control. The American Diabetes Association (ADA) [2] and Diabetes Association of Thailand recommends a hemoglobinA1C (HbA1c) target <7.0% for most patients and for patients with HbA1c >9%; a combination of two or more oral hypoglycemic agents and/or insulin should be considered. Sulfonylurea monotherapy (SU) or in combination with metformin (SU+MET) have been the most commonly prescribed oral antidiabetic drugs in some Asian countries [3]. In Thailand, about one-third of the patients (31%) receive antihyperglycemic agent monotherapy and 69% receive combination therapy[4]. The prescribing patterns showed that Sulfonylurea-based therapies predominate. SU was the most commonly prescribed in monotherapy (42%) and SU+MET was the most commonly prescribed in combination therapy (60.2%) [4].

Diabetes is associated with nearly double the risk of death, mainly from cardiovascular disease and increasing concerns propose that some oral hypoglycemic agents may increase the risk of cardiovascular events [5, 6]. Related studies have shown users of SU had a 43% increased risk of all-cause mortality and 70% increased risk for cardiovascular disease mortality compared with patients treated with metformin [7, 8]. More recently, monotherapy with first or second generation SU was significantly associated with a 24% to 61% increased risk for all-cause mortality and second generation SU with an 18% to 30% increased risk for congestive heart failure [9]. Patients with T2DM treated with SU are at high risk of hypoglycemia, weight gain and cardiovascular diseases. In a review of 1,418

reported cases of severe hypoglycemia, 59% of events were related to SU use [10], and in the first year of the UK Prospective Diabetes (UKPDS) study, 31% of patients treated with glibenclamide experienced hypoglycemic symptoms, which was a similar proportion to those treated with insulin [11].

Patients often gain weight due to the side effects of current therapies, particularly SU, insulin and glitazone therapies. In addition, frequent intake of food between regular meals to avoid hypoglycemic events increases the potential for significant weight gain in a population of patients who are already at increased risk from cardiovascular morbidity and mortality [12]. Due to the barrier of hypoglycemia and weight gain, therapies such as SU may not be able to lower glycemic levels sufficiently or long enough to optimally reduce micro- and macrovascular endpoints. It may be prudent to avoid SU among patients with pre-existing cardiovascular conditions as further research in this area is needed. Therefore, treatment with SU may present a particular risk for patients with pre-existing cardiovascular or renal disease. For patients in these practice settings, treatment patterns, goal attainment rates and long-term diabetes complication rates remain unknown. To address these issues, we assessed the goal attainment rates, frequency and severity of hypoglycemic episodes, weight gain experiences and treatment compliance among Thai T2DM patients who had been treated with SU monotherapy or SU and metformin combination therapy.

MATERIALS AND METHODS

Study design and setting

A multicenter, observational, retrospective and cross-sectional study was conducted in 5 tertiary care hospitals, in Thailand (i.e. Srinagarind, Phramongkutklao, Ramathibodi, King Chulalongkorn Memorial, and Siriraj hospitals). T2DM patients' clinical charts were retrospectively reviewed in order to identify potential patients. The potential patients were

invited and enrolled into the study between February 2013 and March 2015. The potential patients were screened during a 6-month study enrollment period. Eligible patients were enrolled into the study at usual physician office visits. Pre-specified medical data was extracted for the 12-month period before a patient's study enrollment date. This study was approved by the Ethics Committee of each hospital. Patients satisfying the selection criteria were enrolled in the study after providing written informed consent to participate.

Study population

The study population comprised adults diagnosed with T2DM according to ADA criteria, and 30 years of age or older, who had been treated with SU monotherapy or SU and metformin combination (SU+MET) therapy for at least six months in each by an endocrinologist, cardiologist, nephrologist or family practitioner. Patients who required daily concomitant insulin, were pregnant, T1DM or gestational diabetes, receiving oral diabetic medications other than SU or SU+MET, already participating in another clinical study, or could not complete the questionnaire, were excluded.

Sample size

We estimated the sample size by using the following formula[13]; $n = \frac{Z^2 \times P(1-P)}{d^2}$. In the Asia Pacific Real-Life Effectiveness and Care Patterns of Diabetes Management (AP RECAP-DM) Study [14], the prevalence of hypoglycemia was reported at 36% (95%: CI = 33.8% to 37.8%). Assuming a proportion of 0.36, a confidence level of 0.95 and a desired margin of error of ±3.5%, n=723 subjects were required for this study.

Study measurements

Age, gender, height, weight, duration of diabetes, age at diagnosis, smoking status, alcohol consumption, physical activity, family history, presence and type of macro and microvascular complications and co-morbid conditions were retrospectively reviewed by physicians or trained chart reviewers from the patients' medical charts and entered into

standardised data collection form. The pre-specified medical data from charts were extracted for the 12-month period before the patient enrollment date.

On the study enrollment date, all participating patients were subjected to a standard blood draw to cross-sectionally assess $HbA_{1c,}$ fasting plasma glucose (FPG), serum creatinine, total-cholesterol, LDL-cholesterol, HDL-cholesterol, triglyceride and urinary albumin levels after overnight fasting to measure fasting. However, when performing blood and urine tests on enrollment date was difficult, the results of the test could be performed within 7 days after the enrollment date. Each patient's body weight, blood pressure and waist circumference were also cross-sectionally measured and recorded. Goal-attainment was defined as a patient having an HbA_{1c} level at the date of enrollment.

The Experience of Low Blood Sugar (Hypoglycemia) Questionnaire (Supplement I) developed by the Merck Sharp & Dohme Corp. (MSD) was used to measure patients' experience of hypoglycemia during the previous 6 months prior to the enrolment. The questionnaire contains 6 items which should be answered by yes/no or by using a 5-point Likert scale. The patients' hypoglycemia symptoms experienced were then stratified by severity (from none, mild, moderate, severe, and very severe) and subsequently classified according to having experienced hypoglycemia (yes/no) and the maximum severity of hypoglycemic episodes experienced. The patient's worry of hypoglycemia were assessed by using the worry scale of Hypoglycemia Fear Survey Questionnaire (HFS II) [15]. Each item was answered using a 5-point Likert scale from being never, rarely, sometimes, often and almost always, respectively.

A questionnaire was developed by Mapi Values (Supplement II) to measure patients' experience of weight gain during the previous year. The questionnaire contained 5 items which could be answered using a 3-, 5-, or 6-point Likert scales. Fear of Weight Gain Questionnaire developed by Mapi Values was used to measure patients' fears of weight gain (Supplement

III). The questionnaire contained 3 items, which should be answered using a 5-point Likert scale ranging from never, rarely, sometimes, often, and almost always, respectively.

Self-reported compliance with medication were assessed by the Self-Report Adherence and Barriers Questionnaire [16]. The level of compliance with the medication used a 5-point Likert scale (5 items), i.e. always, usually, sometimes, rarely and never taken as prescribed.

Statistical analysis

All comparisons were evaluated statistically using chi-square test, Fisher exact test, t-test, rank-sum test, or F-test as appropriate. The odds ratio (OR) (95% confidence interval, 95%CI) of glycemic goal attainment, occurrence of hypoglycemia and weight gain were predicted using a logistic-regression model.

Multivariate relationships were conceptualized using directed acyclic graphs (DAG), and minimum sets of adjustment variables to obtain unbiased estimates of total and direct effects of various exposure variables on occurrence of hypoglycemia, treatment, compliance, treatment satisfaction, quality of life, worry about hypoglycemia and fear of weight gain compatible with the conceptual graph identified (Supplement IV). The DAG was used as the baseline construct for identifying sets of variables on which it was necessary to condition in subsequent in multivariate logistic or linear regression models in order to minimize bias in the estimated coefficients.

Directed acyclic graphs were constructed using DAGitty software (Version 2.3) and All data analyses were performed using STATA release 14.1 (StatCorp, College Station, TX). *P*-value less than 0.05 was considered statistically significant, unless otherwise specified.

RESULTS

Participants and demographics

From 718 patients screened, 659 patients were eligible for study analysis. The participant flow is shown in **Figure 1**. One half (50.7%) were female and mean age (±SD) was 65.5 (±10.0) years. Median duration (IQR) since diagnosis of T2DM was 10 (5-15) years; 321 (48.8%) patients reported that a first degree relative had been diagnosed with T2DM (**Table 1**). The number of patients treated by an endocrinologist, cardiologist, nephrologist and family practice physician comprised 304 (46.1%), 172 (26.1%), 119 (18.1%) and 64 (9.7%), respectively.

A majority of patients (79.1%) had been treated with a combination of SU and metformin and the others with SU alone (20.9%). The proportion of patients treated with SU alone was highest (41.2%) among those treated in a nephrology clinic and lowest among those treated in an endocrinology clinic (12.5%).

Concomitant medications used in the previous six months are shown in **Table 1**. The majority of patients (84.3%) received anti-hypertensive medications in the six months enrollment. These included angiotensin II receptor blockers (ARBs), angiotensin-converting enzyme (ACE) inhibitors, calcium agonists, beta-blockers and various others. A similarly large proportion of patients (549, 83.3%) were receiving lipid lowering medications. These were mostly statins (77.0%) and fibrate (8%). None of the patients were recorded as having received weight-reducing medication during the six months before enrollment.

Goal attainment and related factors

Goal attainment (HbA_{1c} level <7%) was achieved in 313 (47.5%), overall. The level of HbA_{1c} (6.3±0.5 vs. 8.1±1.2 %, p <0.001) and fasting plasma glucose (125.4±29.8 vs. 160.2±46.8, p <0.001) were significantly lower among patients with goal attainment than patients without. Goal attainment was significantly lower among patients treated with the combination of SU and metformin than among those treated with SU alone (43.5% vs. 63.0%; Odd Ratio (OR): 0.45, 95%CI: 0.31 to 0.66, $p < 0.001$). The other demographic and laboratory

variables did not differ significantly between patients with and without goal attainment (**Table 2**).

Hypoglycemia and related factors

Overall, 202 patients (30.7%) reported experiencing at least one hypoglycemic event in the previous six months. Mild hypoglycemia episodes (27.8%) were more frequently experienced than more severe episodes. Among all patients, the maximum severity of hypoglycemia ranged from mild (n=119, 18.1%) to moderate (n= 67, 10.2%) and severe or very severe (n=15, 2.3%). No significant difference was observed in the proportion experiencing hypoglycemia or in the maximum hypoglycemia severity between treatment with SU alone and treatment with SU and metformin (**Table 3**).

Demographic and health-behaviour variables mostly did not differ significantly between patients experiencing and those not experiencing hypoglycemia. However, the patients having hypoglycemic episodes were slightly younger (63.9±10.6 vs. 66.2±9.6 years, p=0.008), reported higher frequencies of taking a low sugar diet (57.7% vs. 47.6%, OR: 1.61, 95%CI 1.06, 2.44, p=0.018) and were more likely to regularly check their finger-stick blood glucose (22.3% vs. 15.1%, OR; 1.50; 95%CI 1.08 to 2.10, p=0.033). Laboratory results and clinical measurements on the date of enrollment showed no significant differences between the hypoglycemia groups with the exception of a slightly lower waist circumference among those experiencing hypoglycemia (**Table 4**). Worry about hypoglycemia score (ranged from 0 to 4) was progressively greater among patients who experienced greater severity of hypoglycemia (mean (95%CI), 0.28 (0.08, 0.32), 0.48 (0.37, 0.59), 0.79 (0.64, 0.93), and 1.05 (0.75, 1.36); p-value <0.001, for no hypoglycemia, mild, moderate, and severe/very severe hypoglycemia experienced, respectively).

Multivariate analysis showed that greater maximum severity of hypoglycaemia in the previous 6 months was associated with adherence to a regular diabetic diet (OR 1.68; 95% CI 1.06, 2.67), whereas lower severity was associated with adherence to a regular exercise plan (OR 0.63; 95% CI 0.45, 0.88).

Weight gain and related factors

Weight gain in the previous 12 months was reported among 223 patients (35.4%), with no significant differences among clinic settings, but a lower proportion among those receiving SU and metformin compared with those receiving SU alone (33.1% vs. 44.6%, respectively; OR: 0.61, 95%CI: 0.41 to 0.91, p =0.015). The other demographic and laboratory variables did not differ significantly between patients experiencing and not experiencing weight gain except for significantly higher systolic blood pressure was found among patients experiencing weight gain (137.7±17.7 vs. 133.9±16.5 mmHg, p = 0.007) (**Table 5**). Fear of weight gain score (ranges 0–4) was greater among patients experiencing weight gain (mean (95%CI): 1.08 (0.97, 1.18) vs. 0.40 (0.28, 0.44), $p < 0.001$). Two variables, i.e. the hypoglycaemic agents and regular physical activity, identified by the DAG that they effected weight gain. However, only the hypoglycaemic agents were the significant variable from univariate analysis.

Major events and vascular complications

Major events in the previous 12 months were experienced by 68 patients (10.4%), most commonly congestive heart failure (27.9%) and ischemic heart disease (11.8%). Of these, 28 were hospitalised due to the event. Length of hospital stay ranged from less than 1 day to 43 days, with a mean among those hospitalised patients of 6.9 days. Macro and/or micro vascular complications were experienced by 137 patients (20.8%), mostly commonly ischemic heart disease (56.9%), renal failure (13.1%) and stroke (12.4%). For obvious reasons, ischemic heart disease, congestive heart failure and myocardial infarction patients were mostly treated in a

cardiology clinic and renal failure patients in a nephrology clinic. Renal failure was more common among patients treated with SU alone (7.3%) than among those treated with SU and metformin (1.5%).

Compliance with medications

Compliance with medication reported on the 5-level Likert score was collapsed in two categories: always taking the medication exactly as prescribed and less than always. Slightly more than one half of patients (52.2%) reported not always taking their medication as prescribed. Compared with those reporting that they always took their medication as prescribed, those with lower compliance reported a higher percentage of being bothered by side effects (31 (9.1%) vs. 14 (4.5%), p=0.013) and/or having problems with filling their prescription all or most of the time (31 (9.1%) vs. 13 (4.2%), p=0.021). Neither reported experience of hypoglycemia, recorded weight gain, nor treatment type, differed significantly between the two compliance groups.

Table 1. Demographic characteristics of patients receiving SU or SU plus metformin over the previous 6 months (N=659)

Variable	N=659
Female, n (%)	330 (50.7)
Hypoglycemic agents, n (%)	
Sulfonylurea (SU)	138 (20.9)
Combination of SU and metformin	521 (79.1)
Age (years)	65.5 ± 10.0
Body weight (kg)	66.1 ± 13.3
Height (cm)	160.4 ± 8.7
BMI (kg/m^2)	25.73 ± 4.32
Occupation, n (%)	
Employed	187 (28.5)
Retired	217 (33.1)
Homemaker	164 (25.0)
Disabled	14 (2.1)
Other	73 (11.1)
Median duration of DM (years), median (IQR)	10 (5, 15)
Low sugar diet, n (%)	330 (50.7)
Low calorie diet, n (%)	305 (47.0)
No regular physical activity, n (%)	220 (33.5)
Regular fingerstick glucose monitoring, n (%)	114 (17.3)
Adherence to a regular diabetic, n (%)	86 (13.2%)
Alcohol consumption, n (%)	165 (25.1)
Smoking status	
Current or former smoker	228 (33.5)
Current only	41 (6.2)
Family history: DM in 1st degree relatives, n=565	321 (56.8)
Taking anti-hypertensive agents	556 (84.3)
Beta-blockers	233 (35.6)
ACEIs	192 (29.5)
ARBs	203 (31.2)
Calcium antagonists	241 (37.0)
Others	160 (26.5)
Taking lipid-lowering medications	549 (83.3)
Statins	503 (77.0)
Fibrate	52 (8.0)
Niacin	2 (0.3)
Ezetimibe	22 (3.4)
Others	4 (0.7)

All values are expressed as mean ± SD or number and percentage.
Abbreviations: ACEIs, angiotensin converting enzyme inhibitors; ARBs, angiotensin II receptor blockers (ARBs);

Table 2. Goal attainment (HbA_{1c} <7% on the date of enrollment) by patients' demographics, medical history, laboratory and clinical measurements.

Variable	Number (%) or mean (SD) Goal not attained (N=345)	Goal attained (N=313)	*P value
Patient's demographics and medical history			
Female	184 (54.1)	146 (47.1)	0.084
Age (years)	64.9±10.3	66.2±9.9	0.105
Duration of DM (years), median (IQR)	11.4 ±7.1	10.5±6.8	0.087
BMI (kg/m^2)	25.93 ± 4.34	25.51 ±4.29	0.230
Adherence to regular diabetic diet	48 (14.0)	38 (12.3)	0.523
Low sugar diet	166 (49.0)	163 (56.4)	0.389
Low calorie diet	153 (45.4)	151 (48.6)	0.432
No regular physical activity	106 (30.8)	113 (36.3)	0.137
Regular fingerstick glucose monitoring	64 (18.6)	50 (16.0)	0.410
Alcohol consumption	82 (23.8)	82 (26.3)	0.365
Smoking status	112 (32.5)	116 (37.1)	0.220
Family history: DM in 1st degree relatives	161 (54.8)	159 (58.9)	0.350
Any comorbid macro and vascular conditions	69 (20.1)	68 (21.7)	0.632
Any major events	40 (11.7)	28 (9.0)	0.305
Hypoglycemic agents			
Sulfonylurea (SU)	51 (14.8)	87 (27.8)	<0.001**
Combination of SU and metformin	294 (85.2)	226 (72.2)	
Laboratory at enrollment			
HbA_{1C} (%)	8.10±1.21	6.32±0.48	<0.001**
FPG (mg/dL)	160.2±46.8	125.4±29.8	<0.001**
Serum creatinine (mg/dL)	1.23±1.05	1.28±1.00	0.653
LDL-cholesterol (mg/dL)	101.1±33.9	94.0±32.5	0.050
Triglycerides (mf/dL)	154.9±86.1	141.0±82.3	0.149
Urine albumin (mg/gCr)	91.0±187.1	90.7±342.2	0.996
Clinical measurements at enrollment			
Body weight (kg)	66.1±13.2	66.1±13.3	0.991
Weight gain in previous 12 months	1.40±0.91	1.65±1.58	0.137
Waist circumference (cm)	92.0±10.5	91.8±10.7	0.844
Systolic blood pressure (mmHg)	136.2±18.2	133.7±16.2	0.064
Diastolic blood pressure (mmHg)	74.4±10.0	73.9±10.3	0.509

* Chi-square test or Rank-sum test as appropriate for categorical variables and Independent t-test or Wilcoxon Rank Sum test as appropriate for continuous variables.

