Cost-effectiveness of gliclazide MR-based intensive glucose control versus standard glucose control in type 2 diabetes mellitus

Pharmacoeconomic analysis in Thailand based on the ADVANCE trial model

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BACKGROUND

Type 2 diabetes mellitus (T2DM) in Thailand

- The prevalence of T2DM is projected to rise rapidly in Thailand, from 6.5% in 2015 to 10.7% in 2035 (Mahikul *et al.*, 2019).
- Therefore, there is a clear need to reduce the health and economic impact of the disease.

Gliclazide modified released (MR) in T2DM

- Achieving tight glycemic control is essential in managing T2DM. Metformin, combined with lifestyle changes, is the first-line approach (Thrasher, 2017; Davies *et al.*, 2018).
- Second-line therapies include sulfonylureas (SUs), a class of drug with a long-established efficacy (Cordiner *et al.*, 2018), which remain a lower cost option than newer second-line non-insulin agents (Thrasher, 2017; Davies *et al.*, 2018). Consequently, SUs remain the main second-line treatment globally, despite the emergence of newer classes of drugs for glycemic control (Christensen *et al.*, 2016; Lipska *et al.*, 2017; Tan et *et al.*, 2019).
- Gliclazide is a second-generation SU that was shown to have a better safety profile than other drugs in its class (Cordiner *et al.*, 2018).

The ADVANCE trial

- The ADVANCE trial (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation) was a global, randomized controlled trial designed to assess the effects of intensive glucose control (IGC) on major vascular outcomes in a broad cross-section of patients with T2DM.
- Patients were randomized to standard glucose control (SGC; n=5,569) or IGC (n=5,571) based on gliclazide MR (modified release) to achieve an HbA_{1c} level ≤ 6.5% and followed-up for a median duration of 5.0 years (ADVANCE Collaborative Group *et al.*, 2008).
- IGC significantly reduced the risk of combined major macrovascular and microvascular events compared with SGC, largely driven by a 21% relative reduction in the incidence of nephropathy (ADVANCE Collaborative Group *et al.*, 2008).

OBJECTIVE

With the rapidly increasing prevalence of T2DM in Asia and the associated economic burden, it is essential that the most cost-effective interventions are identified.

The objective of this analysis was to assess the cost-effectiveness of intensive glucose control vs standard glucose control from a Thai health care payer perspective, using clinical outcomes identified from the ADVANCE trial.

METHODS

Analytic approach and model structure

- A partitioned survival model was developed to assess the cost-effectiveness of IGC vs SGC.
- The model included five health states representative of T2DM complications: no complications, myocardial infarction (MI), stroke, end-stage renal disease (ESRD), and diabetes-related eye disease (DRED). The model structure is presented in *Figure 1*.
- Costs were reported in US dollars (USD) and health outcomes were expressed in terms of life years, quality-adjusted life years (QALYs), and ESRD events avoided.
- The model had a time horizon of 5 years to be aligned with the ADVANCE follow-up study.
- A discount rate of 3% was applied to both costs and outcomes.

Efficacy and safety outcomes

- Efficacy and safety outcomes for the IGC and SGC treatment approaches were derived from the ADVANCE study (ADVANCE Collaborative Group *et al.*, 2008).
- For each complication, time-to-event curves were informed by the cumulative incidence of events and corresponding hazard ratios.
- Clinical inputs included in the model are presented in Table I.

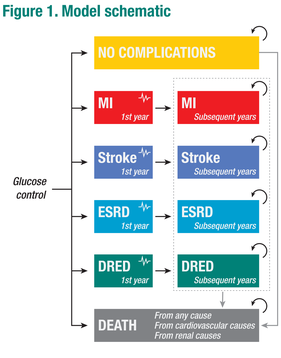
Costs and health utilities

- Costs were expressed in USD 2019 and estimated from a national health care payer perspective. They included treatment costs and health state costs.
- Health state costs were derived from published data in Thailand (Permsuwan *et al.*, 2017), inflated to the year 2019. Cost of death was assumed at zero.
- Health utility weights were derived from published estimates using the EQ-5D-5L instrument in Vietnam (Nguyen *et al.*, 2017).
- Disutility weights were obtained from previous cost-effectiveness studies, notably the Core Diabetes Model (Palmer *et al.*, 2004).
- All costs and health state utilities included in the model are presented in *Tables IIa and IIb*.
- For both costs and health utilities, a distinction was made between the year of occurrence and the subsequent year for each health state.

