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Guideline-Directed Medical Therapies for Diabetic Kidney Disease Among Thai People With Type 2 Diabetes: A Real-World Data Based on Theptarin Diabetes Staging

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Abstract

Background. The "pillar approach" was recently proposed to holistically address diabetic kidney disease (DKD). Theptarin Diabetes Staging (TDS) is a staging system for type 2 diabetes (T2D) designed to prevent or delay the progression to advanced stages.

Objective. To evaluate the rate of guideline-directed medical therapies (GDMT) among individuals with DKD from 2021 to 2025 according to the TDS system.

Methodology. A retrospective review of medical records of T2D patients with TDS stage 4Ka (moderately increased persistent albuminuria), Stage 4Kb (severely increased persistent albuminuria), and stage 5Ka (eGFR <45 mL/min/1.73 m^2) was conducted. The rates of RASi, SGLT2i, GLP-1 RA, and finerenone use, along with achievement of metabolic targets, were evaluated prospectively from 2021 to 2025.

Results. A total of 206 medical records were reviewed (mean age 64.1 ± 10.3 years, A1C 7.3 ± 1.2%, mean eGFR 71.6±24.5 mL/min/1.73 m^2). In 2021, the use of RASi was 78.2%, 51.5% for SGLT2i and 13.6% for GLP-1 RA among all patients. Four years later, rates of GDMT improved as follows: RASi 79.7%, SGLT2i 59.3%, GLP-1 RA 19.8% and finerenone 2.8%. However, only 1.1% of all patients in 2025 received all 4 GDMT items. More stable or improved TDS were observed in patients who received GDMT ≥3 classes across all 4 medication classes, compared with those who received GDMT <3 classes (96.2% vs. 78.8%, *P*-value = 0.036).

Conclusion. The real-world implementation of GDMT among DKD patients remains inadequate, and more efforts are required to improve GDMT adoption. Regular reviews and feedback are warranted to improve attainment of treatment targets and better clinical outcomes.

Key words: guideline-directed medical therapies (GDMT) prescription rates, diabetic kidney disease, Theptarin Diabetes Staging, Thai

INTRODUCTION

Diabetic kidney disease (DKD) is a common complication of type 2 diabetes (T2D) that significantly impacts quality of life and shortens life expectancy.[1] Over the past few decades, cardiovascular and renal outcome trials have reshaped diabetes care by demonstrating the vascular protective effects of certain novel anti-diabetic agents and some organ-protective medications. The concept of the cardiovascular-kidney metabolic (CKM) continuum was introduced in the 2020s, leading to a new era of combination therapy in T2D with chronic kidney disease (CKD), often referred to as a "*pillar approach*" as a result of collaborative care frameworks across various specialties.[2-6] The pillar approach for DKD medications involves a combination of four medication classes with proven benefits, namely renin-angiotensin system inhibitors (RASi), sodium-glucose cotransporter-2 inhibitors (SGLT2i), non-steroidal mineralocorticoid receptor antagonists (nsMRA), and glucagon-like peptide-1 receptor agonists (GLP-1 RA). However, the use of these foundation medications for DKD in clinical practice remains unacceptably low for various reasons.[7,8] While these developments represent major therapeutic advancements, they also introduce greater complexity and cost to DKD management, especially nsMRA and GLP-1 RA medications.

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Suboptimal usage of these medications is widespread, causing clinical therapeutic inertia. Therapeutic inertia is common and driven by various factors from clinicians, patients and health care systems. Clinician-associated barriers to treatment intensification include time and resource constraints, as well as overly cautious prescribing practices to avoid side effects. Moreover, these patients are often seen by multiple health care providers, and inadequate medication reconciliation procedures could affect treatment adherence.[9,10] In our previous study, we found that the prescription rate of SGLT2i was less than 60% among T2D patients with albuminuric DKA.[11] While medication cost contributed to the suboptimal usage, clinical inertia among diabetologists was the most common barrier causing low prescription rates for SGLT2i. The structure of routine clinic visits often discourages proactive treatment intensification in stable patients and promotes the concept of therapeutic inertia.[12] Audit and feedback, together with educational outreach to clinicians, are important quality improvement initiatives to increase adherence to clinical practice guidelines.[13] Since 2010, the Theptarin Diabetes Staging (TDS) system, which was conceptualized by stratifying T2D patients based on the severity of diabetes complications and target organ damage, has been developed and implemented to prevent or delay the progression to advanced stages in individuals with diabetes.[14] The details of the TDS system were illustrated in Supplement Figure 1. Individuals with T2D and target organ damage were categorized as TDS stage 4, and those with advanced diabetes complications were categorized as TDS stage 5. TDS stage 4K (K = kidney), and TDS stage 5Ka (estimated glomerular filtration rate, eGFR <45 mL/min/1.73 m^2) represented the opportunity to monitor long-term adherence to guideline-directed medical therapies (GDMT) in T2D with CKD, as shown in Supplement Figure 2. When compared with the Kidney Disease Improving Global Outcomes (KDIGO) staging system, the TDS system focused more on the severity of increased albuminuria in the early stage of DKD and designated end-organ damage at a lower estimated glomerular filtration rate than the KDIGO system (eGFR <45 mL/min/1.73 m^2 versus eGFR <60 mL/min/1.73 m^2). Our TDS system had previously been validated for quality improvement initiatives at our hospital.[14]

There is a lack of real-world clinical studies on the uptake of GDMT among DKD patients in Southeast Asia. While the landscape of DKD treatment in persons with T2D has changed tremendously in the last 5 years, the use of these therapies remains unknown in routine clinical practice. Therefore, this study aimed to **1)** evaluate the rate of GDMT from each class of DKD medications in the pillar approach concept; **2)** determine the proportion of patients with DKD according to TDS system who attained various multiple treatment targets from 2021 to 2025 in our hospital; and **3)** identify the proportion of patients with DKD who could achieve stabilized or improved TDS five years later.

METHODOLOGY

Study design

The present study is a retrospective analysis of people with T2D who regularly visited the THEPTARIN Diabetes, Thyroid and Endocrine Center, Vimut-Theptarin Hospital, one of the largest diabetes centers in Thailand. Over 1,500 people with T2D regularly follow up at our hospital. Annual medical audit retrieved all data from medical records for the last quarter of each year. Patients with TDS stage 4Ka (moderately increased persistent albuminuria or previously known as microalbuminuria), stage 4Kb (severely increased persistent albuminuria or previously known as overt albuminuria), and stage 5Ka (eGFR <45 mL/min/1.73 m^2) were reviewed.