***p*-value < 0.05

Abbreviations: DM, Diabetes Mellitus; FPG, fasting plasma glucose; $HbA_{1C,}$ Hemoglobin A_{1C}; HDL, high density lipoprotein; LDL, low density lipoprotein1c

Table 3. Experience of hypoglycemic episodes in the previous 6 months and weight gain in the previous 12 months by treatment type. (N=659)

	Number (%)		*p*-value
	SU (N=138)	SU and metformin (N=521)	
Experience of hypoglycemic episodes in the previous 6 months, n (%)			
No hypoglycemia	93 (67.4)	364 (69.9)	0.604*
Hypoglycemia	45 (32.6)	157 (30.1)	
Maximum severity of hypoglycemic episodes experienced[a]			
No hypoglycemia	93 (67.4)	364 (69.9)	0.656#
Mild	29 (21.0)	90 (17.3)	
Moderate	13 (9.4)	54 (10.4)	
Severe/Very severe	3 (2.2)	12 (2.3)	
Hypoglycemic episodes experience by each severity level, n (%)			
Mild	41 (29.7)	141 (27.1)	
Moderate	15 (10.9)	61 (11.7)	
Severe	2 (1.5)	9 (1.7)	
Very severe	2 (1.5)	3 (0.6)	
Frequency of hypoglycemic episodes for each severity level[a]			
Mild hypoglycemic episodes			
1-2 times over the last 6 months	24 (17.4)	93 (17.9)	
3-6 times over the last 6 months	10 (7.3)	30 (5.8)	
more than once per month	5 (3.6)	12 (2.3)	
more than once per week	2 (1.5)	6 (1.2)	
Moderate hypoglycemic episodes			
1-2 times over the last 6 months	10 (7.3)	44 (8.5)	
3-6 times over the last 6 months	1 (0.7)	9 (1.7)	
more than once per month	4 (2.9)	6 (1.2)	
more than once per week	0	2 (0.4)	
Severe hypoglycemic episodes			
1-2 times over the last 6 months	1 (0.7)	4 (0.8)	
3-6 times over the last 6 months	1 (0.7)	1 (0.2)	
more than once per month	0	4 (0.8)	
Very severe hypoglycemic episodes			
1-2 times over the last 6 months	1 (0.7)	1 (0.2)	
3-6 times over the last 6 months	0	1 (0.2)	

*Chi-square or Fisher exact test as appropriate.
#Likelihood ratio test from proportional logit model.
[a] Numbers may not sum to totals owing to missing data.

Table 4. Clinical factors between patient with and without hypoglycemia in previous 6 months

Variable	Number (%) or mean (SD) No hypoglycemia (N=457)	Hypoglycemia (N=202)	*p-value
Patient's demographics and medical history			
Female	221 (49.2)	109 (54.0)	0.272
Age (years)	66.2±9.6	63.9±10.6	0.008**
BMI (kg/m^2)	25.88 ± 4.23	25.38 ± 4.53	0.190
Duration of DM (years)	10.9±7.1	11.1±6.7	0.738
Low sugar diet	214 (47.6)	116 (57.7)	0.018**
Low calorie diet	203 (45.2)	102 (51.0)	0.174
Adherence to regular diabetic diet	52 (11.5)	34 (17.1)	0.050
No regular physical activity	144(31.7)	76 (27.6)	0.152
Regular fingerstick glucose monitoring	69 (15.1)	45 (22.3)	0.033**
Alcohol consumption	117 (25.6)	48 (24.0)	0.502
Smoking status	163 (35.7)	65 (32.1)	0.558
Family history: DM in 1st degree relatives	219 (55.7)	102 (59.3)	0.461
Any comorbid macro and vascular conditions	99 (55.7)	38 (18.8)	0.407
Any major events	50 (21.8)	18 (9.0)	0.490
Hypoglycemic agents			
Sulfonylurea (SU)	93 (20.3)	45 (22.2)	0.604
Combination of SU and metformin	364 (79.7)	157 (77.7)	
Laboratory at enrollment			
HbA1c (%)	7.29±1.28	7.17±1.31	0.247
FPG (mg/dL)	145.6±44.6	139.4±39.7	0.085
Serum creatinine (mg/dL)	1.26±1.08	1.23±0.89	0.767
LDL-cholesterol (mg/dL)	97.7±33.9	98.1±32.4	0.912
Triglycerides (mf/dL)	150.4±88.0	143.4±75.5	0.507
Urine albumin (mg/gCr)	68.3±169.1	125.2±398.1	0.456
Clinical measurements at enrollment			
Body weight (kg)	66.5±12.9	65.2±14.1	0.239
Weight gain in previous 12 months	1.43±1.11	1.74±1.60	0.101
Waist circumference (cm)	92.4±10.1	91.0±11.7	0.119
Systolic blood pressure (mmHg)	135.7±17.1	133.5±17.6	0.128
Diastolic blood pressure (mmHg)	74.5±10.2	73.4±9.8	0.186

* Chi-square test or Rank-sum test as appropriate for categorical variables and Independent t-test or Wilcoxon Rank Sum test as appropriate for continuous variables.

**p-value < 0.05

Abbreviations: DM, Diabetes Mellitus; FPG, fasting plasma glucose; $HbA_{1C,}$ Hemoglobin A_{1C}; HDL, high density lipoprotein; LDL, low density $lipoprotein_{1c}$

Table 5. Clinical factors between patient with and without weight gain in previous 12 months

Variable	Number (%) or mean (SD)		*p-value
	No weight gained (N=406)	Weight gained (N=223)	
Patient's demographics and medical history			
Female (N, %)	207 (51.9)	112 (50.4)	0.738
Age (years)	65.3±10.0	65.8±9.6	0.558
Duration of DM (years)	10.7±6.8	11.6±7.5	0.159
Low sugar diet	212 (52.7)	104 (47.5)	0.240
Low calorie diet	300 (50.0)	95 (43.4)	0.130
No regular physical activity	147 (36.3)	65 (29.4)	0.093
Regular fingerstick glucose monitoring	64 (15.8)	47 (21.1)	0.102
Alcohol consumption	103 (25.5)	55 (24.7)	0.773
Smoking status	137 (33.7)	55 (24.7)	0.930
Family history: DM in 1st degree relatives	203 (57.8)	84 (55.6)	0.649
Any comorbid macro and vascular conditions	70 (17.3)	52 (23.3)	0.074
Any major events	44 (10.9)	20 (9.0)	0.494
Hypoglycemic agents			
Sulfonylurea (SU)	72 (17.7)	58 (26.0)	0.015**
Combination of SU and metformin	334 (82.3)	165 (74.0)	
Laboratory at enrollment			
HbA_{1C} (%)	7.26±1.31	7.17±1.06	0.397
FPG (mg/dL)	143.7±44.0	141.8±40.4	0.600
Serum creatinine (mg/dL)	1.28±1.17	1.14±0.50	0.240
LDL-cholesterol (mg/dL)	96.4±33.3	100.8±31.8	0.244
Triglycerides (mf/dL)	145.0±78.4	158.6±98.8	0.297
Urine albumin (mg/gCr)	117.8±350.3	55.3±147.6	0.400
Clinical measurements at enrollment			
Body weight (kg)	65.4±13.2	667.3±13.7	0.103
Weight gain in previous 12 months (kg)	-	1.52±1.28	-
Waist circumference (cm)	91.4±9.7	92.8±11.4	0.093
Systolic blood pressure (mmHg)	133.9±16.5	137.7±17.7	0.007**
Diastolic blood pressure (mmHg)	74.2±10.1	74.5±10.2	0.708

* Chi-square test or Rank-sum test as appropriate for categorical variables and Independent t-test or Wilcoxon Rank Sum test as appropriate for continuous variables.
**p-value < 0.05
Abbreviations: DM, Diabetes Mellitus; FPG, fasting plasma glucose; $HbA_{1C,}$ Hemoglobin A_{1C}; HDL, high density lipoprotein; LDL, low density lipoprotein

DISSCUSSION

The present study indicated that SU or a combination of SU and metformin were important tools in attaining glycemic control <7% among advanced T2DM patients. The burden of hypoglycemia and weight gain was high in T2DM patients up to ten years after diabetes diagnosis, and a majority of surveyed patients reported mild symptoms of

hypoglycemia. Initiation of treatment with SU alone was followed by a change in average weight-gain. Overall, the findings support recommendations to adopt a patient-centered approach in selecting T2DM interventions and for setting glycemic goals that minimise the risk of hypoglycemia and weight gain.

Overall, 47.5% of patients had HbA_{1c} values less than 7%. The quality of the glycemic control in our study may seem relatively high with SU plus metformin or sulfonylurea alone when compared with the UKPDS intervention group. In our study, the average HbA_{1c} after median follow-up ten years was approximately 7.1 to 7.2% and the reference range of HbA_{1c} was 7.2 to 7.4 % in UKPDS study after six years [17]. The high average age (65 years) and approximately 50% of compliance scores in the present study in comparison with UKPDS may primarily be ascribed to similar glycemic control and goal attainment with HbA1c level <7%.

Sulfonylureas were the most commonly used drug for monotherapy in Thai patients [18], although the American Diabetes Association and the European Association for the Study of Diabetes consensus algorithm for the T2DM treatment recommends beginning metformin[19]. If SU monotherapy fails to achieve the glycemic target, combination therapy with a second agent with a different mechanism of action will be initiated. The most commonly prescribed combination therapy in Thai patients was SU and metformin [18].

In our study, we observed a lower incidence of HbA_{1c} goal attainment in the group with combination of metformin and SU. In addition, more half of the patient treated with SU+MET for at least six months failed to achieve the glycemic control (294 from 521, 56.4%). This may infer that the use of the combination to achieve the glycemic target may be not the way to help these patients to achieve the glycemic control. The study to identify the root causes of the failure or development of new novel diabetic agents still have been required.

Patients with increased numbers of hypoglycemia events are at risk for long term complications and mortality [20, 21], and hypoglycemia remains a major limiting factor in treating patients with T2DM, with an estimated prevalence of 12% to 30% depending on treatment [22-24]. Among the various antidiabetic medications available for T2DM, SU was more likely to be associated with hypoglycemia than non-SU antidiabetic medications [25]. Our study confirmed that patients taking SU with their antidiabetic medications had a high incidence of symptomatic hypoglycemia (30%). However, the actual rate of hypoglycemia may vary from that reported herein due to the study design, study population, differences in diabetes education and social status, that may have affected attitudes toward participating in the medical care. In the present study, patients with T2DM having advanced age and Thai ethnicity, one third of retired status and average baseline HbA_{1c} at 7.1 to 7.2% were more likely to have a high incidence of hypoglycemia. Moreover, the report of hypoglycemic incidence, using a medical survey, might have underestimated the prevalence of hypoglycemia among these patients.

The study results showed that the patients with lower compliance reported a higher percentage of being bothered by side effects while neither self-reported experience of hypoglycaemia nor weight gain differed significantly between the two compliance groups. Further research to explore other side effects in addition to hypoglycemia and weight gain is needed.

In our sub-analysis, the greater number of hypoglycemia events observed which involved a low dietary sugar intake and regular fingerstick glucose monitoring, may possibly be due to relatively aggressive glycemic control monitoring. The increased hypoglycemia events observed in this setting was assumed to be due to implementing more stringent goals for metabolic control. In addition, our observational study did not rule out the role of other confounding variables influencing the positive associated outcomes.

In the present study, physicians largely followed the recommendations given to patients with T2DM, supplying metformin to the most obese patients and SU to patients with lower body weight. Similar to related studies [26, 27], we observed a higher incidence of weight gain in the group with only SU treatment, and body weight did not change following treatment with a combination of metformin and SU. Therefore, for patients with T2DM, whose disease cannot be controlled by SU, biguanides might be an appropriate choice depending on whether the patient is overweight and the severity of symptoms.

Macro- or microvascular complications were present among 20.8% of the patients. Related studies have shown that hypoglycemia increased the risk of cardiovascular diseases possibly because of reduced coronary blood flow in the heart and major metabolic stress leading to cardiac arrhythmia [28, 29]. However, none of the T2DM patients in our study were observed to have cardiovascular symptoms during a hypoglycemia attack.

The study had some limitations. By design, this cross-sectional survey and retrospective cohort study used a convenient sample of patients. The study sample was limited to patients in tertiary care hospitals, so the results may not able to be generalized to patients of primary or secondary care hospitals. The observational nature of this study does not rule out the role of residual confounding variables in observed associations. In addition, hospitals' medical records, patient surveys and self-reported treatment experience generally underestimate hypoglycemia associated with oral hypoglycemic agents.

CONCLUSIONS

The major findings among the patients with Thai T2DM patients receiving SU or SU+MET, was that only about half of the patients achieved glycemic goal and compliance to the treatment. Hypoglycemia and weight gain were an important significant burden. Patients with a pronounced weight gain were often treated with SU monotherapy. The fear and worry about hypoglycemia and weight gain were higher among the patients who experienced

hypoglycemic events and weight gain. Therefore, clinicians should also investigate information about patient's past experience on treatment side effects and treatment compliance combining with the effectiveness of the antidiabetic drugs to find out the root cause when target goals are not met in diabetes care.

Figure legends

Figure 1. Participant flow

Supplementary materials

Supplement I: Experience of Low Blood Sugar (Hypoglycemia) Questionnaire

Supplement II: Experience of Weight Gain Questionnaire

Supplement III: Fear of Weight Gain Questionnaire

Supplement IV: Directed acyclic graphs (DAG),

Abbreviations

ADA, American Diabetes Association; HbA_{1c}, $HemoglobinA_{1C}$; MET, Metformin; OR, odd ratio; T2DM, Type 2 diabetes mellitus; SU, Sulfonylurea; 95%CI, 95% confidence interval.

Availability of data and materials

Other statistical analysis results to support the findings of this study are available for one year after publication from the corresponding author by email upon reasonable request. Individual patient data and materials not provided as supplements will not be shared.

Contributors

BS, TP, BO, SS, YB and WN collected the data, drafted the article, reviewed the literature and revised it critically equally. BS and WN provided valuable input in study design, data collection and literature review. All authors read and approved the manuscript and met the criteria for authorship.

Competing interests

The authors declare that they have no competing interests. Although, MSD (Thailand) Ltd supported for the study funding but the study was conducted and the study results were interpreted without the influence of the pharmaceutical company.

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Consent for publication

Publication consent is not applicable.

Ethics approval and consent to participate

This study was approved by the Human Research Ethics Committee of each hospital. (Royal Thai Army Medical Department IRB. Ref No: P039h/55, KKU EC. Ref No: HE551257, Ramathibodi Hospital EC. Ref No: 11-55-24, Faculty of Medicine, Chulalongkorn University, IRB Ref No: 412/55, Siriraj Hospital Ref No: 636/2555(EC4))

Patient and Public Involvement

Neither patients nor public were involved in study planning, design, management, evaluation or interpretation.

Significance of this study

What is already known about this subject?

Sulfonylurea (SU) or combined SU and metformin (SU+MET) are commonly prescribed to Thai T2DM patient. Hypoglycemia or other adverse effects of treatment (i.e., polypharmacy) are a cause of failure to achieve HbA_{1c} goal per ADA recommendation.

What are the new findings?

- More than half of Thai T2DM patients treated with SU monotherapy or SU+MET could not achieve the glycemic goal attainment.
- One half of the patients reported not always taking their medication as prescribed.
- Goal attainment was significantly lower among the patients treated with the combination.
- Feelings of fear or worry about the treatment effects significantly increased in the patients experiencing side effects.

How might these results change the focus of research or clinical practice?

Our results suggest that glycemic goal failure in T2DM patients treated with SU-based therapy may not only be caused from the limitation of medications due to side effects, but non-compliance to the treatment may be a part of failure. The non-compliance may be a result from fear and worry about treatment side effects that the clinician should monitor. Research to identify the root cause of non-compliance and relationship with the failure of glycemic control should be conducted.

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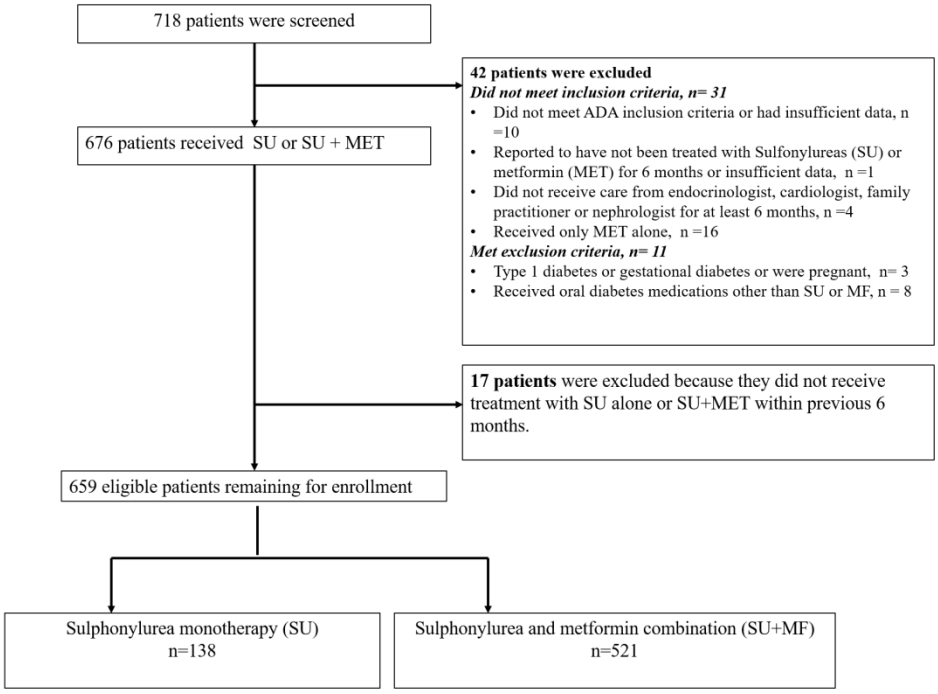


Figure 1. Participant flow

340x253mm (150 x 150 DPI)

SUPPLEMENT I

Experience of Low Blood Sugar (Hypoglycemia)

Below is a list of symptoms you might experience when you have an episode (incident) of hypoglycemia (low blood sugar). Before answering the questions please read the list of symptoms carefully.

Some symptoms of **low blood sugar** (hypoglycemia) are:

- sweating
- shakiness
- dizziness
- hunger
- headache
- pale skin color
- confusion/feeling disoriented
- clumsy or jerky movements
- sudden moodiness or behavior changes
- tingling sensations around the mouth
- difficulty concentrating
- blood sugar is ≤ 70 mg/dL

1. Have you ever felt symptoms of low blood sugar (as described in the box above) in the last 6 months?

☐1 Yes
☐0 No (If no, go to questionnaire HFS)

If **YES**, please tick the box that best describes how severe and how often the symptoms of low blood sugar have been during the last 6 months.

2a. During the last 6 months, did you experience **MILD** symptoms of low blood sugar defined as *Little or no interruption of your activities, and you didn't feel you needed assistance to manage your episode(s) of low blood sugar or symptoms*?

☐1 Yes
☐0 No

2b. How often have you experienced **MILD** symptoms of low blood sugar?

☐0 I did not experience MILD symptoms of low blood sugar
☐1 1 to 2 times over the last 6 months
☐2 3 to 6 times over the last 6 months
☐3 more than once per month
☐4 more than once per week
☐5 everyday

3a. During the last 6 months, did you experience **MODERATE** symptoms of low blood sugar defined as *Some interruption of your activities, but didn't feel you needed assistance to manage your episode (s) of low blood sugar or symptoms*?