Patient selection

Inclusion criteria included patients with TDS stage 4Ka, 4Kb, and 5Ka as defined in **Supplement Figure 1,** who regularly followed up at least 3 times in 2021. Patients aged <15 years or >80 years, patients with normoalbuminuria, eGFR <20 mL/min/1.73 m^2, patients with a duration of follow-up less than 24 months, with acute kidney injury during the follow-up period, patients with type 1 diabetes mellitus and other types of diabetes were excluded. The severity of increased albuminuria was categorized into moderately increased albuminuria (urine albumin-creatinine ratio, UACR 30-300 mg/g) and severely increased albuminuria (UACR >300 mg/g). The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations for eGFR were used to calculate GFR from serum creatinine and eGFR was categorized according to KDIGO guidelines.[4]

Study procedure

Information on patient characteristics, including demographics, comorbidities, prescribed medications and laboratory data, was retrieved in the last quarter of 2021. Finerenone, which is the only approved nsMRA to reduce the risk of CKD progression and cardiovascular events, has been approved in Thailand since late 2023. Therefore, the prescription rate of finerenone was evaluated in 2024 and 2025. The rates of RASi, SGLT2i, GLP-1 RA and finerenone use, together with metabolic attainment targets, were evaluated prospectively in consecutive cases from 2021 to 2025. GDMT uptake was stratified into patients who received ≥2 classes or ≥3 classes from 4 classes and patients who received <2 classes or <3 classes from 4 classes. At the last follow-up in 2025, outcomes evaluated included progression or regression of the TDS system, new-onset macrovascular complications and achievement of treatment targets. The primary outcome was the annual rate of RASi, SGLT2i, GLP-1 RA, and finerenone use from 2021 to 2025. Secondary outcomes included attainment of metabolic targets from 2021 to 2025 and the proportion of patients who could stabilize or improve TDS in 2025 if GDMT uptake was ≥2/4 classes or ≥3/4 classes. This study

was approved by the Institutional Review Board (IRB) committee of Vimut-Theptarin Hospital (EC No.2-2025).

Sample size calculation

According to previous studies,[15-17] the prescription rates of RASi, SGLT2i, GLP-1 RA, and finerenone were 40.4%, 17.8%, 11.3%, and 33%, respectively. Based on these rates, the sample size was based on a prevalence-based calculation, and minimum required sample sizes were calculated using OpenEpi software: 369 for RASi, 227 for SGLT2i, 150 for GLP-1 RA, and 340 for finerenone. The largest calculated sample size (N = 369) was adopted to ensure adequate precision for all prevalence estimates. As this was a retrospective/cross-sectional study based on existing medical records with inclusion and exclusion criteria, attrition was not applicable. All calculations assumed a two-sided significance level (α) of 0.05, power ($1-\beta$) of 0.80, and a 95% confidence interval.

Statistical analyses

Continuous variables were presented as mean ± standard deviation (SD) for normally distributed data or median (interquartile range, IQR) for non-normally distributed data. Categorical variables were presented as proportions. The Kolmogorov-Smirnov test was used to assess the normality of data distribution. If the data were not normally distributed, non-parametric tests were applied. Comparisons among different stages of TDS were performed using one-way ANOVA or the Kruskal-Wallis test for continuous variables. The *t-test* or analysis of variance was used to compare differences in means among groups. The *Chi-squared* test was used to compare differences in percentages between groups. Fisher's Exact test was used alternatively if the expected value in any cell of a contingency table is less than 5. Variables analyzed in the univariate analysis included age ≥65 years, gender, duration of diabetes ≥10 years, body mass index (BMI) ≥25 kg/m^2, eGFR <45 mL/min/1.73 m^2 (TDS Stage 5Ka), the presence of diabetic retinopathy (DR), glycated hemoglobin (A1C) <7.0%, and severely increased albuminuria (>300 mg/g) based on previous literatures for associated factors in GDMT uptake among patients with DKD. Factors such as achieving a *P-value* <0.20 were included in the multivariate models to determine associated factors with ≥2 classes at baseline or ≥3 classes at the last follow-up among DKD patients. Multivariable logistic regression was used to identify factors associated with GDMT prescriptions. Results are presented as adjusted odds ratios (aOR) with 95% confidence intervals. Model fit and multicollinearity were assessed using the Hosmer-Lemeshow test and variance inflation factors, respectively. Comparisons of proportions between patients who could stabilize or improve TDS, stratified by the number of GDMT medication classes were performed using the two-proportion Z-test. A *P*-value of <0.05 was considered statistically significant. Given the exploratory nature of this study, no formal adjustment for multiple comparisons was applied. Patients were retained in analyses where data were available and excluded from analyses of variables with missing values. Therefore, no statistical imputation was performed. All analyses were conducted using Statistical Package for the Social Sciences (SPSS), version 24 (IBM Corp., Armonk, NY, USA).

RESULTS

Baseline demographic and clinical characteristics

The study cohort comprised 206 eligible patients from 1,232 patients who were audited in 2021, as shown in Figure 1. Of the eligible audited patients, the baseline characteristics are

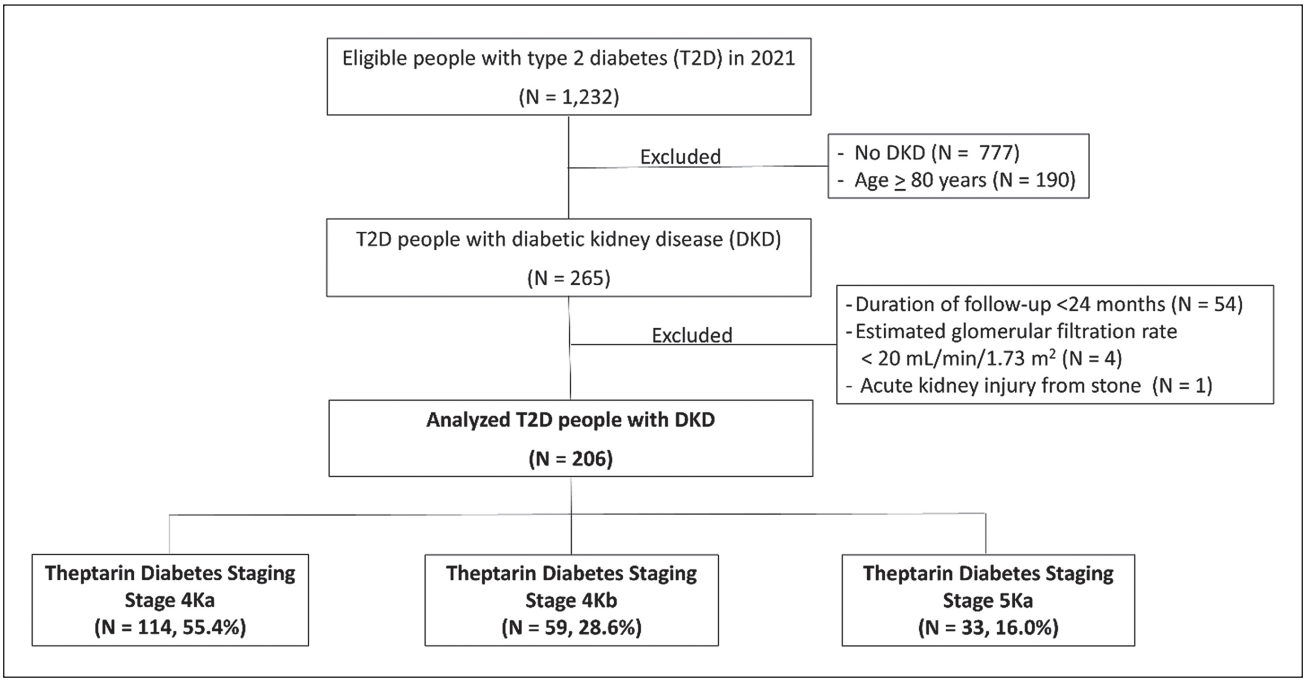

Figure 1. Flow diagram for studied patients' selection.

shown in Table 1 (mean age 64.1 ± 10.3 years, A1C 7.3 ± 1.2%, mean eGFR 71.6 ± 24.5 mL/min/1.73 m^2). Compared with patients TDS stage 4Ka and 4Kb, TDS stage 5Ka patients were older, had heart failure, had higher insulin use, but less SGLT2i/GLP-1RA usage. In 2021, the rates of RASi were 78.2%, SGLT2i was 51.5%, GLP-1 RA was 13.6%, among all patients. None of these patients used finerenone in 2021, as it was not available yet. The mean follow-up duration for the entire cohort was 42.1 ± 4.6 months.

Long-term adherence to GDMT from 2021 to 2025

As shown in Figure 2, the proportion of prescriptions of GDMT classes improved every year. The rate of GDMT uptake ≥2 classes increased from 42.7% in 2021 to 55.9% in 2025, and GDMT uptake ≥3 classes increased from 7.3% in 2021 to 14.7% in 2025. However, the overall number of patients who received a combination of four medication classes for the pillar approach after finerenone became available in Thailand in 2024 remained low at 1.1% in 2025. At the last follow-up, the rate of GDMT was improved as follows: RASi 79.7%, SGLT2i 59.3%, GLP-1 RA 19.8%, finerenone 2.8%. The most common drug combinations for 2-class GDMT in both 2021 and 2025 were RASi and SGLT2i, and the most common drug combinations for 3-class GDMT in both 2021 and 2025 were RASi, SGLT2i and GLP-1 RA, as shown in Supplement Figure 3. The least common drug combinations for 3-class GDMT in 2025 were SGLT2i, GLP-1 RA and finerenone. When stratified by TDS system, TDS stage 5Ka received fewer GDMT medications than TDS stages 4Ka and 4Kb, as shown in Figure 3, but with improvement over time. Details of each class of DKD medication among individuals with TDS stage 5Ka in 2025, compared with the baseline in 202,1 are shown in Supplement Figure 3.

Outcomes of care based on TDS staging

The proportion of patients in each TDS system who attained multiple treatment targets was shown in Figure 4. While the overall treatment attainment targets were below 60% across all parameters, the LDL-cholesterol target of <70 mg/dL improved from 26.7% at baseline to 55.3% at the last follow-up. From 2021 to 2025, migration of the TDS staging system from the overall cohort is shown in Figure 5. Among patients in TDS stage 4Ka to TDS stage 5Ka, stable, improved, and worsening stages were found in 63.1%, 18.0%, and 18.9% respectively. Among all patients, 4

Table 1. Baseline characteristics of studied participants (N = 206 cases)

	Total cases (N = 206)	TDS Stage 4Ka (N = 114, 55.3%)	TDS Stage 4Kb (N = 59, 28.7%)	TDS Stage 5Ka (N = 33, 16.0%)	*P*-value
Female (%)	87 (42.2%)	49 (43.0%)	24 (40.7%)	14 (42.4%)	0.96*
Age (years)	64.1 ± 10.3	63.1 ± 10.7	63.0 ± 10.2	69.8 ± 6.9	<0.01[a]
<65 years	89 (43.2%)	52 (45.6%)	29 (49.1%)	8 (24.2%)	
65-74 years	88 (42.7%)	47 (41.2%)	26 (44.1%)	15 (45.5%)	
≥75-80 years	29 (14.1%)	15 (13.2%)	4 (6.8%)	10 (30.3%)	
Duration of diabetes (years)	18.2 ± 10.3	16.8 ± 9.6	19.8 ± 10.9	19.9 ± 10.5	0.10[a]
Duration ≥10 years (%)	161 (78.2%)	85 (74.6%)	48 (81.4%)	28 (84.8%)	
BMI (kg/m²)	27.5 ± 4.7	27.5 ± 4.9	27.3 ± 4.5	28.0 ± 4.5	0.78[a]
Active or ex-smoking (%)	36 (17.5%)	19 (16.7%)	13 (22.0%)	4 (12.1%)	0.46*
Hypertension (%)	146 (70.9%)	79 (69.3%)	45 (76.3%)	22 (66.7%)	0.54*
Heart failure (%)	10 (4.9%)	3 (2.6%)	3 (5.1%)	4 (25.0%)	0.08*
Coronary artery disease (%)	29 (14.1%)	16 (14.0%)	7 (11.9%)	6 (18.2%)	0.71*
Stroke (%)	10 (4.9%)	6 (5.3%)	4 (6.8%)	0 (0.0%)	0.33*
Peripheral artery disease (%)	9 (4.4%)	4 (3.5%)	4 (6.8%)	1 (3.0%)	0.56*
Diabetic retinopathy (%) [*]	67 (32.5%)	31 (27.2%)	23 (39.0%)	13 (39.4%)	0.19*
A1C (%)	7.3 ± 1.2	7.2 ± 1.1	7.5 ± 1.3	7.4 ± 1.2	0.20[a]
LDL (mg/dL)	85.0 ± 25.1	84.5 ± 24.0	84.5 ± 24.4	87.8 ± 30.2	0.79[a]
estimated GFR (mL/min/1.73 m²)	71.6 ± 24.5	79.2 ± 21.6	76.7 ± 18.5	36.2 ± 6.3	<0.01[a]
Stage 1 eGFR ≥90 mL/min/1.73 m^2 (%)	53 (25.7%)	39 (34.2%)	14 (23.7%)	0	
Stage 2 eGFR = 60-89 mL/min/1.73 m^2 (%)	84 (40.8%)	53 (46.5%)	31 (52.6%)	0	
Stage 3a eGFR = 45-59 mL/min/1.73 m^2 (%)	36 (17.5%)	22 (19.3%)	14 (23.7%)	0	
Stage 3b eGFR = 30-44 mL/min/1.73 m^2 (%)	27 (13.1%)	0	0	27 (81.8%)	
Stage 4 eGFR = 15-29 mL/min/1.73 m^2 (%)	6 (2.9%)	0	0	6 (18.2%)	
Albuminuria (Median/IQR)	139.1 (326.3)	77.8 (79.7)	529.3 (685.1)	147.2 (333.2)	0.47[#]
Normal to mildly increased (<30 mg/g)	2 (1.0%)	0	0	2 (6.0%)	
Moderately increased (30-300 mg/g)	136 (66.0%)	114 (100%)	0	22 (66.7%)	
Severely increased (>300 mg/g)	68 (33.0%)	0	59 (100%)	9 (27.3%)	
RAS inhibitors (%)	161 (78.2%)	88 (77.2%)	49 (83.1%)	24 (72.7%)	0.72*
Statin (%)	193 (93.7%)	106 (93.0%)	55 (93.2%)	32 (97.0%)	0.70*
Anti-diabetic medication (%)					
SGLT2i	106 (51.5%)	54 (47.4%)	38 (64.4%)	14 (42.4%)	0.06*
GLP-1 RA	28 (13.6%)	12 (10.5%)	14 (23.7%)	2 (6.1%)	0.02*
Metformin	171 (83.0%)	98 (86.0%)	52 (88.1%)	21 (63.6%)	0.01*
Sulfonylurea	79 (38.3%)	44 (38.6%)	22 (37.2%)	13 (39.4%)	0.97*
Thiazolidinedione	38 (18.4%)	24 (21.1%)	7 (11.9%)	7 (21.2%)	0.30*
DPP4 inhibitor	106 (51.5%)	59 (51.8%)	29 (49.2%)	18 (54.5%)	0.88*
Insulin	64 (31.1%)	26 (22.8%)	23 (39.0%)	15 (45.5%)	0.01*

Available data 198/206 (96.1%). [#] Kruskal-Wallis test was performed. * Chi-square test was performed. [a] Analysis of Variance was performed.