☐1 Yes
☐0 No

3b. How often have you experienced **MODERATE** symptoms of low blood sugar?

☐0 I did not experience MODERATE symptoms
☐1 1 to 2 times over the last 6 months
☐2 3 to 6 times over the last 6 months
☐3 more than once per month
☐4 more than once per week
☐5 everyday

4a. During the last 6 months, did you experience **SEVERE** symptoms of low blood sugar defined as *Felt that you needed the assistance of others to manage your episode(s) of low blood sugar or symptoms (for example, to bring you food or drink*)?

SUPPLEMENT I

☐1 Yes
☐0 No

4b. How often have you experienced **SEVERE** symptoms of low blood sugar?

☐0 I did not experience SEVERE symptoms
☐1 1 to 2 times over the last 6 months
☐2 3 to 6 times over the last 6 months
☐3 more than once per month
☐4 more than once per week
☐5 everyday

5a. During the last 6 months, did you experience **VERY SEVERE** symptoms of low blood sugar defined as *Needed medical attention (for example, called an ambulance, visited an emergency room or hospital, or saw a doctor or nurse*)?

☐1 Yes
☐0 No

5b. How many times have you experienced **VERY SEVERE** symptoms of low blood sugar?

|__|__| times during the last 6 months

6. Overall, how much were you bothered by your symptoms of your low blood sugar during the last 6 months?

☐0 Not concerned (I did not have low blood sugar symptoms during the last 6 months)
☐1 Not at all
☐2 A little bit
☐3 Somewhat
☐4 Very
☐5 Extremely

SUPPLEMENT II

Experience of Weight Gain

The following questions ask about weight gain. Please answer every question by *ticking the box* that best represents your opinion. There are no right or wrong answers.

1. During the last year, have you experienced a weight gain without meaning to?

- ☐1 Yes
- ☐2 No I lost weight
- ☐3 No my weight was stable

2. During the last year, how much weight did you gain?

- ☐1 Less than 5 Kilos
- ☐2 Between 5 and 9 kilos
- ☐3 Between 10 and 15 kilos
- ☐4 More than 15 kilos

3. How severe was your weight gain during the last year?

- ☐1 Very mild
- ☐2 Mild
- ☐3 Moderate
- ☐4 Severe
- ☐5 Very severe

4. How much were you bothered by your weight gain during the last year?

- ☐1 Not at all
- ☐2 A little bit
- ☐3 Somewhat
- ☐4 Very
- ☐5 Extremely

5. During the last year, was it difficult for you to maintain your weight?

- ☐1 Not at all
- ☐2 A little bit
- ☐3 Somewhat
- ☐4 Very
- ☐5 Extremely

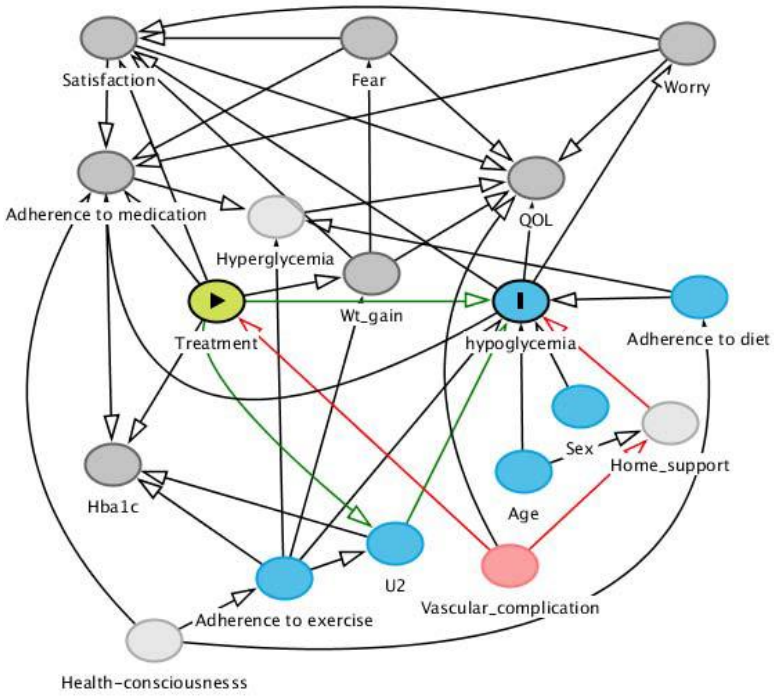
SUPPLEMENT III

Fear of Weight Gain

Please check the box that best describes how often you worry about each of the following items.

	Never	Rarely	Sometimes	Often	Almost Always
1. I worry about gaining weight	☐0	☐1	☐3	☐3	☐4
2. I worry that my diabetic treatment makes me gain weight	☐0	☐1	☐3	☐3	☐4
3. I worry about not being able to stabilise my weight	☐0	☐1	☐3	☐3	☐4

SUPPLEMENT IV



Directed acyclic graph (DAG) linking hypoglycemia, treatment satisfaction, quality of life, worry about hypoglycemia, fear of weight gain and other potentially related variables. In this particular graph hypoglycemia is shown as the outcome of interest and treatment type as the main exposure. Hyperglycemia, home support and the variable labeled U2 areunmeasured variables. U2 represents sensitivity to insulin and other metabolic parameters.

Naturalistic Evaluation of Hypoglycemic Events in Diabetic Subjects (NEEDS STUDY) -

STROBE Statement—checklist of items that should be included in reports of observational studies

	CHECK	Item No	Recommendation
Title and abstract	YES	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract on PAGE 2 - Research Design and Methods: Multicenter cross-sectional, retrospective review study
	YES		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found on PAGE 2 – Abstract
	Introduction		
Background/rationale	YES	2	Explain the scientific background and rationale for the investigation being reported on PAGE 4- Background
Objectives	YES	3	State specific objectives, including any prespecified hypotheses On Page 5 – Line 35 "To address these issues, we assessed the goal attainment rates ……."
	Methods		
Study design	YES	4	Present key elements of study design early in the paper On Page 5 – Line 51 "A multicenter, observational, retrospective and cross-sectional study was conducted ……"
Setting	YES	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection On Page 5-6 – From "5 tertiary care hospitals ……." To " …….Mar 2015"
Participants	YES	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants On Page 6 –Study population
			(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	YES	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable On Page 6 –Study measurements Section
Data sources/	YES	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability

Naturalistic Evaluation of Hypoglycemic Events in Diabetic Subjects (NEEDS STUDY) -

measurement			of assessment methods if there is more than one group On Page 6 –Study measurements Section
Bias	NO	9	Describe any efforts to address potential sources of bias
Study size	YES	10	Explain how the study size was arrived at On Page 6 –Sample Size Section
Quantitative variables	Not related	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	YES	12	(*a*) Describe all statistical methods, On Page 8–Statistical Analysis Section including those used to control for confounding
	NO		(*b*) Describe any methods used to examine subgroups and interactions- **No subgroup analysis**
	NO		(*c*) Explain how missing data were addressed
	NO		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
			(*e*) Describe any sensitivity analyses

Results

Participants	13*	YES	(a) **Report numbers of individuals at each stage of study**—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed On Page 8 : "From 718 patients screened ……." and Figure 1 Participant flow
		YES	(b) Give reasons for non-participation at each stage The reasons are in Figure 1 Participant flow
		YES	(c) Consider use of a flow diagram Figure 1 Participant flow
Descriptive data	14*	YES	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders On page 8 Participants and demographic Section and Table 1.
		YES	(b) Indicate number of participants with missing data for each variable of interest Table 1-5 clearly provided number of participants.
		Not	(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)

Naturalistic Evaluation of Hypoglycemic Events in Diabetic Subjects (NEEDS STUDY) -

		related	
Outcome data	15*	Not related	*Cohort study*—Report numbers of outcome events or summary measures over time
		Not related	*Case-control study*—Report numbers in each exposure category, or summary measures of exposure
		YES	*Cross-sectional study*—Report numbers of outcome events or summary measures Table 1-5 clearly provided number of participants.
Main results	16	YES	(*a*) Give **unadjusted estimates** Table 1-5 clearly provided unadjusted estimates Table 1-5 and Result Section (Page 9-11). For continuous variable, we provide standard deviation. For ratio, we clearly provide the number that can use for 95% CI estimation. All Odd ratios (OR) in Results section were provided along with 95% CI. and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included - -
		NO	(*b*) Report category boundaries when continuous variables were categorized
		Not related	(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Not related	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion			
Key results	18	YES	Summarise key results with reference to study objectives Page 19 line 49, paragraph "Overall, 47.5% of patients had HbA1c values less than 7%. ……."
Limitations	19	YES	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias Page 21 line 26, paragraph "The study had some limitations……."
Interpretation	20	YES	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence Page 21 CONCLUSIONS Section
Generalisability	21	YES	Discuss the generalisability (external validity) of the study results Page 21 Line 30. " The study sample was limited to patients in tertiary care hospitals, so the results may not able to be generalized…"
Other information			

Naturalistic Evaluation of Hypoglycemic Events in Diabetic Subjects (NEEDS STUDY) -

Funding	22	YES	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based Page 22-23, Funding Section.

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Real-world Evaluation of Glycemic Control and Hypoglycemic Events among Type 2 Diabetes Mellitus: A Multicenter, Cross-sectional Study in Thailand (REEDS Study)

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Real-world Evaluation of Glycemic Control and Hypoglycemic Events among Type 2 Diabetes Mellitus: a Multicenter, Cross-sectional Study in Thailand (REEDS Study)

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Abstract

Objective: Patients with type 2 diabetes mellitus (T2DM) often experience hypoglycemia and weight gain due to treatment side effects. Sulfonylureas (SU) and the combination of SU and metformin (SU+MET) were the most common monotherapy and combination therapy in Thailand tertiary care hospitals. This study aimed to assess the glycemic goal attainment rates, hypoglycemic episodes, weight gain, and treatment compliance among T2DM patients receiving SU or SU+MET.

Research Design and Methods: A multicenter cross-sectional survey and retrospective review was conducted in 5 tertiary care hospitals, Thailand. The well-defined T2DM patients aged ≥30 were included consecutively during a 12-month period. Glycemic control, experiences of hypoglycemia, weight gain and compliance were evaluated. Glycemic goal attainment was HbA_{1c} level less than 7%.

Results: Out of the 659 patients (mean age (±SD)), 65.5 (10.0) years and median duration of T2DM (IQR), 10 (5-15) years), 313 (47.5%) achieved the glycemic goal. HbA_{1c} levels in the patients with goal attainment was significantly lower compared to those without (6.3±0.5 vs 8.1±1.2%, p<0.001). Goal attainment was significantly lower among patients treated with SU+MET than those treated with SU alone (43.5% vs. 63.0%; OR: 0.45, 95%CI: 0.31, 0.66, p<0.001). One-third of patients reported experiencing hypoglycemia (30.7%) and weight gain (35.4%). Weight gain in SU+MET group was lower than those receiving SU alone (33.1% vs 44.6%, p=0.015), but there was no difference for hypoglycemic events. Major events in the previous 12 months were experienced by 68 patients, most commonly congestive heart failure and ischemic heart disease. Approximately half of the patients (52.2%) reported not always taking their medication as prescribed.

Conclusions: Among T2DM patients receiving SU or SU+MET, only about half of the patients achieved glycemic goal and compliance with the treatment. Hypoglycemia and weight gain posed a more significant burden and weight gain was related to SU alone.

Strengths and limitations of this study

- Glycemic goal attainment and clinical laboratory results in this study were naturalistic results from the Thai T2DM patients treated with Sulfonylurea (SU) monotherapy or combined SU and Metformin.
- Self-reported hypoglycemia, worry of hypoglycemia, weight gain, fear of weight gain and compliance with medication were collected and reported along with the related factors.
- The study was carried out in tertiary care hospitals, so the results may not able to be generalized to patients of other hospital levels.
- The observational nature of this study does not rule out the role of residual confounding variables in observed associations.
- Use of the patient surveys and self-reported treatment experiences generally underestimate hypoglycemia associated with oral hypoglycemic agents.

BACKGROUND

Type 2 diabetes mellitus (T2DM) is the most common form of DM, accounting for approximately 90% of all cases diagnosed worldwide. The clinical heterogeneity of T2DM patients, in terms of characteristics such as duration of diabetes and comorbid illnesses greatly increases the challenge of providing care[1]. A longer duration of diabetes is associated with more complications and more difficulty maintaining glycemic control. The American Diabetes Association (ADA) [2] and Diabetes Association of Thailand recommends a hemoglobinA1C (HbA1c) target <7.0% for most patients and for patients with HbA1c >9%; a combination of two or more oral hypoglycemic agents and/or insulin should be considered. Sulfonylurea monotherapy (SU) or in combination with metformin (SU+MET) have been the most commonly prescribed oral antidiabetic drugs in some Asian countries [3]. In Thailand, about one-third of the patients (31%) receive antihyperglycemic agent monotherapy and 69% receive combination therapy[4]. The prescribing patterns showed that Sulfonylurea-based therapies predominate. SU was the most commonly prescribed in monotherapy (42%) and SU+MET was the most commonly prescribed in combination therapy (60.2%) [4].

Diabetes is associated with nearly double the risk of death, mainly from cardiovascular disease and increasing concerns propose that some oral hypoglycemic agents may increase the risk of cardiovascular events [5, 6]. Related studies have shown users of SU had a 43% increased risk of all-cause mortality and 70% increased risk for cardiovascular disease mortality compared with patients treated with metformin [7, 8]. More recently, monotherapy with first or second generation SU was significantly associated with a 24% to 61% increased risk for all-cause mortality and second generation SU with an 18% to 30% increased risk for congestive heart failure [9]. Patients with T2DM treated with SU are at high risk of hypoglycemia, weight gain and cardiovascular diseases. In a review of 1,418

reported cases of severe hypoglycemia, 59% of events were related to SU use [10], and in the first year of the UK Prospective Diabetes (UKPDS) study, 31% of patients treated with glibenclamide experienced hypoglycemic symptoms, which was a similar proportion to those treated with insulin [11].

Patients often gain weight due to the side effects of current therapies, particularly SU, insulin and glitazone therapies. In addition, frequent intake of food between regular meals to avoid hypoglycemic events increases the potential for significant weight gain in a population of patients who are already at increased risk from cardiovascular morbidity and mortality [12]. Due to the barrier of hypoglycemia and weight gain, therapies such as SU may not be able to lower glycemic levels sufficiently or long enough to optimally reduce micro- and macrovascular endpoints. It may be prudent to avoid SU among patients with pre-existing cardiovascular conditions as further research in this area is needed. Therefore, treatment with SU may present a particular risk for patients with pre-existing cardiovascular or renal disease. For patients in these practice settings, treatment patterns, goal attainment rates and long-term diabetes complication rates remain unknown. To address these issues, we assessed the goal attainment rates, frequency and severity of hypoglycemic episodes, weight gain experiences and treatment compliance among Thai T2DM patients who had been treated with SU monotherapy or SU and metformin combination therapy.

MATERIALS AND METHODS

Study design and setting

A multicenter, observational, retrospective and cross-sectional study was conducted in 5 tertiary care hospitals, in Thailand (i.e. Srinagarind, Phramongkutklao, Ramathibodi, King Chulalongkorn Memorial, and Siriraj hospitals). T2DM patients' clinical charts were retrospectively reviewed in order to identify potential patients. The potential patients were

invited and enrolled into the study between February 2013 and March 2015. The potential patients were screened during a 6-month study enrollment period. Eligible patients were enrolled into the study at usual physician office visits. Pre-specified medical data was extracted for the 12-month period before a patient's study enrollment date. This study was approved by the Ethics Committee of each hospital. Patients satisfying the selection criteria were enrolled in the study after providing written informed consent to participate.

Study population

The study population comprised adults diagnosed with T2DM according to ADA criteria, and 30 years of age or older, who had been treated with SU monotherapy or SU and metformin combination (SU+MET) therapy for at least six months in each by an endocrinologist, cardiologist, nephrologist or family practitioner. Patients who required daily concomitant insulin, were pregnant, T1DM or gestational diabetes, receiving oral diabetic medications other than SU or SU+MET, already participating in another clinical study, or could not complete the questionnaire, were excluded.

Sample size

We estimated the sample size by using the following formula[13]; $n = \frac{Z^2 \times P(1-P)}{d^2}$. In the Asia Pacific Real-Life Effectiveness and Care Patterns of Diabetes Management (AP RECAP-DM) Study [14], the prevalence of hypoglycemia was reported at 36% (95%: CI = 33.8% to 37.8%). Assuming a proportion of 0.36, a confidence level of 0.95 and a desired margin of error of ±3.5%, n=723 subjects were required for this study.

Study measurements

Age, gender, height, weight, duration of diabetes, age at diagnosis, smoking status, alcohol consumption, physical activity, family history, presence and type of macro and microvascular complications and co-morbid conditions were retrospectively reviewed by physicians or trained chart reviewers from the patients' medical charts and entered into

standardised data collection form. The pre-specified medical data from charts were extracted for the 12-month period before the patient enrollment date.

On the study enrollment date, all participating patients were subjected to a standard blood draw to cross-sectionally assess $HbA_{1c,}$ fasting plasma glucose (FPG), serum creatinine, total-cholesterol, LDL-cholesterol, HDL-cholesterol, triglyceride and urinary albumin levels after overnight fasting to measure fasting. However, when performing blood and urine tests on enrollment date was difficult, the results of the test could be performed within 7 days after the enrollment date. Each patient's body weight, blood pressure and waist circumference were also cross-sectionally measured and recorded. Goal-attainment was defined as a patient having an HbA_{1c} level at the date of enrollment.

The Experience of Low Blood Sugar (Hypoglycemia) Questionnaire (Supplement I) developed by the Merck Sharp & Dohme Corp. (MSD) was used to measure patients' experience of hypoglycemia during the previous 6 months prior to the enrolment. The questionnaire contains 6 items which should be answered by yes/no or by using a 5-point Likert scale. The patients' hypoglycemia symptoms experienced were then stratified by severity (from none, mild, moderate, severe, and very severe) and subsequently classified according to having experienced hypoglycemia (yes/no) and the maximum severity of hypoglycemic episodes experienced. The patient's worry of hypoglycemia were assessed by using the worry scale of Hypoglycemia Fear Survey Questionnaire (HFS II) [15]. Each item was answered using a 5-point Likert scale from being never, rarely, sometimes, often and almost always, respectively.

A questionnaire was developed by Mapi Values (Supplement II) to measure patients' experience of weight gain during the previous year. The questionnaire contained 5 items which could be answered using a 3-, 5-, or 6-point Likert scales. Fear of Weight Gain Questionnaire developed by Mapi Values was used to measure patients' fears of weight gain (Supplement

III). The questionnaire contained 3 items, which should be answered using a 5-point Likert scale ranging from never, rarely, sometimes, often, and almost always, respectively.

Self-reported compliance with medication were assessed by the Self-Report Adherence and Barriers Questionnaire [16]. The level of compliance with the medication used a 5-point Likert scale (5 items), i.e. always, usually, sometimes, rarely and never taken as prescribed.

Statistical analysis

All comparisons were evaluated statistically using chi-square test, Fisher exact test, t-test, rank-sum test, or F-test as appropriate. The odds ratio (OR) (95% confidence interval, 95%CI) of glycemic goal attainment, occurrence of hypoglycemia and weight gain were predicted using a logistic-regression model.

Multivariate relationships were conceptualized using directed acyclic graphs (DAG), and minimum sets of adjustment variables to obtain unbiased estimates of total and direct effects of various exposure variables on occurrence of hypoglycemia, treatment, compliance, treatment satisfaction, quality of life, worry about hypoglycemia and fear of weight gain compatible with the conceptual graph identified (Supplement IV). The DAG was used as the baseline construct for identifying sets of variables on which it was necessary to condition in subsequent in multivariate logistic or linear regression models in order to minimize bias in the estimated coefficients.

Directed acyclic graphs were constructed using DAGitty software (Version 2.3) and All data analyses were performed using STATA release 14.1 (StatCorp, College Station, TX). *P*-value less than 0.05 was considered statistically significant, unless otherwise specified.

RESULTS

Participants and demographics

From 718 patients screened, 659 patients were eligible for study analysis. The participant flow is shown in **Figure 1**. One half (50.7%) were female and mean age (±SD) was 65.5 (±10.0) years. Median duration (IQR) since diagnosis of T2DM was 10 (5-15) years; 321 (48.8%) patients reported that a first degree relative had been diagnosed with T2DM (**Table 1**). The number of patients treated by an endocrinologist, cardiologist, nephrologist and family practice physician comprised 304 (46.1%), 172 (26.1%), 119 (18.1%) and 64 (9.7%), respectively.

A majority of patients (79.1%) had been treated with a combination of SU and metformin and the others with SU alone (20.9%). The proportion of patients treated with SU alone was highest (41.2%) among those treated in a nephrology clinic and lowest among those treated in an endocrinology clinic (12.5%).

Concomitant medications used in the previous six months are shown in **Table 1**. The majority of patients (84.3%) received anti-hypertensive medications in the six months enrollment. These included angiotensin II receptor blockers (ARBs), angiotensin-converting enzyme (ACE) inhibitors, calcium agonists, beta-blockers and various others. A similarly large proportion of patients (549, 83.3%) were receiving lipid lowering medications. These were mostly statins (77.0%) and fibrate (8%). None of the patients were recorded as having received weight-reducing medication during the six months before enrollment.

Goal attainment and related factors

Goal attainment (HbA_{1c} level <7%) was achieved in 313 (47.5%), overall. The level of HbA_{1c} (6.3±0.5 vs. 8.1±1.2 %, p <0.001) and fasting plasma glucose (125.4±29.8 vs. 160.2±46.8, p <0.001) were significantly lower among patients with goal attainment than patients without. Goal attainment was significantly lower among patients treated with the combination of SU and metformin than among those treated with SU alone (43.5% vs. 63.0%; Odd Ratio (OR): 0.45, 95%CI: 0.31 to 0.66, $p < 0.001$). The other demographic and laboratory

variables did not differ significantly between patients with and without goal attainment (**Table 2**).

Hypoglycemia and related factors

Overall, 202 patients (30.7%) reported experiencing at least one hypoglycemic event in the previous six months. Mild hypoglycemia episodes (27.8%) were more frequently experienced than more severe episodes. Among all patients, the maximum severity of hypoglycemia ranged from mild (n=119, 18.1%) to moderate (n= 67, 10.2%) and severe or very severe (n=15, 2.3%). No significant difference was observed in the proportion experiencing hypoglycemia or in the maximum hypoglycemia severity between treatment with SU alone and treatment with SU and metformin (**Table 3**).

Demographic and health-behaviour variables mostly did not differ significantly between patients experiencing and those not experiencing hypoglycemia. However, the patients having hypoglycemic episodes were slightly younger (63.9±10.6 vs. 66.2±9.6 years, p=0.008), reported higher frequencies of taking a low sugar diet (57.7% vs. 47.6%, OR: 1.61, 95%CI 1.06, 2.44, p=0.018) and were more likely to regularly check their finger-stick blood glucose (22.3% vs. 15.1%, OR; 1.50; 95%CI 1.08 to 2.10, p=0.033). Laboratory results and clinical measurements on the date of enrollment showed no significant differences between the hypoglycemia groups with the exception of a slightly lower waist circumference among those experiencing hypoglycemia (**Table 4**). Worry about hypoglycemia score (ranged from 0 to 4) was progressively greater among patients who experienced greater severity of hypoglycemia (mean (95%CI), 0.28 (0.08, 0.32), 0.48 (0.37, 0.59), 0.79 (0.64, 0.93), and 1.05 (0.75, 1.36); p-value <0.001, for no hypoglycemia, mild, moderate, and severe/very severe hypoglycemia experienced, respectively).

Multivariate analysis showed that greater maximum severity of hypoglycemia in the previous 6 months was associated with adherence to a regular diabetic diet (OR 1.68; 95% CI 1.06, 2.67), whereas lower severity was associated with adherence to a regular exercise plan (OR 0.63; 95% CI 0.45, 0.88).

Weight gain and related factors

Weight gain in the previous 12 months was reported among 223 patients (35.4%), with no significant differences among clinic settings, but a lower proportion among those receiving SU and metformin compared with those receiving SU alone (33.1% vs. 44.6%, respectively; OR: 0.61, 95%CI: 0.41 to 0.91, p =0.015). The other demographic and laboratory variables did not differ significantly between patients experiencing and not experiencing weight gain except for significantly higher systolic blood pressure was found among patients experiencing weight gain (137.7±17.7 vs. 133.9±16.5 mmHg, p = 0.007) (**Table 5**). Fear of weight gain score (ranges 0–4) was greater among patients experiencing weight gain (mean (95%CI): 1.08 (0.97, 1.18) vs. 0.40 (0.28, 0.44), $p < 0.001$). Two variables, i.e. the hypoglycemic agents and regular physical activity, identified by the DAG that they effected weight gain. However, only the hypoglycemic agents were the significant variable from univariate analysis.

Major events and vascular complications

Major events in the previous 12 months were experienced by 68 patients (10.4%), most commonly congestive heart failure (27.9%) and ischemic heart disease (11.8%). There was no difference of the major cardiac events, i.e. ischemic heart disease, myocardial infarction, and stroke, between the patients treated with SU and SU+MET (Supplement V). Of these, 28 were hospitalised due to the event. Length of hospital stay ranged from less than 1 day to 43 days, with a mean among those hospitalised patients of 6.9 days. Macro and/or micro vascular complications were experienced by 137 patients (20.8%), mostly commonly ischemic heart

disease (56.9%), renal failure (13.1%) and stroke (12.4%). For obvious reasons, ischemic heart disease, congestive heart failure and myocardial infarction patients were mostly treated in a cardiology clinic and renal failure patients in a nephrology clinic. Renal failure was more common among patients treated with SU alone (7.3%) than among those treated with SU and metformin (1.5%).

Compliance with medications

Compliance with medication reported on the 5-level Likert score was collapsed in two categories: always taking the medication exactly as prescribed and less than always. Slightly more than one half of patients (52.2%) reported not always taking their medication as prescribed. Compared with those reporting that they always took their medication as prescribed, those with lower compliance reported a higher percentage of being bothered by side effects (31 (9.1%) vs. 14 (4.5%), p=0.013) and/or having problems with filling their prescription all or most of the time (31 (9.1%) vs. 13 (4.2%), p=0.021). Neither reported experience of hypoglycemia, recorded weight gain, nor treatment type, differed significantly between the two compliance groups.

Table 1. Demographic characteristics of patients receiving SU or SU plus metformin over the previous 6 months (N=659)

Variable	N=659
Female, n (%)	330 (50.7)
Hypoglycemic agents, n (%)	
Sulfonylurea (SU)	138 (20.9)
Combination of SU and metformin	521 (79.1)
Age (years)	65.5 ± 10.0
Body weight (kg)	66.1 ± 13.3
Height (cm)	160.4 ± 8.7
BMI (kg/m^2)	25.73 ± 4.32
Occupation, n (%)	
Employed	187 (28.5)
Retired	217 (33.1)
Homemaker	164 (25.0)
Disabled	14 (2.1)
Other	73 (11.1)
Median duration of DM (years), median (IQR)	10 (5, 15)
Low sugar diet, n (%)	330 (50.7)
Low calorie diet, n (%)	305 (47.0)
No regular physical activity, n (%)	220 (33.5)
Regular fingerstick glucose monitoring, n (%)	114 (17.3)
Adherence to a regular diabetic, n (%)	86 (13.2%)
Alcohol consumption, n (%)	165 (25.1)
Smoking status	
Current or former smoker	228 (33.5)
Current only	41 (6.2)
Family history: DM in 1st degree relatives, n=565	321 (56.8)
Taking anti-hypertensive agents	556 (84.3)
Beta-blockers	233 (35.6)
ACEIs	192 (29.5)
ARBs	203 (31.2)
Calcium antagonists	241 (37.0)
Others	160 (26.5)
Taking lipid-lowering medications	549 (83.3)
Statins	503 (77.0)
Fibrate	52 (8.0)
Niacin	2 (0.3)
Ezetimibe	22 (3.4)
Others	4 (0.7)

All values are expressed as mean ± SD or number and percentage.
Abbreviations: ACEIs, angiotensin converting enzyme inhibitors; ARBs, angiotensin II receptor blockers (ARBs);

Table 2. Goal attainment (HbA_{1c} <7% on the date of enrollment) by patients' demographics, medical history, laboratory and clinical measurements.

Variable	Number (%) or mean (SD) Goal not attained (N=345)	Goal attained (N=313)	*P value
Patient's demographics and medical history			
Female	184 (54.1)	146 (47.1)	0.084
Age (years)	64.9±10.3	66.2±9.9	0.105
Duration of DM (years)	11.4 ±7.1	10.5±6.8	0.087
BMI (kg/m^2)	25.93 ± 4.34	25.51 ±4.29	0.230
Adherence to regular diabetic diet	48 (14.0)	38 (12.3)	0.523
Low sugar diet	166 (49.0)	163 (56.4)	0.389
Low calorie diet	153 (45.4)	151 (48.6)	0.432
No regular physical activity	106 (30.8)	113 (36.3)	0.137
Regular fingerstick glucose monitoring	64 (18.6)	50 (16.0)	0.410
Alcohol consumption	82 (23.8)	82 (26.3)	0.365
Smoking status	112 (32.5)	116 (37.1)	0.220
Family history: DM in 1st degree relatives	161 (54.8)	159 (58.9)	0.350
Any comorbid macro and vascular conditions	69 (20.1)	68 (21.7)	0.632
Any major events	40 (11.7)	28 (9.0)	0.305
Hypoglycemic agents			
Sulfonylurea (SU)	51 (14.8)	87 (27.8)	<0.001**
Combination of SU and metformin	294 (85.2)	226 (72.2)	
Laboratory at enrollment			
HbA_{1C} (%)	8.10±1.21	6.32±0.48	<0.001**
FPG (mg/dL)	160.2±46.8	125.4±29.8	<0.001**
Serum creatinine (mg/dL)	1.23±1.05	1.28±1.00	0.653
LDL-cholesterol (mg/dL)	101.1±33.9	94.0±32.5	0.050
Triglycerides (mf/dL)	154.9±86.1	141.0±82.3	0.149
Urine albumin (mg/gCr)	91.0±187.1	90.7±342.2	0.996
Clinical measurements at enrollment			
Body weight (kg)	66.1±13.2	66.1±13.3	0.991
Weight gain in previous 12 months	1.40±0.91	1.65±1.58	0.137
Waist circumference (cm)	92.0±10.5	91.8±10.7	0.844
Systolic blood pressure (mmHg)	136.2±18.2	133.7±16.2	0.064
Diastolic blood pressure (mmHg)	74.4±10.0	73.9±10.3	0.509

* Chi-square test or Rank-sum test as appropriate for categorical variables and Independent t-test or Wilcoxon Rank Sum test as appropriate for continuous variables.

***p*-value < 0.05

Abbreviations: DM, Diabetes Mellitus; FPG, fasting plasma glucose; $HbA_{1C,}$ Hemoglobin A_{1C}; HDL, high density lipoprotein; LDL, low density lipoprotein1c

Table 3. Experience of hypoglycemic episodes in the previous 6 months and weight gain in the previous 12 months by treatment type. (N=659)

	Number (%)		*p*-value
	SU (N=138)	SU and metformin (N=521)	
Experience of hypoglycemic episodes in the previous 6 months, n (%)			
No hypoglycemia	93 (67.4)	364 (69.9)	0.604*
Hypoglycemia	45 (32.6)	157 (30.1)	
Maximum severity of hypoglycemic episodes experienced[a]			
No hypoglycemia	93 (67.4)	364 (69.9)	0.656#
Mild	29 (21.0)	90 (17.3)	
Moderate	13 (9.4)	54 (10.4)	
Severe/Very severe	3 (2.2)	12 (2.3)	
Hypoglycemic episodes experience by each severity level, n (%)			
Mild	41 (29.7)	141 (27.1)	
Moderate	15 (10.9)	61 (11.7)	
Severe	2 (1.5)	9 (1.7)	
Very severe	2 (1.5)	3 (0.6)	
Frequency of hypoglycemic episodes for each severity level[a]			
Mild hypoglycemic episodes			
1-2 times over the last 6 months	24 (17.4)	93 (17.9)	
3-6 times over the last 6 months	10 (7.3)	30 (5.8)	
more than once per month	5 (3.6)	12 (2.3)	
more than once per week	2 (1.5)	6 (1.2)	
Moderate hypoglycemic episodes			
1-2 times over the last 6 months	10 (7.3)	44 (8.5)	
3-6 times over the last 6 months	1 (0.7)	9 (1.7)	
more than once per month	4 (2.9)	6 (1.2)	
more than once per week	0	2 (0.4)	
Severe hypoglycemic episodes			
1-2 times over the last 6 months	1 (0.7)	4 (0.8)	
3-6 times over the last 6 months	1 (0.7)	1 (0.2)	
more than once per month	0	4 (0.8)	
Very severe hypoglycemic episodes			
1-2 times over the last 6 months	1 (0.7)	1 (0.2)	
3-6 times over the last 6 months	0	1 (0.2)	

*Chi-square or Fisher exact test as appropriate.
#Likelihood ratio test from proportional logit model.
[a] Numbers may not sum to totals owing to missing data.

Table 4. Clinical factors between patient with and without hypoglycemia in previous 6 months

Variable	Number (%) or mean (SD) No hypoglycemia (N=457)	Number (%) or mean (SD) Hypoglycemia (N=202)	*p-value
Patient's demographics and medical history			
Female	221 (49.2)	109 (54.0)	0.272
Age (years)	66.2±9.6	63.9±10.6	0.008**
BMI (kg/m^2)	25.88 ± 4.23	25.38 ± 4.53	0.190
Duration of DM (years)	10.9±7.1	11.1±6.7	0.738
Low sugar diet	214 (47.6)	116 (57.7)	0.018**
Low calorie diet	203 (45.2)	102 (51.0)	0.174
Adherence to regular diabetic diet	52 (11.5)	34 (17.1)	0.050
No regular physical activity	144(31.7)	76 (27.6)	0.152
Regular fingerstick glucose monitoring	69 (15.1)	45 (22.3)	0.033**
Alcohol consumption	117 (25.6)	48 (24.0)	0.502
Smoking status	163 (35.7)	65 (32.1)	0.558
Family history: DM in 1st degree relatives	219 (55.7)	102 (59.3)	0.461
Any comorbid macro and vascular conditions	99 (55.7)	38 (18.8)	0.407
Any major events	50 (21.8)	18 (9.0)	0.490
Hypoglycemic agents			
Sulfonylurea (SU)	93 (20.3)	45 (22.2)	0.604
Combination of SU and metformin	364 (79.7)	157 (77.7)	
Laboratory at enrollment			
HbA1c (%)	7.29±1.28	7.17±1.31	0.247
FPG (mg/dL)	145.6±44.6	139.4±39.7	0.085
Serum creatinine (mg/dL)	1.26±1.08	1.23±0.89	0.767
LDL-cholesterol (mg/dL)	97.7±33.9	98.1±32.4	0.912
Triglycerides (mf/dL)	150.4±88.0	143.4±75.5	0.507
Urine albumin (mg/gCr)	68.3±169.1	125.2±398.1	0.456
Clinical measurements at enrollment			
Body weight (kg)	66.5±12.9	65.2±14.1	0.239
Weight gain in previous 12 months	1.43±1.11	1.74±1.60	0.101
Waist circumference (cm)	92.4±10.1	91.0±11.7	0.119
Systolic blood pressure (mmHg)	135.7±17.1	133.5±17.6	0.128
Diastolic blood pressure (mmHg)	74.5±10.2	73.4±9.8	0.186

* Chi-square test or Rank-sum test as appropriate for categorical variables and Independent t-test or Wilcoxon Rank Sum test as appropriate for continuous variables.

**p-value < 0.05

Abbreviations: DM, Diabetes Mellitus; FPG, fasting plasma glucose; $HbA_{1C,}$ Hemoglobin A_{1C}; HDL, high density lipoprotein; LDL, low density $lipoprotein_{1c}$

Table 5. Clinical factors between patient with and without weight gain in previous 12 months

Variable	Number (%) or mean (SD)		*p-value
	No weight gained (N=406)	Weight gained (N=223)	
Patient's demographics and medical history			
Female (N, %)	207 (51.9)	112 (50.4)	0.738
Age (years)	65.3±10.0	65.8±9.6	0.558
Duration of DM (years)	10.7±6.8	11.6±7.5	0.159
Low sugar diet	212 (52.7)	104 (47.5)	0.240
Low calorie diet	300 (50.0)	95 (43.4)	0.130
No regular physical activity	147 (36.3)	65 (29.4)	0.093
Regular fingerstick glucose monitoring	64 (15.8)	47 (21.1)	0.102
Alcohol consumption	103 (25.5)	55 (24.7)	0.773
Smoking status	137 (33.7)	55 (24.7)	0.930
Family history: DM in 1st degree relatives	203 (57.8)	84 (55.6)	0.649
Any comorbid macro and vascular conditions	70 (17.3)	52 (23.3)	0.074
Any major events	44 (10.9)	20 (9.0)	0.494
Hypoglycemic agents			
Sulfonylurea (SU)	72 (17.7)	58 (26.0)	0.015**
Combination of SU and metformin	334 (82.3)	165 (74.0)	
Laboratory at enrollment			
HbA_{1C} (%)	7.26±1.31	7.17±1.06	0.397
FPG (mg/dL)	143.7±44.0	141.8±40.4	0.600
Serum creatinine (mg/dL)	1.28±1.17	1.14±0.50	0.240
LDL-cholesterol (mg/dL)	96.4±33.3	100.8±31.8	0.244
Triglycerides (mf/dL)	145.0±78.4	158.6±98.8	0.297
Urine albumin (mg/gCr)	117.8±350.3	55.3±147.6	0.400
Clinical measurements at enrollment			
Body weight (kg)	65.4±13.2	667.3±13.7	0.103
Weight gain in previous 12 months (kg)	-	1.52±1.28	-
Waist circumference (cm)	91.4±9.7	92.8±11.4	0.093
Systolic blood pressure (mmHg)	133.9±16.5	137.7±17.7	0.007**
Diastolic blood pressure (mmHg)	74.2±10.1	74.5±10.2	0.708

* Chi-square test or Rank-sum test as appropriate for categorical variables and Independent t-test or Wilcoxon Rank Sum test as appropriate for continuous variables.
**p-value < 0.05
Abbreviations: DM, Diabetes Mellitus; FPG, fasting plasma glucose; $HbA_{1C,}$ Hemoglobin A_{1C}; HDL, high density lipoprotein; LDL, low density lipoprotein

DISSCUSSION

The present study indicated that SU or a combination of SU and metformin were important tools in attaining glycemic control <7% among advanced T2DM patients. The burden of hypoglycemia and weight gain was high in T2DM patients up to ten years after diabetes diagnosis, and a majority of surveyed patients reported mild symptoms of

hypoglycemia. Initiation of treatment with SU alone was followed by a change in average weight-gain. Overall, the findings support recommendations to adopt a patient-centered approach in selecting T2DM interventions and for setting glycemic goals that minimise the risk of hypoglycemia and weight gain.