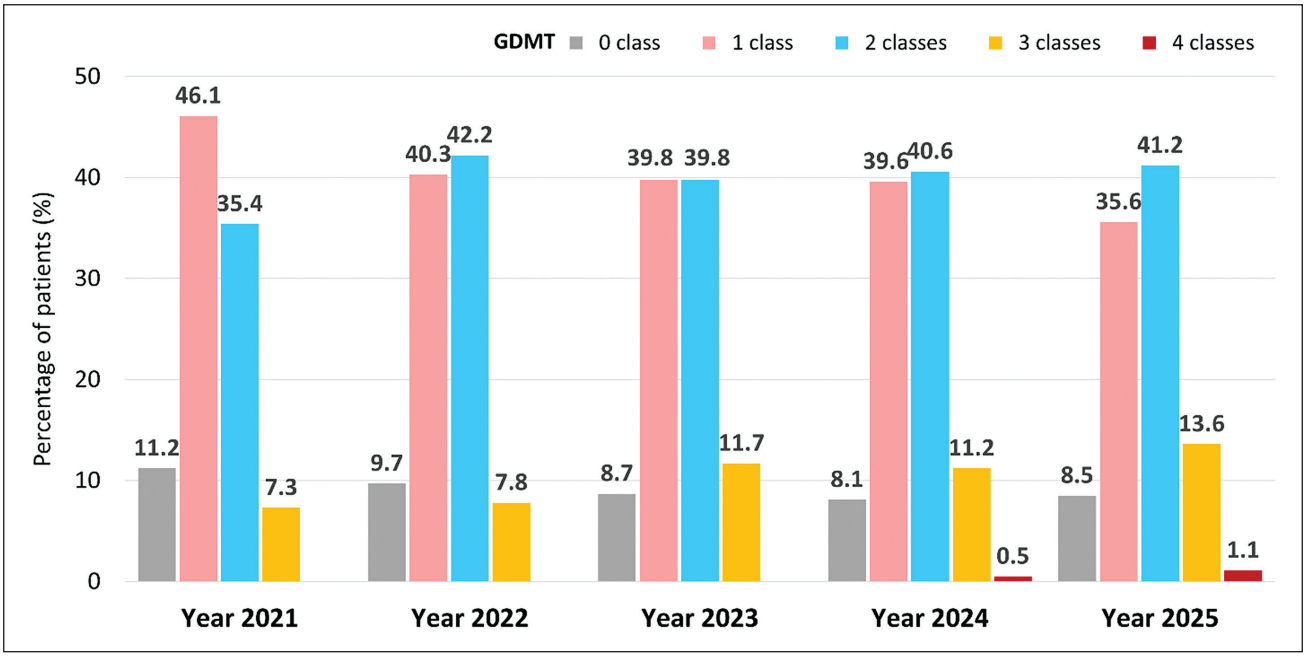

Figure 2. The proportion of numbers of pillar therapies for diabetic kidney disease from 2021 to 2025.

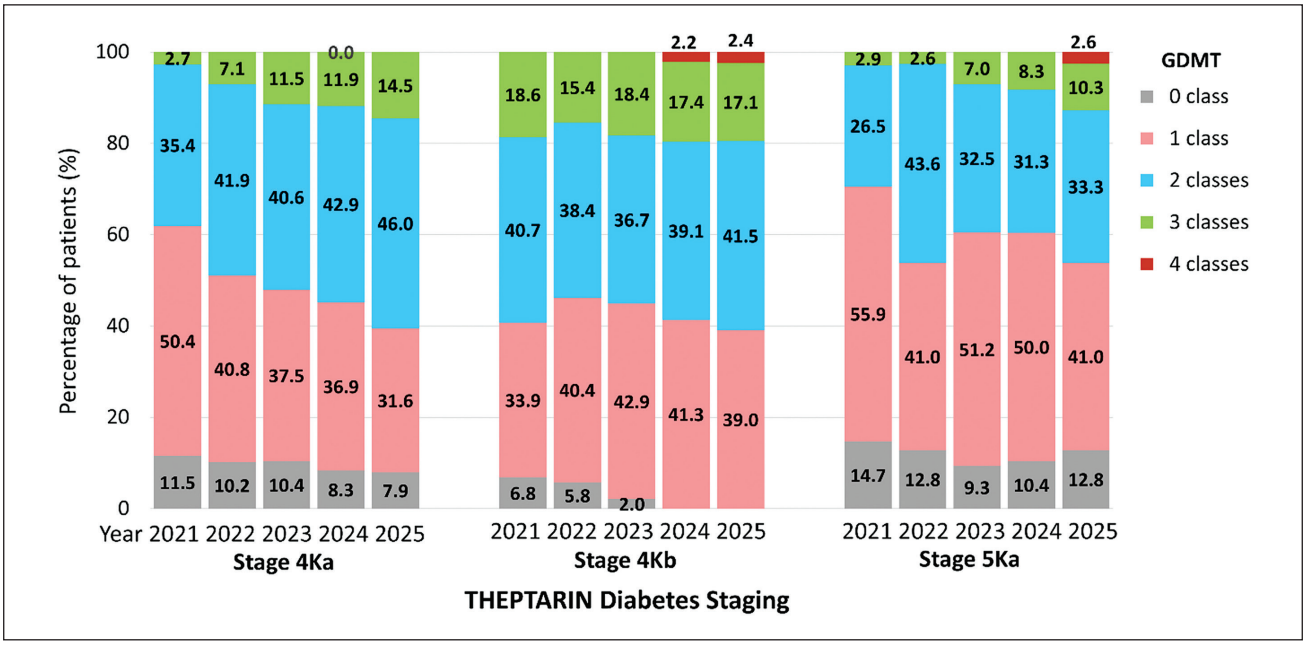

Figure 3. The proportion of prescriptions of each class of guideline-directed medical therapies (GDMT) from the baseline in 2021 to the latest follow-up in 2025 according to the Theptarin Diabetes Staging (TDS) system.

deaths (1.9%) occurred during the mean follow-up period of 3.6 years. The causes of death included cardiovascular events (50%), kidney failure (25%) and hepatobiliary infection (25%).

More TDS patients were stabilized or improved when they received GDMT ≥3 classes from all 4 medication classes when compared with those who received GDMT <3 classes (96.2% vs. 78.8%, *P*-value = 0.036), as shown in Figure 6. Female gender and elderly (aged ≥65 years) were associated with GDMT <2 classes in baseline (OR = 0.35; CI 95% 0.20-0.64 and OR = 0.46; CI 95% 0.25-0.83, respectively), as shown in Table 2. At the last follow-up, only BMI ≥25 kg/m^2 was associated with receiving GDMT ≥3 classes (OR = 3.40; CI 95% 0.93-12.36) as shown in Table 3.

DISCUSSION

In this retrospective study, we highlighted significant delays in transitioning from the evidence-based pillar approach for DKD management in T2D to real-world implementation of GDMT. Metabolic attainments among people with chronic kidney disease and T2D treated by specialists were still inadequate, and more efforts are required to

improve GDMT prescription rates in routine practice. Our findings identify opportunities for improvement in the management of T2D patients with both albuminuric DKD and normoalbuminuric DKD.

CKD is itself a major risk factor for cardiovascular disease, with reduced eGFR and albuminuria both independently associated with cardiovascular morbidity and mortality.[18] In addition to lifestyle modification, the management of DKD emphasized on the four 'pillars' of treatment.[6] Each pillar of pharmacotherapy has different mechanisms of

Table 2. Univariate and multivariate analysis of factors associated with receiving guideline-directed medical therapies (GDMT) ≥2 classes at the baseline

	Univariate analysis			Multivariate analysis		
	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Female	0.39	0.22-0.68	<0.01#	0.35	0.20-0.64	<0.01*
Age ≥65 years	0.48	0.27-0.84	0.01#	0.46	0.25-0.83	0.01*
Duration of diabetes ≥10 years	0.81	0.42-1.57	0.53#			
BMI (≥25 kg/m²)	1.72	0.95-3.12	0.08#	1.60	0.86-3.00	0.14*
TDS Stage 5Ka	0.61	0.29-1.28	0.19#			
Heart Failure	0.56	0.14-2.23	0.41#			
Diabetic retinopathy	1.12	0.69-1.82	0.66#			
Optimal A1C <7.0 %	0.81	0.46-1.43	0.47#			
Severely increased albuminuria	0.66	0.35-1.22	0.19#			

Binary logistic regression test was performed. * Multivariable logistic regression test was performed.

Table 3. Univariate and multivariate analysis of factors associated with receiving guideline-directed medical therapies (GDMT) ≥3 classes at the last follow-up in year 2025

	Univariate analysis			Multivariate analysis		
	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Female	0.59	0.24-1.44	0.24#			
Age ≥65 years	0.46	0.20-1.08	0.07#	0.50	0.21-1.19	0.12*
Duration of diabetes ≥10 years	1.04	0.36-2.99	0.94#			
BMI (≥25 kg/m²)	3.68	1.05-12.86	0.04#	3.40	0.93-12.36	0.06*
TDS Stage 5Ka	1.19	0.46-3.07	0.72#			
Diabetic retinopathy	1.57	0.67-3.68	0.30#			
Optimal A1C <7.0 %	0.90	0.39-2.09	0.80#			
Severely increased albuminuria	1.25	0.52-3.00	0.62#			

Binary logistic regression test was performed. * Multivariable logistic regression test was performed.

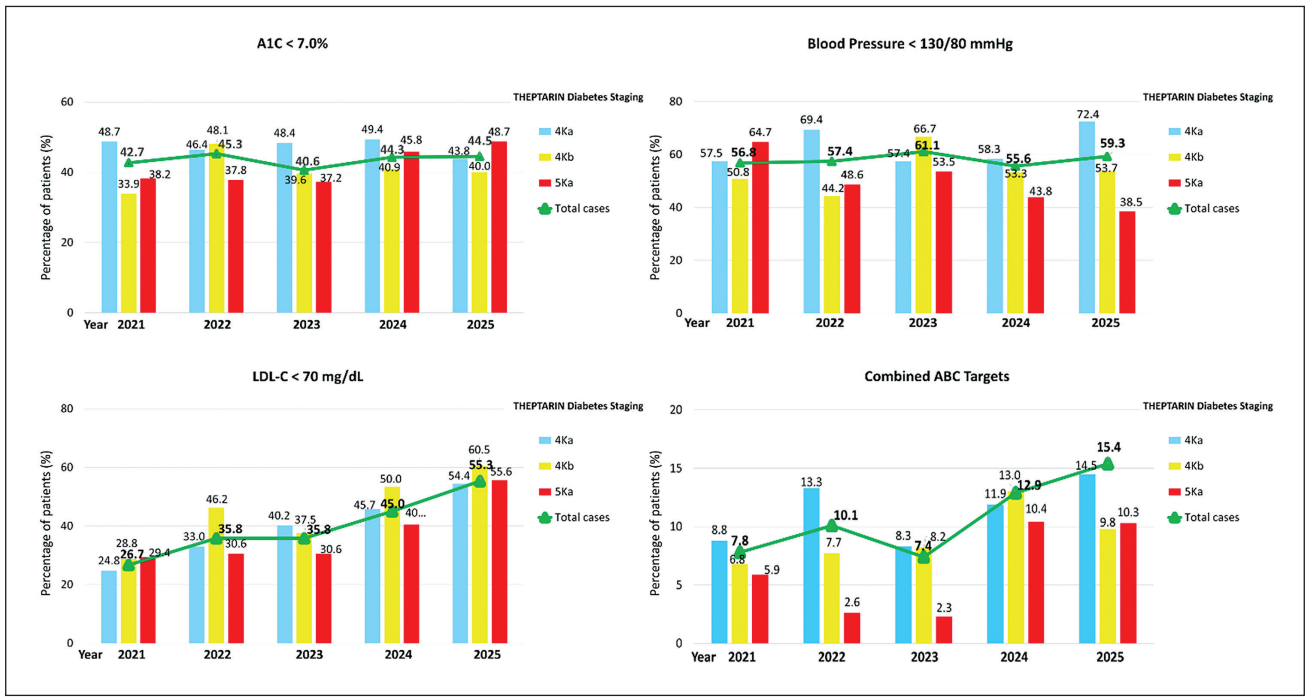

Figure 4. The proportion of patients in each Theptarin Diabetes Staging (TDS) system who attained various multiple treatment targets from 2021 to 2025