Overall, 47.5% of patients had HbA_{1c} values less than 7%. The quality of the glycemic control in our study may seem relatively high with SU plus metformin or sulfonylurea alone when compared with the UKPDS intervention group. In our study, the average HbA_{1c} after median follow-up ten years was approximately 7.1 to 7.2% and the reference range of HbA_{1c} was 7.2 to 7.4 % in UKPDS study after six years [17]. The high average age (65 years) and approximately 50% of compliance scores in the present study in comparison with UKPDS may primarily be ascribed to similar glycemic control and goal attainment with HbA1c level <7%.

Sulfonylureas were the most commonly used drug for monotherapy in Thai patients [18], although the American Diabetes Association and the European Association for the Study of Diabetes consensus algorithm for the T2DM treatment recommends beginning metformin[19]. If SU monotherapy fails to achieve the glycemic target, combination therapy with a second agent with a different mechanism of action will be initiated. The most commonly prescribed combination therapy in Thai patients was SU and metformin [18].

In our study, we observed a significant lower incidence of HbA_{1c} goal attainment among patients treated with SU+MET than those treated with SU alone. There was no difference of diabetes duration between SU and SU + MET groups (median (IQR), 10 (5, 15) and 10 (6, 15) years, respectively, p=0.416). More half of the patient treated with SU+MET for at least six months failed to achieve the glycemic control (294 from 521, 56.4%) in our study. This may infer that the use of the combination to achieve the glycemic target may be not the way to help these patients to achieve the glycemic control. It might be the

confounding variables such delay initiation of combination therapy in uncontrolled diabetes and patient compliance in the observational nature of this study. Moreover, the patients in this study had very low adherence to a regular diabetic treatment (13%). The study to identify the root causes of the failure or development of new novel diabetic agents still have been required.

Patients with increased numbers of hypoglycemia events are at risk for long term complications and mortality [20, 21], and hypoglycemia remains a major limiting factor in treating patients with T2DM, with an estimated prevalence of 12% to 30% depending on treatment [22-24]. Among the various antidiabetic medications available for T2DM, SU was more likely to be associated with hypoglycemia than non-SU antidiabetic medications [25]. Our study confirmed that patients taking SU with their antidiabetic medications had a high incidence of symptomatic hypoglycemia (30%). However, the actual rate of hypoglycemia may vary from that reported herein due to the study design, study population, differences in diabetes education and social status, that may have affected attitudes toward participating in the medical care. In the present study, patients with T2DM having advanced age and Thai ethnicity, one third of retired status and average baseline HbA_{1c} at 7.1 to 7.2% were more likely to have a high incidence of hypoglycemia. Moreover, the report of hypoglycemic incidence, using a medical survey, might underestimate the prevalence of hypoglycemia among these patients because the patients may be unable to recognize the symptoms of mild hypoglycemic events [26]. A study in Europe found that many diabetes patients rarely or never informed their general practitioner/specialist about hypoglycemia events [27]. Therefore, the real burden of hypoglycemia may be underestimated.

The study results showed that the patients with lower compliance reported a higher percentage of being bothered by side effects while neither self-reported experience of hypoglycemia nor weight gain differed significantly between the two compliance groups.

Further research to explore other side effects in addition to hypoglycemia and weight gain is needed.

In our sub-analysis, the greater number of hypoglycemia events observed which involved a low dietary sugar intake and regular fingerstick glucose monitoring, may possibly be due to relatively aggressive glycemic control monitoring. The increased hypoglycemia events observed in this setting was assumed to be due to implementing more stringent goals for metabolic control. In addition, our observational study did not rule out the role of other confounding variables influencing the positive associated outcomes.

In the present study, physicians largely followed the recommendations given to patients with T2DM, supplying metformin to the most obese patients and SU to patients with lower body weight. Similar to related studies [28, 29], we observed a higher incidence of weight gain in the group with only SU treatment, and body weight did not change following treatment with a combination of metformin and SU. Therefore, for patients with T2DM, whose disease cannot be controlled by SU, biguanides might be an appropriate choice depending on whether the patient is overweight and the severity of symptoms.

Macro- or microvascular complications were present among 20.8% of the patients. Related studies have shown that hypoglycemia increased the risk of cardiovascular diseases possibly because of reduced coronary blood flow in the heart and major metabolic stress leading to cardiac arrhythmia [30, 31]. However, none of the T2DM patients in our study were observed to have cardiovascular symptoms during a hypoglycemia attack.

The study had some limitations. By design, this cross-sectional survey and retrospective cohort study used a convenient sample of patients. The study sample was limited to patients in tertiary care hospitals, so the results may not able to be generalized to patients of primary or secondary care hospitals. The observational nature of this study does not rule out the role of residual confounding variables in observed associations. In addition,

hospitals' medical records, patient surveys and self-reported treatment experience generally underestimate hypoglycemia associated with oral hypoglycemic agents.

CONCLUSIONS

The major findings among the patients with Thai T2DM patients receiving SU or SU+MET, was that only about half of the patients achieved glycemic goal and compliance to the treatment. Hypoglycemia and weight gain were an important significant burden. Patients with a pronounced weight gain were often treated with SU monotherapy. The fear and worry about hypoglycemia and weight gain were higher among the patients who experienced hypoglycemic events and weight gain. Therefore, clinicians should also investigate information about patient's past experience on treatment side effects and treatment compliance combining with the effectiveness of the antidiabetic drugs to find out the root cause when target goals are not met in diabetes care.

Figure legends

Figure 1. Participant flow

Supplementary materials

Supplement I: Experience of Low Blood Sugar (Hypoglycemia) Questionnaire

Supplement II: Experience of Weight Gain Questionnaire

Supplement III: Fear of Weight Gain Questionnaire

Supplement IV: Directed acyclic graphs (DAG)

Supplement V: Co-morbid vascular conditions and major events in the previous 12 months by treatments.

Abbreviations

ADA, American Diabetes Association; HbA_{1c}, HemoglobinA_{1C}; MET, Metformin; OR, odd ratio; T2DM, Type 2 diabetes mellitus; SU, Sulfonylurea; 95%CI, 95% confidence interval.

Availability of data and materials

Other statistical analysis results to support the findings of this study are available for one year after publication from the corresponding author by email upon reasonable request. Individual patient data and materials not provided as supplements will not be shared.

Contributors

BS, TP, BO, SS, YB and WN collected the data, drafted the article, reviewed the literature and revised it critically equally. BS and WN provided valuable input in study design, data collection and literature review. All authors read and approved the manuscript and met the criteria for authorship.

Competing interests

The authors declare that they have no competing interests. Although, MSD (Thailand) Ltd supported for the study funding but the study was conducted and the study results were interpreted without the influence of the pharmaceutical company.

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Consent for publication

Publication consent is not applicable.

Ethics approval and consent to participate

This study was approved by the Human Research Ethics Committee of each hospital. (Royal Thai Army Medical Department IRB. Ref No: P039h/55, KKU EC. Ref No: HE551257, Ramathibodi Hospital EC. Ref No: 11-55-24, Faculty of Medicine, Chulalongkorn University, IRB Ref No: 412/55, Siriraj Hospital Ref No: 636/2555(EC4))

Patient and Public Involvement

Neither patients nor public were involved in study planning, design, management, evaluation or interpretation.

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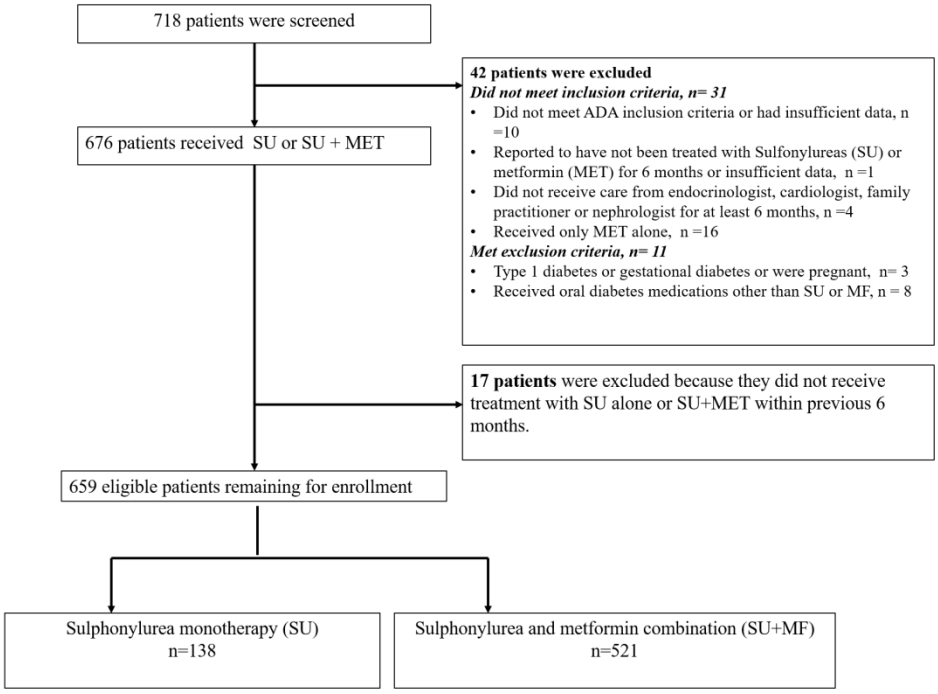


Figure 1. Participant flow

340x253mm (150 x 150 DPI)

SUPPLEMENT I

Experience of Low Blood Sugar (Hypoglycemia)

Below is a list of symptoms you might experience when you have an episode (incident) of hypoglycemia (low blood sugar). Before answering the questions please read the list of symptoms carefully.

Some symptoms of **low blood sugar** (hypoglycemia) are:

- sweating
- shakiness
- dizziness
- hunger
- headache
- pale skin color
- confusion/feeling disoriented
- clumsy or jerky movements
- sudden moodiness or behavior changes
- tingling sensations around the mouth
- difficulty concentrating
- blood sugar is ≤ 70 mg/dL

1. Have you ever felt symptoms of low blood sugar (as described in the box above) in the last 6 months?

☐1 Yes
☐0 No (If no, go to questionnaire HFS)

If **YES**, please tick the box that best describes how severe and how often the symptoms of low blood sugar have been during the last 6 months.

2a. During the last 6 months, did you experience **MILD** symptoms of low blood sugar defined as *Little or no interruption of your activities, and you didn't feel you needed assistance to manage your episode(s) of low blood sugar or symptoms*?

☐1 Yes
☐0 No

2b. How often have you experienced **MILD** symptoms of low blood sugar?

☐0 I did not experience MILD symptoms of low blood sugar
☐1 1 to 2 times over the last 6 months
☐2 3 to 6 times over the last 6 months
☐3 more than once per month
☐4 more than once per week
☐5 everyday

3a. During the last 6 months, did you experience **MODERATE** symptoms of low blood sugar defined as *Some interruption of your activities, but didn't feel you needed assistance to manage your episode (s) of low blood sugar or symptoms*?

☐1 Yes
☐0 No

3b. How often have you experienced **MODERATE** symptoms of low blood sugar?

☐0 I did not experience MODERATE symptoms
☐1 1 to 2 times over the last 6 months
☐2 3 to 6 times over the last 6 months
☐3 more than once per month
☐4 more than once per week
☐5 everyday

4a. During the last 6 months, did you experience **SEVERE** symptoms of low blood sugar defined as *Felt that you needed the assistance of others to manage your episode(s) of low blood sugar or symptoms (for example, to bring you food or drink*)?

SUPPLEMENT I

☐1 Yes
☐0 No

4b. How often have you experienced **SEVERE** symptoms of low blood sugar?

☐0 I did not experience SEVERE symptoms
☐1 1 to 2 times over the last 6 months
☐2 3 to 6 times over the last 6 months
☐3 more than once per month
☐4 more than once per week
☐5 everyday

5a. During the last 6 months, did you experience **VERY SEVERE** symptoms of low blood sugar defined as *Needed medical attention (for example, called an ambulance, visited an emergency room or hospital, or saw a doctor or nurse*)?

☐1 Yes
☐0 No

5b. How many times have you experienced **VERY SEVERE** symptoms of low blood sugar?

|__|__| times during the last 6 months

6. Overall, how much were you bothered by your symptoms of your low blood sugar during the last 6 months?

☐0 Not concerned (I did not have low blood sugar symptoms during the last 6 months)
☐1 Not at all
☐2 A little bit
☐3 Somewhat
☐4 Very
☐5 Extremely

SUPPLEMENT II

Experience of Weight Gain

The following questions ask about weight gain. Please answer every question by *ticking the box* that best represents your opinion. There are no right or wrong answers.

1. During the last year, have you experienced a weight gain without meaning to?

- ☐1 Yes
- ☐2 No I lost weight
- ☐3 No my weight was stable

2. During the last year, how much weight did you gain?

- ☐1 Less than 5 Kilos
- ☐2 Between 5 and 9 kilos
- ☐3 Between 10 and 15 kilos
- ☐4 More than 15 kilos

3. How severe was your weight gain during the last year?

- ☐1 Very mild
- ☐2 Mild
- ☐3 Moderate
- ☐4 Severe
- ☐5 Very severe

4. How much were you bothered by your weight gain during the last year?

- ☐1 Not at all
- ☐2 A little bit
- ☐3 Somewhat
- ☐4 Very
- ☐5 Extremely

5. During the last year, was it difficult for you to maintain your weight?

- ☐1 Not at all
- ☐2 A little bit
- ☐3 Somewhat
- ☐4 Very
- ☐5 Extremely

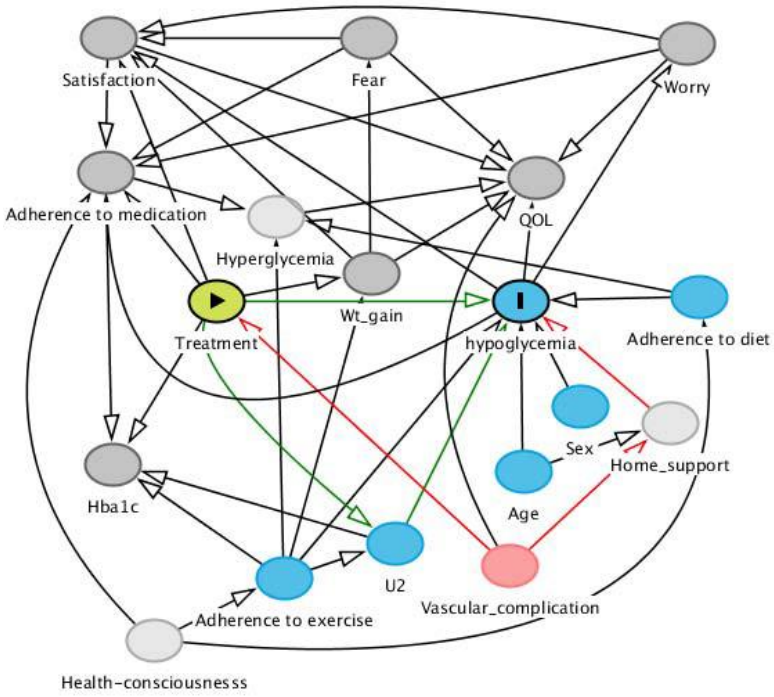
SUPPLEMENT III

Fear of Weight Gain

Please check the box that best describes how often you worry about each of the following items.

	Never	Rarely	Sometimes	Often	Almost Always
1. I worry about gaining weight	☐0	☐1	☐3	☐3	☐4
2. I worry that my diabetic treatment makes me gain weight	☐0	☐1	☐3	☐3	☐4
3. I worry about not being able to stabilise my weight	☐0	☐1	☐3	☐3	☐4

SUPPLEMENT IV



Directed acyclic graph (DAG) linking hypoglycemia, treatment satisfaction, quality of life, worry about hypoglycemia, fear of weight gain and other potentially related variables. In this particular graph hypoglycemia is shown as the outcome of interest and treatment type as the main exposure. Hyperglycemia, home support and the variable labeled U2 areunmeasured variables. U2 represents sensitivity to insulin and other metabolic parameters.

Supplement V: Co-morbid vascular conditions and major events in the previous 12 months by treatment (N=659).

Condition/Event	Total n= 659	SU n=138	SU+MET n=521	P-value*
Co-morbid macro and vascular conditions				
Any	137 (20.8)	36 (26.1)	101 (19.5)	0.099
Ischemic heart disease	78 (11.8)	14 (10.1)	64 (12.3)	0.555
Congestive heart failure	12 (1.8)	2 (1.5)	10 (1.9)	1.000
Myocardial infarction	9 (1.4)	1 (0.7)	8 (1.5)	0.643
Stroke	17 (2.6)	4 (2.9)	13 (2.5)	0.765
Atrial fibrillation	10 (1.5)	3 (2.2)	7 (1.4)	0.445
Blindness	2 (0.3)	1 (0.7)	1 (0.2)	0.376
Renal failure	18 (2.7)	10 (7.3)	8 (1.5)	0.001
Amputation of digit or limb	2 (0.3)	2 (1.5)	0	0.044
Peripheral vascular disease	12 (1.8)	4 (2.9)	8 (1.5)	0.288
Major events				
Any	68 (10.4)	19 (13.8)	48 (9.4)	0.156
Ischemic heart disease	8 (1.2)	3 (2.2)	5 (1.0)	0.375
Congestive heart failure	19 (2.9)	4 (2.9)	15 (2.9)	1.000
Myocardial infarction	3 (0.5)	0	3 (0.6)	1.000
Stroke	2 (0.3)	0	2 (0.4)	1.000
Atrial fibrillation	2 (0.3)	1 (0.7)	1 (0.2)	0.376
Blindness	1 (0.2)	0	1 (0.2)	1.000
Renal failure	3 (0.5)	1 (0.7)	2 (0.4)	0.508
Amputation of digit or limb	2 (0.3)	2 (1.5)	0	0.044
Peripheral vascular disease	2 (0.3)	1 (0.7)	1 (0.2)	0.376
Cancer/malignancy	4 (0.6)	0	4 (0.8)	0.584
Other	26 (4.0)	8 (5.8)	18 (3.5)	0.221

* Fisher exact test.