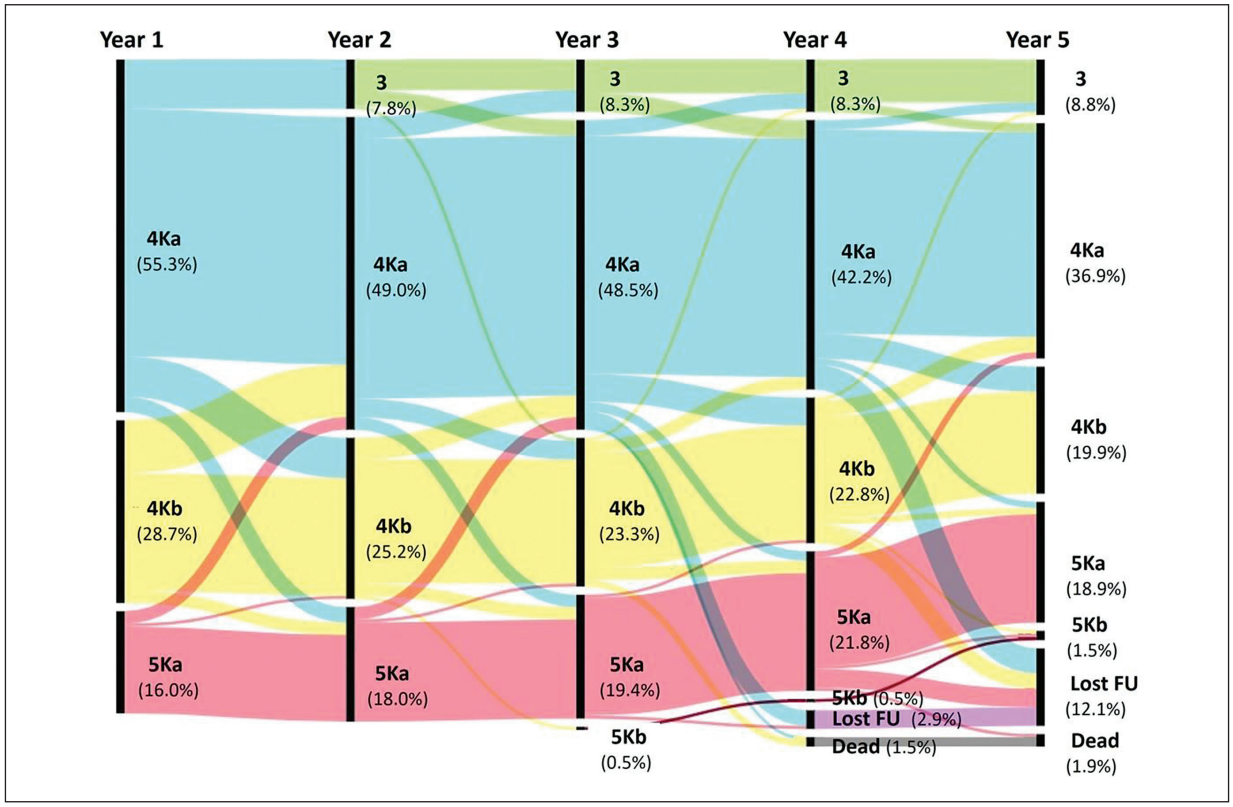

Figure 5. The migration of Theptarin Diabetes Staging (TDS) staging system from overall cohort from 2021 to 2025.

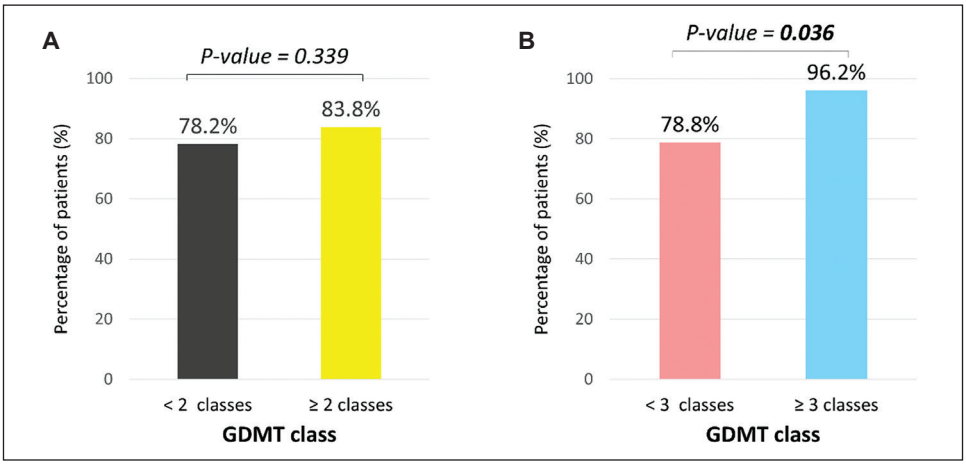

Figure 6. Comparisons the proportion of patients who could stabilize or improve Theptarin Diabetes Staging (TDS) at the last follow-up with numbers of guideline-directed medical therapies (GDMT) **(A)** patients who received GDMT <2 classes versus ≥2 classes **(B)** patients who received GDMT <3 classes versus ≥3 classes (the two-proportion Z-test was used to determine if the difference between two proportions is statistically significant).

action to address the abnormalities in hemodynamics, metabolism, inflammation and fibrosis that characterize the progression of DKD. Early implementation of these therapies is likely to confer substantial long-term gains in survival, free from cardiovascular and kidney disease.[19] It is important to stress that these medications reduced major adverse cardiovascular events, kidney events, and all-cause mortality, irrespective of baseline glycemic control. Despite conventional treatment for DKD, high-risk patients may have a decline in eGFR of up to 5 mL/min/1.73 m^2 per year. This underscores the need for additional therapies to further reduce the rate of kidney function decline to the level of normal healthy aging (about 1 mL/min/1.73 m^2 per year).[20] A recent study showed that if individuals were using all four pillars of therapy, it delays the progression of CKD for at least 5 years compared with conventional use of RASi alone.[21] However, despite this remarkable progress in the evidence-based treatment landscape, access to these therapies remains a challenge in low to middle-income countries. While RASi have been a backbone therapy for

CKD for almost 3 decades in T2D patients with DKD, and generic SGLT2is are now available, finerenone and GLP-1 RA are still unaffordable for most patients with economic difficulties. Primary physicians, especially diabetologists, play a vital role in the management of most T2D patients with DKD, while nephrologists typically oversee those at higher risk and with advanced disease.[22] Therefore, clinical inertia among diabetologists should be addressed with regular reviews and feedback. Our present study showed a detectable increase in GDMT uptake over the past 5 years, as seen in annual audits and feedback.

A further analysis in this study showed that when individuals used at least 3 medication classes, clinical staging could be stabilized or improved in some cases. Clinical staging of type 2 diabetes (T2D) might play a role in more individualized diabetes treatment and would permit timely implementation of effective strategies to prevent or delay progression to advanced stages in individuals with diabetes. Our TDS system had been used locally for more than 10 years to holistically address microvascular and macrovascular complications of diabetes.[14] The TDS system offers clinicians and other healthcare personnel a useful tool for understanding the concept of T2D continuum and defining needs for each patient. The TDS stage 5Ka (eGFR <45 mL/min/1.73 m^2) spanned both albuminuric and normoalbuminuric DKD. Previous studies showed that normoalbuminuric DKD is closely associated with prior RASi use and is more common in older patients with good glycemic control.[23] Unfortunately, the pillar approach is currently unclear since no trials have been conducted specifically on patients with eGFR reduction alone. However, SGLT2i and GLP-1 RA should already be used in patients with established atherosclerotic cardiovascular disease (ASCVD) or high risk for ASCVD. As shown in our present study, most patients with TDS stage 5Ka had a long duration of diabetes and higher rates of macrovascular complications. Both renal and cardiovascular risks should be addressed holistically, using proven pharmacotherapies when affordable.

Concerns about polypharmacy and adverse events should be addressed among patients and multi-disciplinary teams, especially elderly patients with frailty. The presence of multiple comorbidities in patients with CKD requires more comprehensive clinical assessments, not only pharmacotherapy, but also on the optimal control of other comorbidities and nutritional status.[5] While GLP-1 RA has dramatically altered the treatment of patients with obesity, elderly patients are at increased risk for sarcopenia if protein intake and exercise training are inadequate.[24] In patients started on finerenone, careful monitoring of blood pressure, serum potassium level and eGFR is necessary to mitigate adverse events from this new medication. Like RASi and SGLT2i, finerenone can cause a predictable slight drop in eGFR within a few weeks after initiation, but kidney function is expected to recover and stabilize.[25] Additional efforts for patient counseling before introducing this new medication should be emphasized.

There is a substantial opportunity to increase adherence to GDMT uptakes in DKD patients. The TDS system addressed this gap by stratifying patients into subgroups with distinct complication profiles, enabling more focused monitoring and preventive strategies. Improved and stabilized staging between baseline and the last follow-up cohort at 4 years later in patients with TDS stage 4K and TDS stage 5A provided indirect evidence that risk stratification could lead to timely management of DKD. Therefore, regular reviews and feedback are warranted to improve treatment target attainment and outcomes. Electronically delivered activation tools to intensify medications in suitable patients could be one option to remind treating clinicians. Previous study among DKD patients showed that patient empowerment with team-based care assisted by personalized reports to estimate the 5-year probability of major clinical events could improve risk factor control and clinical outcomes in Asian people with DKD.[26] Emerging evidence also suggested that accelerated initiation of multiple therapies within a compressed timeframe, rather than a stepwise sequential approach could benefit patients at high risk of CKD progression and prevent clinical inertia.[27] This method of implementation has drawn parallels with the pillars of GDMT for heart failure.[28] Assessment of the overall cardiovascular-kidney-metabolic risk profile in each patient to match the intensity of treatments is an important step for successful DKD management. The collection and delivery of performance data to quality improvement teams and clinicians, along with educational outreach to clinicians, are also a critical step to increase adherence to clinical practice guidelines. Addressing therapeutic inertia and promoting the timely initiation of GDMT are continuous processes to overcome complex barriers at multiple levels across the health care ecosystem.

Our study has several limitations. First, a substantial proportion of individuals after implementation of the TDS system to track outcomes of care were excluded due to missing data or lost to follow-up. Routine assessment of associated complications is a prerequisite for designating the TDS system, but care deficits arising from the COVID-19 pandemic resulted in missing data. Those who were lost to follow-up before 24 months had a follow-up duration of less than 6 months in 2022 during the COVID-19 pandemic. We excluded them from further analysis due to short follow-up period to track the benefits of GDMT effectiveness. As a result, our single-center retrospective cohort is smaller than the sample sizes required to detect an absolute ±5% difference with 80% power for several medication classes. Consequently, estimates for some medication classes have limited power and precision. Nonetheless, these real-world data offer important clinical insights into contemporary prescribing patterns and are informative for planning larger or multicenter studies. Despite the challenges associated with delivering and documenting care in the follow-up cohort, our current data can verify the usefulness and stage migration in the remaining patients receiving care after the TDS implementation. Second, due to the inherent

limitations of retrospective data and the relatively short follow-up period from a single tertiary private diabetes center in Thailand, our present study should be interpreted with caution. Third, the variability in UACR values and eGFR levels can misclassify some patients, but both tests are considered valid surrogates for CKD progression and reflect a real-world scenario for a single timepoint collection. Fourth, the main purpose of the TDS is to stratify the patients with T2D complications in the busy clinic and facilitate communication between multi-disciplinary teams. Our TDS system was different from the KDIGO guidelines, which used stage-specific recommendations. Therefore, stage-specific DKD guidelines should still adhere to the KDIGO guidelines. However, the UACR-centric TDS stage 4 and KDIGO system were similar and should prompt physicians to consider kidney-protective medications. Finally, other potential confounders, including lifestyle factors, therapy adherence, and socioeconomic status, were not evaluated which may have influenced the outcomes.

CONCLUSION

The landscape of DKD treatment has changed dramatically with the four pillars of pharmacotherapy (RASi, SGLT2i, nsMRA, and GLP-1 RA) in conjunction with comprehensive lifestyle modification. The real-world implementation of GDMT among Thai DKD patients remained inadequate and further efforts are required to improve GDMT uptake in routine practice. Regular reviews and feedback are warranted to improve treatment target attainment and outcomes. Stratifying risk of disease progression with the TDS system could enable more focused monitoring and preventive strategies.

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Statement of Authorship
All authors certified fulfillment of ICMJE authorship criteria.

CRediT Author Statement
CP: Conceptualization, Formal analysis, Data curation, Writing – original draft preparation; **CW**: Writing – review and editing, Visualization; **WE**: Investigation, Writing – review and editing; **BS**: Validation; **NS**: Software, Resources, Visualization, Project administration; **HT:** Funding acquisition; **TY**: Methodology, Writing – review and editing, Supervision.

Data Availability Statement
Datasets are not publicly available because participants in the study did not give written consent for their data to be shared.

Author Disclosure
The authors declared no conflict of interest.