Numbers may not sum to totals owing to missing data.

Naturalistic Evaluation of Hypoglycemic Events in Diabetic Subjects (NEEDS STUDY) -

STROBE Statement—checklist of items that should be included in reports of observational studies

	CHECK	Item No	Recommendation
Title and abstract	YES	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract on PAGE 2 - Research Design and Methods: Multicenter cross-sectional, retrospective review study
	YES		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found on PAGE 2 – Abstract
	Introduction		
Background/rationale	YES	2	Explain the scientific background and rationale for the investigation being reported on PAGE 4- Background
Objectives	YES	3	State specific objectives, including any prespecified hypotheses On Page 5 – Line 35 "To address these issues, we assessed the goal attainment rates ……."
	Methods		
Study design	YES	4	Present key elements of study design early in the paper On Page 5 – Line 51 "A multicenter, observational, retrospective and cross-sectional study was conducted ……"
Setting	YES	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection On Page 5-6 – From "5 tertiary care hospitals ……." To " …….Mar 2015"
Participants	YES	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants On Page 6 –Study population
			(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	YES	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable On Page 6 –Study measurements Section
Data sources/	YES	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability

Naturalistic Evaluation of Hypoglycemic Events in Diabetic Subjects (NEEDS STUDY) -

measurement			of assessment methods if there is more than one group On Page 6 –Study measurements Section
Bias	NO	9	Describe any efforts to address potential sources of bias
Study size	YES	10	Explain how the study size was arrived at On Page 6 –Sample Size Section
Quantitative variables	Not related	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	YES	12	(*a*) Describe all statistical methods, On Page 8–Statistical Analysis Section including those used to control for confounding
	NO		(*b*) Describe any methods used to examine subgroups and interactions- **No subgroup analysis**
	NO		(*c*) Explain how missing data were addressed
	NO		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
			(*e*) Describe any sensitivity analyses

Results

Participants	13*	YES	(a) **Report numbers of individuals at each stage of study**—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed On Page 8 : "From 718 patients screened ……." and Figure 1 Participant flow
		YES	(b) Give reasons for non-participation at each stage The reasons are in Figure 1 Participant flow
		YES	(c) Consider use of a flow diagram Figure 1 Participant flow
Descriptive data	14*	YES	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders On page 8 Participants and demographic Section and Table 1.
		YES	(b) Indicate number of participants with missing data for each variable of interest Table 1-5 clearly provided number of participants.
		Not	(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)

Naturalistic Evaluation of Hypoglycemic Events in Diabetic Subjects (NEEDS STUDY) -

		related	
Outcome data	15*	Not related	*Cohort study*—Report numbers of outcome events or summary measures over time
		Not related	*Case-control study*—Report numbers in each exposure category, or summary measures of exposure
		YES	*Cross-sectional study*—Report numbers of outcome events or summary measures Table 1-5 clearly provided number of participants.
Main results	16	YES	(*a*) Give **unadjusted estimates** Table 1-5 clearly provided unadjusted estimates Table 1-5 and Result Section (Page 9-11). For continuous variable, we provide standard deviation. For ratio, we clearly provide the number that can use for 95% CI estimation. All Odd ratios (OR) in Results section were provided along with 95% CI. and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included - -
		NO	(*b*) Report category boundaries when continuous variables were categorized
		Not related	(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Not related	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion			
Key results	18	YES	Summarise key results with reference to study objectives Page 19 line 49, paragraph "Overall, 47.5% of patients had HbA1c values less than 7%. ……."
Limitations	19	YES	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias Page 21 line 26, paragraph "The study had some limitations……."
Interpretation	20	YES	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence Page 21 CONCLUSIONS Section
Generalisability	21	YES	Discuss the generalisability (external validity) of the study results Page 21 Line 30. " The study sample was limited to patients in tertiary care hospitals, so the results may not able to be generalized…"
Other information			

Naturalistic Evaluation of Hypoglycemic Events in Diabetic Subjects (NEEDS STUDY) -

Funding	22	YES	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based Page 22-23, Funding Section.

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Real-world Evaluation of Glycemic Control and Hypoglycemic Events among Type 2 Diabetes Mellitus: A Multicenter, Cross-sectional Study in Thailand (REEDS Study)

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Real-world Evaluation of Glycemic Control and Hypoglycemic Events among Type 2 Diabetes Mellitus: a Multicenter, Cross-sectional Study in Thailand (REEDS Study)

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Abstract

Objective: Patients with type 2 diabetes mellitus (T2DM) often experience hypoglycemia and weight gain due to treatment side effects. Sulfonylureas (SU) and the combination of SU and metformin (SU+MET) were the most common monotherapy and combination therapies used in Thailand tertiary care hospitals. This study aimed to assess the glycemic goal attainment rates, hypoglycemic episodes, weight gain, and treatment compliance among T2DM patients receiving SU or SU+MET.

Research Design and Methods: A multicenter cross-sectional survey and retrospective review was conducted in 5 tertiary care hospitals, Thailand. T2DM patients age ≥30 years old were included consecutively during a 12-month period. Glycemic control, experiences of hypoglycemia, weight gain and compliance were evaluated. Glycemic goal attainment was defined by HbA_{1c} level less than 7%.

Results: Out of the 659 patients (mean age (±SD)), 65.5 (10.0) years and median duration of T2DM (IQR), 10 (5-15) years), 313 (47.5%) achieved the glycemic goal. HbA_{1c} levels in the patients with goal attainment was significantly lower compared to those without (6.3±0.5 vs 8.1±1.2%, p<0.001). Goal attainment was significantly lower among patients treated with SU+MET than those treated with SU alone (43.5% vs. 63.0%; OR: 0.45, 95%CI: 0.31, 0.66, p<0.001). One-third of patients reported experiencing hypoglycemia (30.7%) and weight gain (35.4%). Weight gain in SU+MET group was lower than those receiving SU alone (33.1% vs 44.6%, p=0.015), but there was no difference for hypoglycemic events. Major events in the previous 12 months were experienced by 68 patients, most commonly congestive heart failure and ischemic heart disease. Approximately half of the patients (52.2%) reported not always taking their medication as prescribed.

Conclusions: Among T2DM patients receiving SU or SU+MET, only about half of the patients achieved glycemic goal and compliance with the treatment. Hypoglycemia and weight gain posed a significant burden with risk of weight gain higher in SU group.

Strengths and limitations of this study

- Glycemic goal attainment and clinical laboratory results in this study were collected in real-world settings in patients with T2DM who were treated with either Sulfonylurea (SU) monotherapy or combined treatment of SU and Metformin.
- Self-reported hypoglycemia, worry of hypoglycemia, weight gain, fear of weight gain and compliance with medication were collected and reported along with the related factors.
- The study was carried out in tertiary care hospitals, so the results may not able generalizable to patients from other settings.
- The observational nature of this study does not rule out the role of residual confounding variables in observed associations.
- Use of the patient surveys and self-reported treatment experiences can underestimate hypoglycemia associated with oral hypoglycemic agents.

BACKGROUND

Type 2 diabetes mellitus (T2DM) is the most common form of DM, accounting for approximately 90% of all cases diagnosed worldwide. The clinical heterogeneity of T2DM patients, in terms of characteristics such as duration of diabetes and comorbid illnesses greatly increase the challenge of providing care [1]. A longer duration of diabetes is associated with more complications and difficulty maintaining glycemic control. The American Diabetes Association (ADA) [2] and Diabetes Association of Thailand recommends a hemoglobin A_{1C} (HbA_{1c}) target of <7.0% for most patients. For patients with HbA1c >9%, a combination of two or more oral hypoglycemic agents and/or insulin should be considered. Sulfonylurea monotherapy (SU) or the combination with metformin (SU+MET) have been the most commonly prescribed oral antidiabetic drugs in some Asian countries [3]. In Thailand, about one-third of the patients (31%) receive monotherapy and vast majority (69%) receive combination therapy [4]. The prescribing patterns showed that Sulfonylurea-based monotherapies are very common. SU was the most commonly prescribed monotherapy treatment (42%), more so than metformin monotherapy, and SU+MET was the most commonly prescribed combination therapy (60.2%) [4].

Diabetes is associated with nearly double the risk of death, mainly from cardiovascular disease. Some oral hypoglycemic agents may increase the risk of cardiovascular events [5, 6]. Related studies have shown users of SU had a 43% increased risk of all-cause mortality and 70% increased risk for cardiovascular disease mortality compared with patients treated with metformin [7, 8]. More recently, monotherapy with first or second generation SU was significantly associated with a 24% to 61% increased risk for all-cause mortality and second generation SU drugs had 18% to 30% increased risk for congestive heart failure [9]. Patients with T2DM treated with SU are at high risk of hypoglycemia, weight gain, and cardiovascular disease. In a review of 1,418 reported cases

of severe hypoglycemia, 59% of events were related to SU use [10], and in the first year of the UK Prospective Diabetes (UKPDS) study, 31% of patients treated with glibenclamide experienced hypoglycemic symptoms, which was a similar proportion to those receiving insulin [11].

Patients often gain weight due to the side effects of current therapies, particularly SU, insulin and glitazone therapies. In addition, frequent intake of food between regular meals to avoid hypoglycemic events increases the potential for significant weight gain in a population of patients who are already at an increased risk from cardiovascular morbidity and mortality [12]. Due to the barrier of hypoglycemia and weight gain, therapies such as SU may not be able to lower glycemic levels sufficiently or long enough to optimally reduce micro- and macrovascular endpoints. It may be prudent to avoid SU monotherapy as first line treatment, among patients with pre-existing cardiovascular conditions as further research in this area is needed. Therefore, treatment with SU may present a particular risk for patients with pre-existing cardiovascular or renal disease. For patients in these practice settings, treatment patterns, goal attainment rates, and long-term diabetes complication rates remain unknown. To address these issues, we assessed the goal attainment rates, frequency and severity of hypoglycemic episodes, weight gain experiences and treatment compliance among Thai T2DM patients who had been treated with SU monotherapy or SU and metformin combination therapy.

MATERIALS AND METHODS

Study design and setting

A multicenter, observational, retrospective and cross-sectional study was conducted in 5 tertiary care hospitals, in Thailand (i.e. Srinagarind, Phramongkutklao, Ramathibodi, King Chulalongkorn Memorial, and Siriraj Hospitals). T2DM patients' clinical charts were

retrospectively reviewed in order to identify potential patients. The potential patients were invited and enrolled into the study between February 2013 and March 2015. The potential patients were screened during a 6-month study enrollment period. Eligible patients were enrolled into the study at usual physician office visits. Pre-specified medical data was extracted for the 12-month period before a patient's study enrollment date. This study was approved by the Ethics Committee of each hospital. Patients satisfying the selection criteria were enrolled in the study after providing written informed consent to participate.

Study population

The study population comprised of adults diagnosed with T2DM according to ADA criteria, and 30 years of age or older, who had been treated with SU monotherapy or SU and metformin combination (SU+MET) therapy for at least six months by an endocrinologist, cardiologist, nephrologist or family practitioner. Patients who required daily concomitant insulin, were pregnant, had diagnosis of T1DM or gestational diabetes, receiving oral diabetic medications other than SU or SU+MET, already participating in another clinical study, or could not complete the questionnaire, were excluded.

Sample size

We estimated the sample size by using the following formula [13]; $n = \frac{Z^2 \times P(1-P)}{d^2}$. In the Asia Pacific Real-Life Effectiveness and Care Patterns of Diabetes Management (AP RECAP-DM) Study [14], the prevalence of hypoglycemia was reported at 36% (95%: CI = 33.8% to 37.8%). Assuming a proportion of 0.36, a confidence level of 0.95 and a desired margin of error of ±3.5%, 723 subjects were required for this study.

Study measurements

Age, gender, height, weight, duration of diabetes, age at diagnosis, smoking status, alcohol consumption, physical activity, family history, presence and type of macro and microvascular complications and co-morbid conditions were retrospectively reviewed by

physicians or trained chart reviewers utilizing the patients' medical charts and data was entered into standardized data collection forms. The pre-specified information from medical charts was extracted for the 12-month period before the patient enrollment date.

On the study enrollment date, all participating patients were subjected to a standard blood draw to cross-sectionally assess HbA_{1c}, fasting plasma glucose (FPG), serum creatinine, total-cholesterol, LDL-cholesterol, HDL-cholesterol, triglyceride and urinary albumin levels after overnight fasting. Since performing the blood and urine tests on enrollment date was not always possible, the collection of blood or urine samples could be performed within 7 days after the enrollment date. Each patient's body weight, blood pressure, and waist circumference were also cross-sectionally measured and recorded. Goal-attainment was defined as having HbA_{1c} <7% on the date of enrollment.

The Experience of Low Blood Sugar (hypoglycemia) Questionnaire (Supplement I) developed by the Merck Sharp & Dohme Corp. (MSD) was used to measure patients' experience of hypoglycemia during the previous 6 months. The questionnaire contained 6 items which could be answered by yes/no or by using a 5-point Likert scale. The patients' hypoglycemia symptoms were then stratified by severity (from none, mild, moderate, severe, and very severe) and subsequently classified according to having experienced hypoglycemia (yes/no) and the maximum severity of hypoglycemic episodes experienced. The patient's worry of hypoglycemia was assessed by using the worry scale of Hypoglycemia Fear Survey Questionnaire (HFS II) [15]. Each item was answered using a 5-point Likert scale from being never, rarely, sometimes, often and almost always worried, respectively.

A questionnaire was developed by Mapi Values (Supplement II) to measure patients' experiences of weight gain during the previous year. The questionnaire contained 5 items which could be answered using a 3-, 5-, or 6-point Likert scales. In addition, Fear of Weight Gain Questionnaire developed by Mapi Values was used to measure patients' fears of weight

gain (Supplement III). The questionnaire contained 3 items, which were answered using a 5-point Likert scale ranging from never, rarely, sometimes, often, and almost always worry, respectively.

Self-reported compliance with medication was assessed by the Self-Report Adherence and Barriers Questionnaire [16]. The level of compliance with the medication was assessed on a 5-point Likert scale (5 items), i.e. always, usually, sometimes, rarely and never take as prescribed.

Statistical analysis

All comparisons were evaluated using chi-square test, Fisher exact test, t-test, rank-sum test, or F-test as appropriate. The odds ratio (OR) (95% confidence interval, 95%CI) of glycemic goal attainment, occurrence of hypoglycemia, and weight gain were predicted using a logistic-regression model.

Multivariate relationships were conceptualized using directed acyclic graphs (DAG), and minimum sets of adjustment variables to obtain unbiased estimates of total and direct effects of various exposure variables on occurrence of hypoglycemia, treatment, compliance, treatment satisfaction, quality of life, worry about hypoglycemia and fear of weight gain compatible with the conceptual graph identified (Supplement IV). The DAG was used as the baseline construct for identifying sets of variables on which it was necessary to condition subsequent multivariate logistic or linear regression models in order to minimize bias in the estimated coefficients. Directed acyclic graphs were constructed using DAGitty software (Version 2.3) and all data analyses were performed using STATA release 14.1 (StatCorp, College Station, TX). *P*-values less than 0.05 were considered statistically significant, unless otherwise specified.

Patient and Public Involvement

Neither patients nor public were involved in study planning, design, management, evaluation or interpretation.

RESULTS

Participants and demographics

From 718 patients screened, 659 patients were eligible for study analysis. The participant flow is shown in **Figure 1**. One half (50.7%) were female and mean age (±SD) was 65.5 (±10.0) years. Median duration (IQR) since diagnosis of T2DM was 10 (5-15) years; 321 (48.8%) patients reported that a first degree relative had been diagnosed with T2DM (**Table 1**). The number of patients treated by an endocrinologist, cardiologist, nephrologist and family practice physician comprised 304 (46.1%), 172 (26.1%), 119 (18.1%) and 64 (9.7%) of the enrolled patients, respectively.

A majority of patients (79.1%) had been treated with a combination of SU and metformin, while the remaining patients were treated with SU monotherapy (20.9%). The proportion of patients treated with SU alone was highest (41.2%) among those treated in a nephrology clinic and lowest among those treated in an endocrinology clinic (12.5%).

Concomitant medications used in the previous six months are shown in **Table 1**. The majority of patients (84.3%) received anti-hypertensive medications in the previous six months. These included angiotensin II receptor blockers (ARBs), angiotensin-converting enzyme (ACE) inhibitors, calcium antagonists, beta-blockers and others. A similarly large proportion of patients (549, 83.3%) received lipid lowering medications. These were mostly statins (77.0%) and fibrate class drugs (8%). None of the patients were recorded as having received weight-reducing medication during the six months before enrollment.

Goal attainment and related factors

Goal attainment (HbA_{1c} level <7%) was achieved in 313 (47.5%), overall. The level of HbA_{1c} (6.3±0.5 vs. 8.1±1.2 %, p <0.001) and fasting plasma glucose (125.4±29.8 vs. 160.2±46.8, p <0.001) were significantly lower among patients with goal attainment than patients without. Goal attainment was significantly lower among patients treated with SU and metformin combination than among those treated with SU alone (43.5% vs. 63.0%; Odd Ratio (OR): 0.45, 95%CI: 0.31 to 0.66, $p < 0.001$). The other demographic and laboratory variables did not differ significantly between patients with and without goal attainment (**Table 2**).

Hypoglycemia and related factors

Overall, 202 patients (30.7%) reported experiencing at least one hypoglycemic event in the previous six months. Mild hypoglycemia episodes (27.8%) were more frequently experienced than severe episodes. Among all patients, the maximum severity of hypoglycemia ranged from mild (n=119, 18.1%) to moderate (n= 67, 10.2%) and severe or very severe (n=15, 2.3%). No significant difference was observed in the proportion experiencing hypoglycemia, or the maximum hypoglycemia severity, between treatment with SU alone and treatment with SU and metformin combination (**Table 3**).

Demographic and health-behavior variables generally did not differ significantly between patients experiencing and those not experiencing hypoglycemia. However, the patients having hypoglycemic episodes were slightly younger (63.9±10.6 vs. 66.2±9.6 years, p=0.008), reported higher frequencies of taking a low sugar diet (57.7% vs. 47.6%, OR: 1.61, 95% CI 1.06, 2.44, p=0.018) and were more likely to regularly check their finger-stick blood glucose (22.3% vs. 15.1%, OR; 1.50; 95% CI 1.08 to 2.10, p=0.033). Laboratory results and clinical measurements on the date of enrollment showed no significant differences between hypoglycemia groups with the exception of a slightly lower waist circumference among those

experiencing hypoglycemia (**Table 4**). Worry about hypoglycemia score (ranged from 0 to 4) was progressively greater among patients who experienced greater severity of hypoglycemia with mean (95%CI) values of 0.28 (0.08, 0.32), 0.48 (0.37, 0.59), 0.79 (0.64, 0.93), and 1.05 (0.75, 1.36); *p*-value <0.001, for no hypoglycemia, mild, moderate, and severe/very severe hypoglycemia, respectively.