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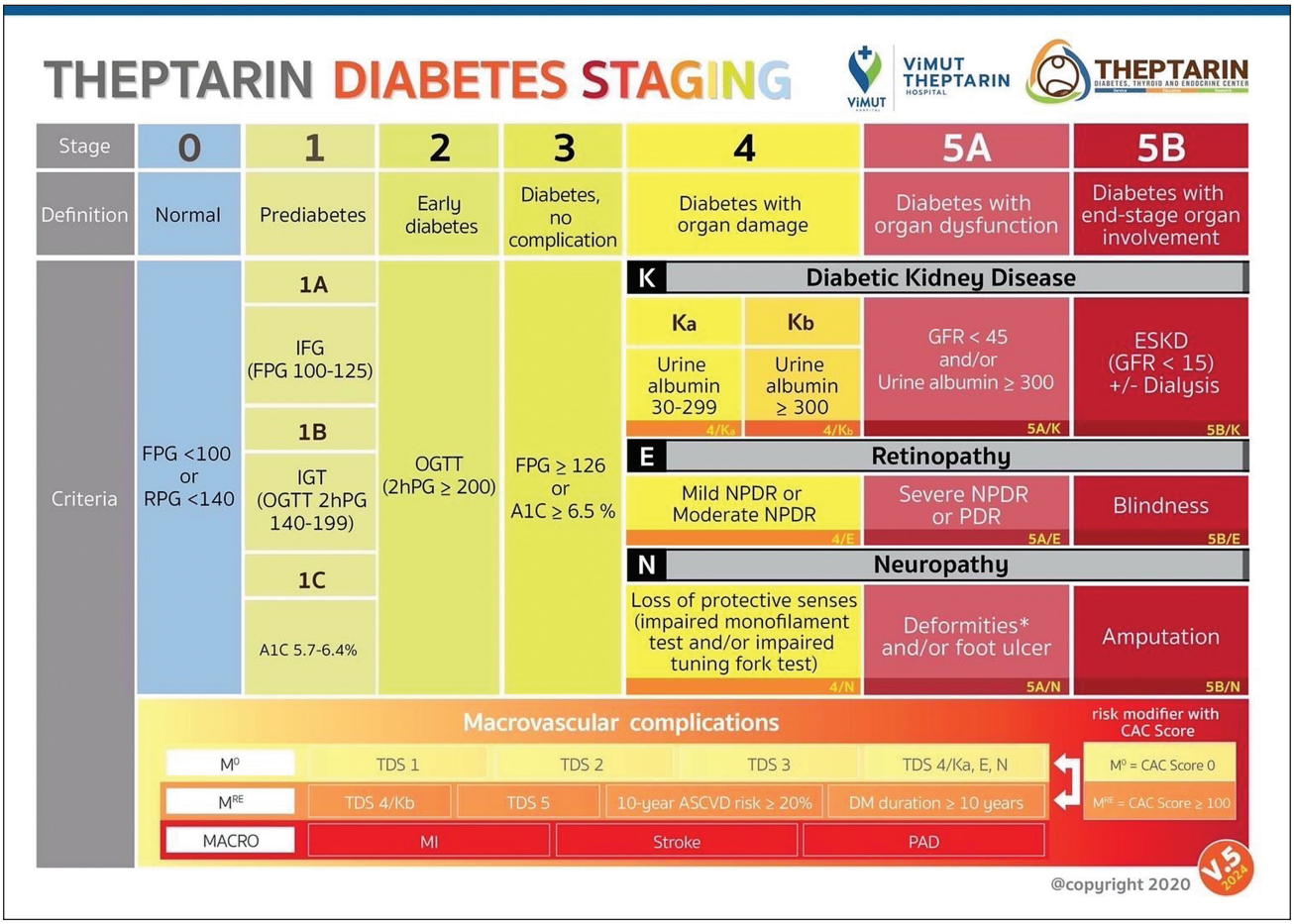
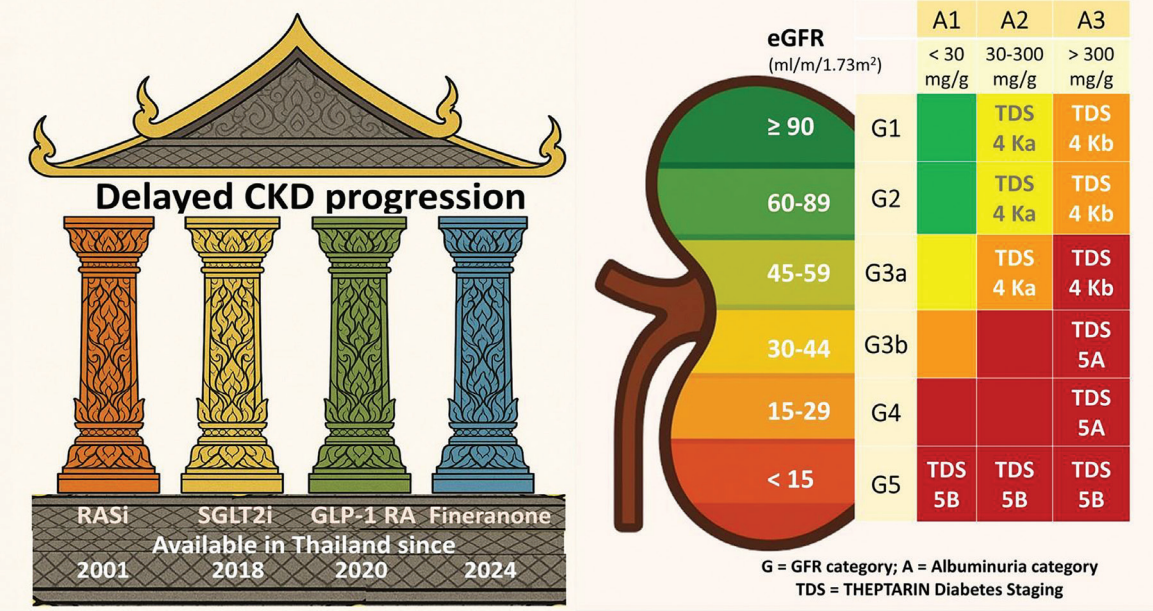
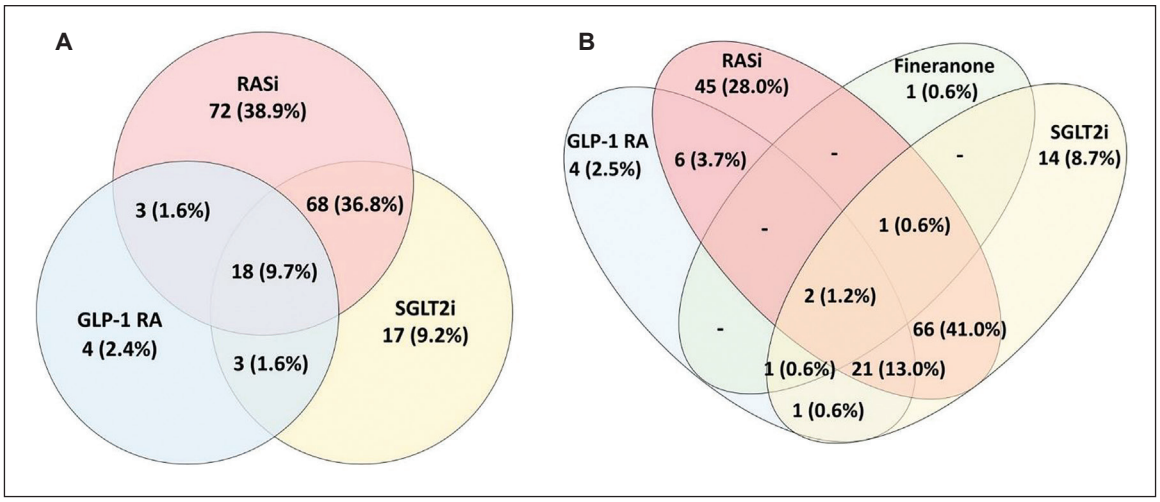
SUPPLEMENTARY FIGURES



Supplementary Figure 1. The Theptarin Diabetes Staging (TDS) system which based on pathophysiology of diabetes and progression of diabetic complications.



Supplementary Figure 2. The pillar approach for diabetic kidney disease medications involves a combination of four medication classes with proven benefits namely renin-angiotensin system inhibitors (RASi), sodium-glucose cotransporter-2 inhibitors (SGLT2i), non-steroidal mineralocorticoid receptor antagonists (nsMRA), and glucagon-like peptide-1 receptor agonists (GLP-1 RA).



Supplementary Figure 3. (A) Details of each class of guideline-directed medical therapies (GDMT) at baseline in 2021. **(B)** Details of each class of guideline-directed medical therapies (GDMT) in 2025.