Multivariate analysis showed that greater maximum severity of hypoglycemia in the previous 6 months was associated with adherence to a regular diabetic diet (OR 1.68; 95% CI 1.06, 2.67), whereas lower severity was associated with adherence to a regular exercise plan (OR 0.63; 95% CI 0.45, 0.88).

Weight gain and related factors

Weight gain in the previous 12 months was reported among 223 patients (35.4%), with no significant differences among clinic settings, but a lower proportion among those receiving SU and metformin combination compared to those receiving SU alone (33.1% vs. 44.6%, respectively; OR: 0.61, 95%CI: 0.41 to 0.91, p =0.015). The other demographic and laboratory variables did not differ significantly between patients experiencing and not experiencing weight gain except for significantly higher systolic blood pressure found among patients experiencing weight gain (137.7±17.7 vs. 133.9±16.5 mmHg, p = 0.007) (**Table 5**). Fear of weight gain score (ranges 0–4) was greater among patients experiencing weight gain (mean (95%CI): 1.08 (0.97, 1.18) vs. 0.40 (0.28, 0.44), p < 0.001). Two variables, the hypoglycemic agents and regular physical activity were identified by the DAG to have an effect on weight gain. However, only the hypoglycemic agents were significant variable based on univariate analysis.

Major events and vascular complications

Major events in the previous 12 months were experienced by 68 patients (10.4%), most commonly congestive heart failure (27.9%) and ischemic heart disease (11.8%). There was no difference in the number of the major cardiac events, i.e. ischemic heart disease, myocardial infarction, and stroke, between the patients treated with SU and SU+MET (Supplement V). Twenty-eight patients were hospitalized due to the major event. Length of hospital stay ranged from less than 1 day to 43 days, with a mean hospital stay of 6.9 days. Macro and/or micro vascular complications were experienced by 137 patients (20.8%), ischemic heart disease (56.9%), renal failure (13.1%) and stroke (12.4%). For obvious reasons, ischemic heart disease, congestive heart failure and myocardial infarction patients were mostly treated in a cardiology clinic and renal failure patients in a nephrology clinic. Renal failure was more common among patients treated with SU alone (7.3%) than among those treated with SU and metformin combination (1.5%) which was statistically significant.

Compliance with medications

Compliance with medication reported on the 5-level Likert score was collapsed into two categories: always taking the medication exactly as prescribed and less than always. Slightly more than one half of patients (52.2%) reported not always taking their medication as prescribed. Compared with those reporting that they always took their medication as prescribed, those with lower compliance reported a higher percentage of being bothered by side effects (31 (9.1%) vs. 14 (4.5%), p=0.013) and/or having problems with filling their prescription all or most of the time (31 (9.1%) vs. 13 (4.2%), p=0.021). There was no difference in the experience of hypoglycemia, recorded weight gain, and the treatment (SU vs. SU+MET) between the two compliance groups.

Table 1. Demographic characteristics of patients receiving SU or SU plus metformin over the previous 6 months (N=659)

Variable	N=659
Female, n (%)	330 (50.7)
Hypoglycemic agents, n (%)	
Sulfonylurea (SU)	138 (20.9)
Combination of SU and metformin	521 (79.1)
Age (years)	65.5 ± 10.0
Body weight (kg)	66.1 ± 13.3
Height (cm)	160.4 ± 8.7
BMI (kg/m^2)	25.73 ± 4.32
Occupation, n (%)	
Employed	187 (28.5)
Retired	217 (33.1)
Homemaker	164 (25.0)
Disabled	14 (2.1)
Other	73 (11.1)
Median duration of DM (years), median (IQR)	10 (5, 15)
Low sugar diet, n (%)	330 (50.7)
Low calorie diet, n (%)	305 (47.0)
No regular physical activity, n (%)	220 (33.5)
Regular fingerstick glucose monitoring, n (%)	114 (17.3)
Adherence to a regular diabetic diet, n (%)	86 (13.2)
Alcohol consumption, n (%)	165 (25.1)
Smoking status	
Current or former smoker	228 (33.5)
Current only	41 (6.2)
Family history: DM in 1st degree relatives, n=565	321 (56.8)
Taking anti-hypertensive agents	556 (84.3)
Beta-blockers	233 (35.6)
ACEIs	192 (29.5)
ARBs	203 (31.2)
Calcium antagonists	241 (37.0)
Others	160 (26.5)
Taking lipid-lowering medications	549 (83.3)
Statins	503 (77.0)
Fibrate	52 (8.0)
Niacin	2 (0.3)
Ezetimibe	22 (3.4)
Others	4 (0.7)

All values are expressed as mean ± SD or number and percentage.
Abbreviations: ACEIs, angiotensin converting enzyme inhibitors; ARBs, angiotensin II receptor blockers (ARBs);

Table 2. Goal attainment (HbA_{1c} <7% on the date of enrollment) by patients' demographics, medical history, laboratory and clinical measurements.

Variable	Number (%) or mean (SD) Goal not attained (N=345)	Goal attained (N=313)	*P value
Patient's demographics and medical history			
Female	184 (54.1)	146 (47.1)	0.084
Age (years)	64.9±10.3	66.2±9.9	0.105
Duration of DM (years)	11.4 ±7.1	10.5±6.8	0.087
BMI (kg/m^2)	25.93 ± 4.34	25.51 ±4.29	0.230
Adherence to regular diabetic diet	48 (14.0)	38 (12.3)	0.523
Low sugar diet	166 (49.0)	163 (56.4)	0.389
Low calorie diet	153 (45.4)	151 (48.6)	0.432
No regular physical activity	106 (30.8)	113 (36.3)	0.137
Regular fingerstick glucose monitoring	64 (18.6)	50 (16.0)	0.410
Alcohol consumption	82 (23.8)	82 (26.3)	0.365
Smoking status	112 (32.5)	116 (37.1)	0.220
Family history: DM in 1st degree relatives	161 (54.8)	159 (58.9)	0.350
Any comorbid macro and vascular conditions	69 (20.1)	68 (21.7)	0.632
Any major events	40 (11.7)	28 (9.0)	0.305
Hypoglycemic agents			
Sulfonylurea (SU)	51 (14.8)	87 (27.8)	<0.001**
Combination of SU and metformin	294 (85.2)	226 (72.2)	
Laboratory at enrollment			
HbA_{1C} (%)	8.10±1.21	6.32±0.48	<0.001**
FPG (mg/dL)	160.2±46.8	125.4±29.8	<0.001**
Serum creatinine (mg/dL)	1.23±1.05	1.28±1.00	0.653
LDL-cholesterol (mg/dL)	101.1±33.9	94.0±32.5	0.050
Triglycerides (mg/dL)	154.9±86.1	141.0±82.3	0.149
Urine albumin (mg/gCr)	91.0±187.1	90.7±342.2	0.996
Clinical measurements at enrollment			
Body weight (kg)	66.1±13.2	66.1±13.3	0.991
Weight gain in previous 12 months	1.40±0.91	1.65±1.58	0.137
Waist circumference (cm)	92.0±10.5	91.8±10.7	0.844
Systolic blood pressure (mmHg)	136.2±18.2	133.7±16.2	0.064
Diastolic blood pressure (mmHg)	74.4±10.0	73.9±10.3	0.509

* Chi-square test or Rank-sum test as appropriate for categorical variables and Independent t-test or Wilcoxon Rank Sum test as appropriate for continuous variables.

***p*-value < 0.05

Abbreviations: DM, Diabetes Mellitus; FPG, fasting plasma glucose; $HbA_{1C,}$ Hemoglobin A_{1C}; HDL, high density lipoprotein; LDL, low density lipoprotein1c

Table 3. Experience of hypoglycemic episodes in the previous 6 months by treatment type. (N=659)

	Number (%)		*p*-value
	SU (N=138)	SU and metformin (N=521)	
Experience of hypoglycemic episodes in the previous 6 months, n (%)			
No hypoglycemia	93 (67.4)	364 (69.9)	0.604*
Hypoglycemia	45 (32.6)	157 (30.1)	
Maximum severity of hypoglycemic episodes experienced[a]			
No hypoglycemia	93 (67.4)	364 (69.9)	0.656#
Mild	29 (21.0)	90 (17.3)	
Moderate	13 (9.4)	54 (10.4)	
Severe/Very severe	3 (2.2)	12 (2.3)	
Hypoglycemic episodes experience by each severity level, n (%)			
Mild	41 (29.7)	141 (27.1)	
Moderate	15 (10.9)	61 (11.7)	
Severe	2 (1.5)	9 (1.7)	
Very severe	2 (1.5)	3 (0.6)	
Frequency of hypoglycemic episodes for each severity level[a]			
Mild hypoglycemic episodes			
1-2 times over the last 6 months	24 (17.4)	93 (17.9)	
3-6 times over the last 6 months	10 (7.3)	30 (5.8)	
more than once per month	5 (3.6)	12 (2.3)	
more than once per week	2 (1.5)	6 (1.2)	
Moderate hypoglycemic episodes			
1-2 times over the last 6 months	10 (7.3)	44 (8.5)	
3-6 times over the last 6 months	1 (0.7)	9 (1.7)	
more than once per month	4 (2.9)	6 (1.2)	
more than once per week	0	2 (0.4)	
Severe hypoglycemic episodes			
1-2 times over the last 6 months	1 (0.7)	4 (0.8)	
3-6 times over the last 6 months	1 (0.7)	1 (0.2)	
more than once per month	0	4 (0.8)	
Very severe hypoglycemic episodes			
1-2 times over the last 6 months	1 (0.7)	1 (0.2)	
3-6 times over the last 6 months	0	1 (0.2)	

*Chi-square or Fisher exact test as appropriate.
#Likelihood ratio test from proportional logit model.
[a] Numbers may not sum to totals owing to missing data.

Table 4. Clinical factors between patient with and without hypoglycemia in previous 6 months

Variable	Number (%) or mean (SD) No hypoglycemia (N=457)	Number (%) or mean (SD) Hypoglycemia (N=202)	*p-value
Patient's demographics and medical history			
Female	221 (49.2)	109 (54.0)	0.272
Age (years)	66.2±9.6	63.9±10.6	0.008**
BMI (kg/m^2)	25.88 ± 4.23	25.38 ± 4.53	0.190
Duration of DM (years)	10.9±7.1	11.1±6.7	0.738
Low sugar diet	214 (47.6)	116 (57.7)	0.018**
Low calorie diet	203 (45.2)	102 (51.0)	0.174
Adherence to regular diabetic diet	52 (11.5)	34 (17.1)	0.050
No regular physical activity	144(31.7)	76 (27.6)	0.152
Regular fingerstick glucose monitoring	69 (15.1)	45 (22.3)	0.033**
Alcohol consumption	117 (25.6)	48 (24.0)	0.502
Smoking status	163 (35.7)	65 (32.1)	0.558
Family history: DM in 1st degree relatives	219 (55.7)	102 (59.3)	0.461
Any comorbid macro and vascular conditions	99 (55.7)	38 (18.8)	0.407
Any major events	50 (21.8)	18 (9.0)	0.490
Hypoglycemic agents			
Sulfonylurea (SU)	93 (20.3)	45 (22.2)	0.604
Combination of SU and metformin	364 (79.7)	157 (77.7)	
Laboratory at enrollment			
HbA1c (%)	7.29±1.28	7.17±1.31	0.247
FPG (mg/dL)	145.6±44.6	139.4±39.7	0.085
Serum creatinine (mg/dL)	1.26±1.08	1.23±0.89	0.767
LDL-cholesterol (mg/dL)	97.7±33.9	98.1±32.4	0.912
Triglycerides (mg/dL)	150.4±88.0	143.4±75.5	0.507
Urine albumin (mg/gCr)	68.3±169.1	125.2±398.1	0.456
Clinical measurements at enrollment			
Body weight (kg)	66.5±12.9	65.2±14.1	0.239
Weight gain in previous 12 months	1.43±1.11	1.74±1.60	0.101
Waist circumference (cm)	92.4±10.1	91.0±11.7	0.119
Systolic blood pressure (mmHg)	135.7±17.1	133.5±17.6	0.128
Diastolic blood pressure (mmHg)	74.5±10.2	73.4±9.8	0.186

* Chi-square test or Rank-sum test as appropriate for categorical variables and Independent t-test or Wilcoxon Rank Sum test as appropriate for continuous variables.

**p-value < 0.05

Abbreviations: DM, Diabetes Mellitus; FPG, fasting plasma glucose; $HbA_{1C,}$ Hemoglobin A_{1C}; HDL, high density lipoprotein; LDL, low density $lipoprotein_{1c}$

Table 5. Clinical factors between patient with and without weight gain in previous 12 months

Variable	Number (%) or mean (SD)		*p-value
	No weight gained (N=406)	Weight gained (N=223)	
Patient's demographics and medical history			
Female (N, %)	207 (51.9)	112 (50.4)	0.738
Age (years)	65.3±10.0	65.8±9.6	0.558
Duration of DM (years)	10.7±6.8	11.6±7.5	0.159
Low sugar diet	212 (52.7)	104 (47.5)	0.240
Low calorie diet	300 (50.0)	95 (43.4)	0.130
No regular physical activity	147 (36.3)	65 (29.4)	0.093
Regular fingerstick glucose monitoring	64 (15.8)	47 (21.1)	0.102
Alcohol consumption	103 (25.5)	55 (24.7)	0.773
Smoking status	137 (33.7)	55 (24.7)	0.930
Family history: DM in 1st degree relatives	203 (57.8)	84 (55.6)	0.649
Any comorbid macro and vascular conditions	70 (17.3)	52 (23.3)	0.074
Any major events	44 (10.9)	20 (9.0)	0.494
Hypoglycemic agents			
Sulfonylurea (SU)	72 (17.7)	58 (26.0)	0.015**
Combination of SU and metformin	334 (82.3)	165 (74.0)	
Laboratory at enrollment			
HbA_{1C} (%)	7.26±1.31	7.17±1.06	0.397
FPG (mg/dL)	143.7±44.0	141.8±40.4	0.600
Serum creatinine (mg/dL)	1.28±1.17	1.14±0.50	0.240
LDL-cholesterol (mg/dL)	96.4±33.3	100.8±31.8	0.244
Triglycerides (mg/dL)	145.0±78.4	158.6±98.8	0.297
Urine albumin (mg/gCr)	117.8±350.3	55.3±147.6	0.400
Clinical measurements at enrollment			
Body weight (kg)	65.4±13.2	667.3±13.7	0.103
Weight gain in previous 12 months (kg)	-	1.52±1.28	-
Waist circumference (cm)	91.4±9.7	92.8±11.4	0.093
Systolic blood pressure (mmHg)	133.9±16.5	137.7±17.7	0.007**
Diastolic blood pressure (mmHg)	74.2±10.1	74.5±10.2	0.708

* Chi-square test or Rank-sum test as appropriate for categorical variables and Independent t-test or Wilcoxon Rank Sum test as appropriate for continuous variables.
**p-value < 0.05
Abbreviations: DM, Diabetes Mellitus; FPG, fasting plasma glucose; $HbA_{1C,}$ Hemoglobin A_{1C}; HDL, high density lipoprotein; LDL, low density lipoprotein

DISCUSSION

The present study indicated that SU or a combination of SU and metformin were important tools in attaining glycemic control <7% among advanced T2DM patients in Thailand. The burden of hypoglycemia and weight gain was high in T2DM patients up to ten years after diabetes diagnosis, with majority of surveyed patients reporting mild symptoms of

hypoglycemia. Initiation of treatment with SU alone was associated with higher average weight-gain. Overall, the findings support recommendations to adopt a patient-centered approach in selecting T2DM interventions. Choice of treatment should prioritize achievement of glycemic goals that at the same times minimizes the risk of hypoglycemia and weight gain.

Overall, 47.5% of patients had HbA_{1c} values less than 7%. The quality of the glycemic control in our study may seem relatively high with SU plus metformin or sulfonylurea alone when compared with the UKPDS intervention group. In our study, the average HbA_{1c} after median follow-up of ten years was approximately 7.1 to 7.2%, depending on treatment group, and the reference range of HbA_{1c} was 7.2 to 7.4 % in UKPDS study after six years [17]. Similar to UKPDS, the average age (65 years) of the study population and approximately 50% compliance that was reported may explain the results for glycemic control and HbA1c goal attainment.

Sulfonylureas were the most commonly used monotherapy in Thai patients [18], although the American Diabetes Association and the European Association for the Study of Diabetes algorithm for the T2DM treatment recommends starting with metformin [19]. If SU monotherapy fails to achieve the glycemic target, combination therapy with a second agent with a different mechanism of action is usually initiated. The most commonly prescribed combination therapy in Thai patients is SU plus metformin [18].

In our study, we observed a significant lower incidence of HbA_{1c} goal attainment among patients treated with SU+MET than those treated with SU alone. There was no difference in the duration of diabetes between SU and SU + MET groups (median (IQR), 10 (5, 15) and 10 (6, 15) years, respectively, p=0.416). More than half of the patients treated with SU+MET for at least six months failed to achieve the glycemic control (294 from 521, 56.4%) in our study. This may infer that the use of the combination to achieve the glycemic

target may be insufficient to help these patients achieve the desired glycemic control. Other confounding variables might have affected the outcomes in this observational study design, such as delay in initiating combination therapy in uncontrolled diabetes and patient noncompliance. The patients in this study had a very low adherence to a regular diabetic diet (13%). The root cause for failure to achieve glycemic control and/or to prevent complications will require additional investigation and development of novel diabetic agents.

Patients with increased numbers of hypoglycemia events are at risk for long term complications and mortality [20-22], and hypoglycemia remains a major limiting factor in treating patients with T2DM, with the approximate prevalence ranging from 10-30% depending on treatment [22-25]. Among the various antidiabetic medications available for T2DM, SU was more likely to be associated with hypoglycemia than non-SU antidiabetic medications [22, 26]. Our study confirmed that patients taking SU with their antidiabetic medications had a high incidence of symptomatic hypoglycemia (30%). However, the actual rate of hypoglycemia may vary from that reported herein due to the study design, study population, differences in diabetes education and social status. In the present study, patients with T2DM having advanced age and Thai ethnicity, were more likely to have a high incidence of hypoglycemia. Moreover, hypoglycemic events, captured using a medical survey, might have underestimated the true incidence of hypoglycemia due to a recall bias and missed symptoms of mild hypoglycemia [27]. A study in Europe found that many diabetic patients rarely or never informed their general practitioner/specialist about hypoglycemia events [28]. Therefore, the real burden of hypoglycemia may be underestimated.

The study results showed that the patients with lower compliance reported a higher percentage of being bothered by side effects while self-reported experience of hypoglycemia and weight gain did not differ significantly between the two compliance groups. Further

research to explore other side effects that might be drivers for non-compliance, in addition to hypoglycemia and weight gain, is needed.

In our sub-analysis, the greater number of hypoglycemia events observed in patients with a low dietary sugar intake and frequent fingerstick glucose monitoring, may be due to more aggressive glycemic control measures taken by the patient. The increased hypoglycemia events observed in this setting was assumed to be due to implementing more stringent goals for metabolic control. In addition, our observational study did not rule out the role of other confounding variables.

In the present study, physicians largely followed the recommendations to recommend metformin to the most obese patients and SU to patients with lower body weight. Similar to related studies [29, 30], we observed a higher incidence of weight gain in the group with only SU treatment, and body weight did not change following treatment with a combination of metformin and SU. Therefore, for patients with T2DM, whose disease cannot be controlled by SU, biguanides might be an appropriate choice depending on whether the patient is overweight and the severity of their symptoms.

Macro- or microvascular complications were present among 20.8% of the patients. Related studies have shown that hypoglycemia increased the risk of cardiovascular disease possibly because of reduced coronary blood flow in the heart and major metabolic stress leading to cardiac arrhythmia [31, 32]. However, none of the T2DM patients in our study were observed to have cardiovascular symptoms during a hypoglycemia attack.

By design, this was a cross-sectional survey and retrospective cohort study, limited to patients from tertiary care hospitals, so the results may not be generalizable to patients in other healthcare settings. The observational nature of this study does not rule out the role of residual confounding variables in the observed associations. In addition, hospitals' medical

records, patient surveys and self-reported treatment experience might have underestimated the true incidence of hypoglycemia events.

CONCLUSIONS

The major finding among the patients with Thai T2DM receiving SU or SU+MET was that only about half of the patients achieved glycemic goal and compliance with the treatment was low in both groups. Hypoglycemia and weight gain were common. Patients with a pronounced weight gain were often treated with SU monotherapy. The fear and worry about hypoglycemia and weight gain were higher among the patients who experienced hypoglycemic events and weight gain. Therefore, clinicians should collect information about patient's past experiences and treatment of prior side effects. Improving compliance and selecting the most effective treatments with lowest risk of side effects, among patients failing to achieve their target glycemic goals, will have the greatest likelihood of improving their treatment outcomes.

Figure legends

Figure 1. Participant flow

Supplementary materials

Supplement I: Experience of Low Blood Sugar (Hypoglycemia) Questionnaire

Supplement II: Experience of Weight Gain Questionnaire

Supplement III: Fear of Weight Gain Questionnaire

Supplement IV: Directed acyclic graphs (DAG)

Supplement V: Co-morbid vascular conditions and major events in the previous 12 months by treatments.

Abbreviations

ADA, American Diabetes Association; HbA_{1c}, $HemoglobinA_{1C}$; MET, Metformin; OR, odd ratio; T2DM, Type 2 diabetes mellitus; SU, Sulfonylurea; 95%CI, 95% confidence interval.

Availability of data and materials

Other statistical analysis results to support the findings of this study are available for one year after publication from the corresponding author by email upon reasonable request. Individual patient data and materials not provided as supplements will not be shared.

Contributors

BS, TP, BO, SS, YB and WN collected the data, drafted the article, reviewed the literature and revised it critically equally. BS and WN provided valuable input in study design, data collection and literature review. All authors read and approved the manuscript and met the criteria for authorship.

Competing interests

The authors declare that they have no competing interests. Although, MSD (Thailand) Ltd supported for the study funding but the study was conducted and the study results were interpreted without the influence of the pharmaceutical company.

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Consent for publication

Publication consent is not applicable.

Ethics approval and consent to participate

This study was approved by the Human Research Ethics Committee of each hospital. (Royal Thai Army Medical Department IRB. Ref No: P039h/55, KKU EC. Ref No: HE551257, Ramathibodi Hospital EC. Ref No: 11-55-24, Faculty of Medicine, Chulalongkorn University, IRB Ref No: 412/55, Siriraj Hospital Ref No: 636/2555(EC4))

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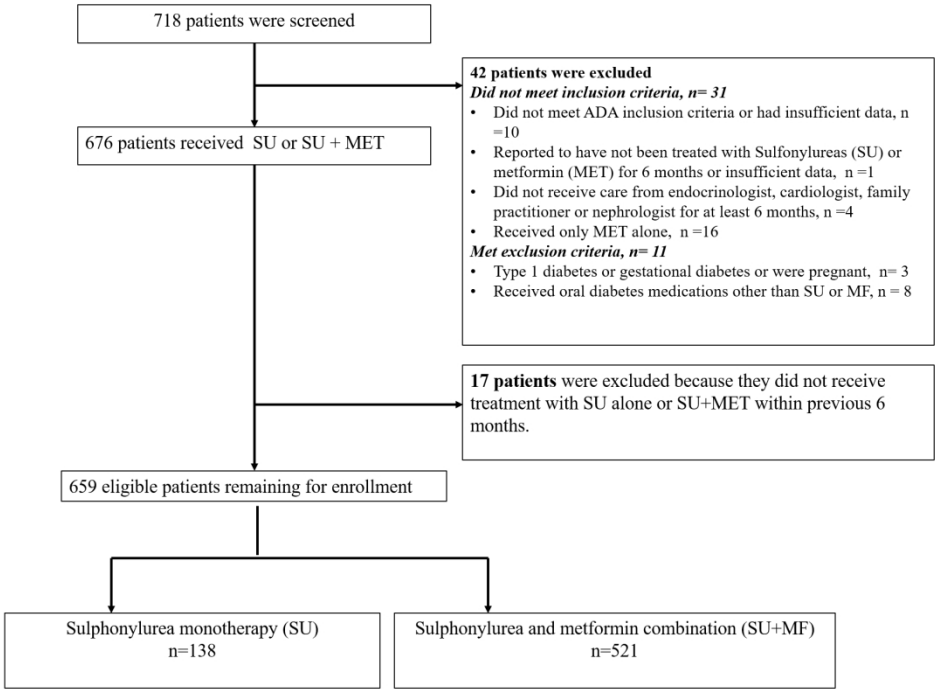


Figure 1. Participant flow

340x253mm (150 x 150 DPI)

SUPPLEMENT I

Experience of Low Blood Sugar (Hypoglycemia)

Below is a list of symptoms you might experience when you have an episode (incident) of hypoglycemia (low blood sugar). Before answering the questions please read the list of symptoms carefully.

Some symptoms of **low blood sugar** (hypoglycemia) are:

- sweating
- shakiness
- dizziness
- hunger
- headache
- pale skin color
- confusion/feeling disoriented
- clumsy or jerky movements
- sudden moodiness or behavior changes
- tingling sensations around the mouth
- difficulty concentrating
- blood sugar is ≤ 70 mg/dL

1. Have you ever felt symptoms of low blood sugar (as described in the box above) in the last 6 months?

☐1 Yes
☐0 No (If no, go to questionnaire HFS)

If **YES**, please tick the box that best describes how severe and how often the symptoms of low blood sugar have been during the last 6 months.

2a. During the last 6 months, did you experience **MILD** symptoms of low blood sugar defined as *Little or no interruption of your activities, and you didn't feel you needed assistance to manage your episode(s) of low blood sugar or symptoms*?

☐1 Yes
☐0 No

2b. How often have you experienced **MILD** symptoms of low blood sugar?

☐0 I did not experience MILD symptoms of low blood sugar
☐1 1 to 2 times over the last 6 months
☐2 3 to 6 times over the last 6 months
☐3 more than once per month
☐4 more than once per week
☐5 everyday

3a. During the last 6 months, did you experience **MODERATE** symptoms of low blood sugar defined as *Some interruption of your activities, but didn't feel you needed assistance to manage your episode (s) of low blood sugar or symptoms*?

☐1 Yes
☐0 No

3b. How often have you experienced **MODERATE** symptoms of low blood sugar?

☐0 I did not experience MODERATE symptoms
☐1 1 to 2 times over the last 6 months
☐2 3 to 6 times over the last 6 months
☐3 more than once per month
☐4 more than once per week
☐5 everyday

4a. During the last 6 months, did you experience **SEVERE** symptoms of low blood sugar defined as *Felt that you needed the assistance of others to manage your episode(s) of low blood sugar or symptoms (for example, to bring you food or drink*)?

SUPPLEMENT I

☐1 Yes
☐0 No

4b. How often have you experienced **SEVERE** symptoms of low blood sugar?

☐0 I did not experience SEVERE symptoms
☐1 1 to 2 times over the last 6 months
☐2 3 to 6 times over the last 6 months
☐3 more than once per month
☐4 more than once per week
☐5 everyday

5a. During the last 6 months, did you experience **VERY SEVERE** symptoms of low blood sugar defined as *Needed medical attention (for example, called an ambulance, visited an emergency room or hospital, or saw a doctor or nurse*)?

☐1 Yes
☐0 No

5b. How many times have you experienced **VERY SEVERE** symptoms of low blood sugar?

|__|__| times during the last 6 months

6. Overall, how much were you bothered by your symptoms of your low blood sugar during the last 6 months?

☐0 Not concerned (I did not have low blood sugar symptoms during the last 6 months)
☐1 Not at all
☐2 A little bit
☐3 Somewhat
☐4 Very
☐5 Extremely

SUPPLEMENT II

Experience of Weight Gain

The following questions ask about weight gain. Please answer every question by *ticking the box* that best represents your opinion. There are no right or wrong answers.

1. During the last year, have you experienced a weight gain without meaning to?

- ☐1 Yes
- ☐2 No I lost weight
- ☐3 No my weight was stable

2. During the last year, how much weight did you gain?

- ☐1 Less than 5 Kilos
- ☐2 Between 5 and 9 kilos
- ☐3 Between 10 and 15 kilos
- ☐4 More than 15 kilos

3. How severe was your weight gain during the last year?

- ☐1 Very mild
- ☐2 Mild
- ☐3 Moderate
- ☐4 Severe
- ☐5 Very severe

4. How much were you bothered by your weight gain during the last year?

- ☐1 Not at all
- ☐2 A little bit
- ☐3 Somewhat
- ☐4 Very
- ☐5 Extremely

5. During the last year, was it difficult for you to maintain your weight?

- ☐1 Not at all
- ☐2 A little bit
- ☐3 Somewhat
- ☐4 Very
- ☐5 Extremely

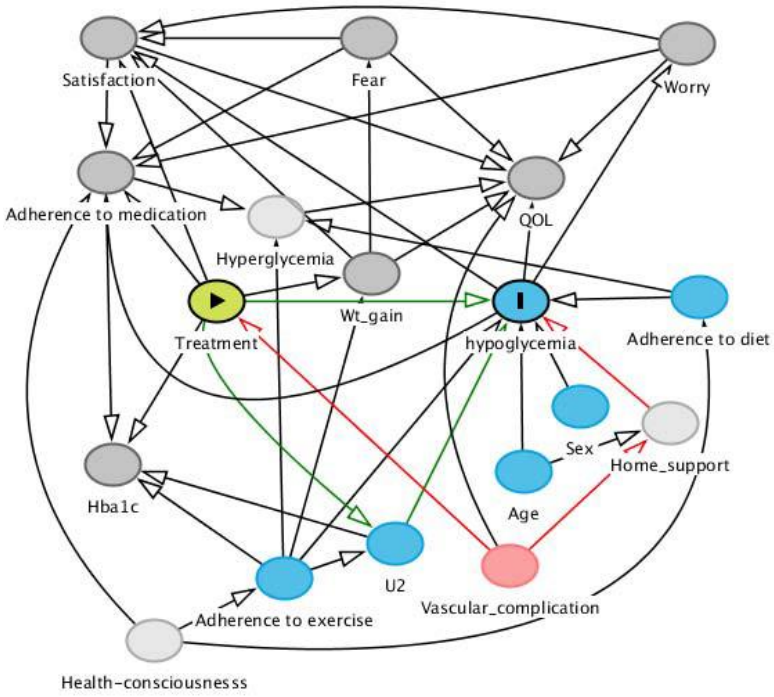
SUPPLEMENT III

Fear of Weight Gain

Please check the box that best describes how often you worry about each of the following items.

	Never	Rarely	Sometimes	Often	Almost Always
1. I worry about gaining weight	☐0	☐1	☐3	☐3	☐4
2. I worry that my diabetic treatment makes me gain weight	☐0	☐1	☐3	☐3	☐4
3. I worry about not being able to stabilise my weight	☐0	☐1	☐3	☐3	☐4

SUPPLEMENT IV



Directed acyclic graph (DAG) linking hypoglycemia, treatment satisfaction, quality of life, worry about hypoglycemia, fear of weight gain and other potentially related variables. In this particular graph hypoglycemia is shown as the outcome of interest and treatment type as the main exposure. Hyperglycemia, home support and the variable labeled U2 areunmeasured variables. U2 represents sensitivity to insulin and other metabolic parameters.

Supplement V: Co-morbid vascular conditions and major events in the previous 12 months by treatment (N=659).

Condition/Event	Total n= 659	SU n=138	SU+MET n=521	P-value*
Co-morbid macro and vascular conditions				
Any	137 (20.8)	36 (26.1)	101 (19.5)	0.099
Ischemic heart disease	78 (11.8)	14 (10.1)	64 (12.3)	0.555
Congestive heart failure	12 (1.8)	2 (1.5)	10 (1.9)	1.000
Myocardial infarction	9 (1.4)	1 (0.7)	8 (1.5)	0.643
Stroke	17 (2.6)	4 (2.9)	13 (2.5)	0.765
Atrial fibrillation	10 (1.5)	3 (2.2)	7 (1.4)	0.445
Blindness	2 (0.3)	1 (0.7)	1 (0.2)	0.376
Renal failure	18 (2.7)	10 (7.3)	8 (1.5)	0.001
Amputation of digit or limb	2 (0.3)	2 (1.5)	0	0.044
Peripheral vascular disease	12 (1.8)	4 (2.9)	8 (1.5)	0.288
Major events				
Any	68 (10.4)	19 (13.8)	48 (9.4)	0.156
Ischemic heart disease	8 (1.2)	3 (2.2)	5 (1.0)	0.375
Congestive heart failure	19 (2.9)	4 (2.9)	15 (2.9)	1.000
Myocardial infarction	3 (0.5)	0	3 (0.6)	1.000
Stroke	2 (0.3)	0	2 (0.4)	1.000
Atrial fibrillation	2 (0.3)	1 (0.7)	1 (0.2)	0.376
Blindness	1 (0.2)	0	1 (0.2)	1.000
Renal failure	3 (0.5)	1 (0.7)	2 (0.4)	0.508
Amputation of digit or limb	2 (0.3)	2 (1.5)	0	0.044
Peripheral vascular disease	2 (0.3)	1 (0.7)	1 (0.2)	0.376
Cancer/malignancy	4 (0.6)	0	4 (0.8)	0.584
Other	26 (4.0)	8 (5.8)	18 (3.5)	0.221

* Fisher exact test.

Numbers may not sum to totals owing to missing data.

Naturalistic Evaluation of Hypoglycemic Events in Diabetic Subjects (NEEDS STUDY) -

STROBE Statement—checklist of items that should be included in reports of observational studies

	CHECK	Item No	Recommendation
Title and abstract	YES	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract on PAGE 2 - Research Design and Methods: Multicenter cross-sectional, retrospective review study
	YES		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found on PAGE 2 – Abstract
	Introduction		
Background/rationale	YES	2	Explain the scientific background and rationale for the investigation being reported on PAGE 4- Background
Objectives	YES	3	State specific objectives, including any prespecified hypotheses On Page 5 – Line 35 "To address these issues, we assessed the goal attainment rates ……."
	Methods		
Study design	YES	4	Present key elements of study design early in the paper On Page 5 – Line 51 "A multicenter, observational, retrospective and cross-sectional study was conducted ……"
Setting	YES	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection On Page 5-6 – From "5 tertiary care hospitals ……." To " …….Mar 2015"
Participants	YES	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants On Page 6 –Study population
			(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	YES	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable On Page 6 –Study measurements Section
Data sources/	YES	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability

Naturalistic Evaluation of Hypoglycemic Events in Diabetic Subjects (NEEDS STUDY) -

measurement			of assessment methods if there is more than one group On Page 6 –Study measurements Section
Bias	NO	9	Describe any efforts to address potential sources of bias
Study size	YES	10	Explain how the study size was arrived at On Page 6 –Sample Size Section
Quantitative variables	Not related	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	YES	12	(*a*) Describe all statistical methods, On Page 8–Statistical Analysis Section including those used to control for confounding
	NO		(*b*) Describe any methods used to examine subgroups and interactions- **No subgroup analysis**
	NO		(*c*) Explain how missing data were addressed
	NO		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
			(*e*) Describe any sensitivity analyses

Results

Participants	13*	YES	(a) **Report numbers of individuals at each stage of study**—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed On Page 8 : "From 718 patients screened ……." and Figure 1 Participant flow
		YES	(b) Give reasons for non-participation at each stage The reasons are in Figure 1 Participant flow
		YES	(c) Consider use of a flow diagram Figure 1 Participant flow
Descriptive data	14*	YES	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders On page 8 Participants and demographic Section and Table 1.
		YES	(b) Indicate number of participants with missing data for each variable of interest Table 1-5 clearly provided number of participants.
		Not	(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)

Naturalistic Evaluation of Hypoglycemic Events in Diabetic Subjects (NEEDS STUDY) -

		related	
Outcome data	15*	Not related	*Cohort study*—Report numbers of outcome events or summary measures over time
		Not related	*Case-control study*—Report numbers in each exposure category, or summary measures of exposure
		YES	*Cross-sectional study*—Report numbers of outcome events or summary measures Table 1-5 clearly provided number of participants.
Main results	16	YES	(*a*) Give **unadjusted estimates** Table 1-5 clearly provided unadjusted estimates Table 1-5 and Result Section (Page 9-11). For continuous variable, we provide standard deviation. For ratio, we clearly provide the number that can use for 95% CI estimation. All Odd ratios (OR) in Results section were provided along with 95% CI. and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included - -
		NO	(*b*) Report category boundaries when continuous variables were categorized
		Not related	(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Not related	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion			
Key results	18	YES	Summarise key results with reference to study objectives Page 19 line 49, paragraph "Overall, 47.5% of patients had HbA1c values less than 7%. ……."
Limitations	19	YES	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias Page 21 line 26, paragraph "The study had some limitations……."
Interpretation	20	YES	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence Page 21 CONCLUSIONS Section
Generalisability	21	YES	Discuss the generalisability (external validity) of the study results Page 21 Line 30. " The study sample was limited to patients in tertiary care hospitals, so the results may not able to be generalized…"
Other information			

Naturalistic Evaluation of Hypoglycemic Events in Diabetic Subjects (NEEDS STUDY) -

Funding	22	YES	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based Page 22-23, Funding Section.

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.