Scenario and sensitivity analyses

- Drug costs were varied within 9 scenario analyses. For deterministic sensitivity analyses, base-case values were varied within their 95% confidence interval (CI) bounds (when available) or within a ±30% range.
- Probabilistic sensitivity analyses were also performed, varying multiple parameter values simultaneously (1,000 iterations). For utility and treatment efficacy parameter values, a beta distribution was assumed, whereas cost parameters were assumed to follow a gamma distribution (results not shown but available from the authors).

Figure 1. Model schematic



Abbreviations: DRED, diabetes-related eye disease; ESRD, end-stage renal disease; MI, myocardial infarction.

Table I. Clinical inputs

	Base case	Lower value	Upper value
Deaths from any cause			
Standard	9.6%	6.7%	12.5%
HR Intensive vs standard	0.93	0.83	1.06
Major macrovascular events			
Standard	10.6%	7.4%	13.8%
HR Intensive vs standard	0.94	0.84	1.06
Death from cardiovascular causes			
Standard	5.2%	3.6%	6.8%
HR Intensive vs standard	0.88	0.74	1.04
Myocardial infarction			
Standard	3.4%	2.4%	4.4%
HR Intensive vs standard	1.01	0.83	1.24
Stroke			
Standard	4.4%	3.1%	5.7%
HR Intensive vs standard	0.96	0.81	1.15
Major microvascular events			
Standard	4.4%	3.1%	5.7%
HR Intensive vs standard	0.86	0.72	1.03
ESRD			
Standard	1.0%	0.7%	1.3%
HR Intensive vs standard	0.35	0.15	0.83
Death from renal causes			
Standard	0.4%	0.3%	0.5%
HR Intensive vs standard	0.85	0.45	1.62
DRED			
Standard	3.9%	2.7%	5.1%
HR Intensive vs standard	0.90	0.74	1.09
Major hypoglycemia			
Standard	1.5%	1.1%	2.0%
HR Intensive vs standard	1.85	1.42	2.42

Sources: ADVANCE Collaborative Group *et al.*, 2008.
Abbreviations: DRED, diabetes-related eye disease; ESRD, end-stage renal disease; HR, hazard ratio.
Note: Lower and upper values are 95% CI interval bounds.

Table IIa. Costs inputs

	Base case	Lower value	Upper value
Annual costs of drug regimen (USD)[a]			
Standard glucose control	47	33	82
Intensive glucose control	110	77	143
Health state costs (USD)			
Myocardial infarction[b]			
1st year	3,952	2,766	5,138
Subsequent years	990	693	1,287
Stroke[b]			
1st year	2,652	1,856	3,448
Subsequent years	888	622	1,154
ESRD[b]			
1st year	17,102	11,971	22,233
Subsequent years	15,168	10,618	19,718
DRED[b]			
1st year	1,149	804	1,494
Subsequent years	698	489	907
Major hypoglycemia[b]			
Per event	1,035	725	1,346

Sources: [a] Drug Administration of Thailand; [b] Permsuwan et al., 2017. Abbreviations: DRED, diabetes-related eye disease; ESRD, end-stage renal disease; USD, United States dollar.
Note: Lower and upper values are ±30% range limits.

Table IIb. Health utilities inputs

	Base case	Lower value	Upper value
Health state utilities			
Population norms[a]			
Baseline age (ie, 66 years)	0.810	0.567	1.000
5 years after (ie, 71 years)	0.808	0.566	0.810
Events disutilities (%)			
Myocardial infarction[a]			
1st year	-15.9	-11.1	-20.6
Subsequent years	-9.6	-6.7	-12.5
Stroke[a]			
1st year	-22.2	-15.6	-28.9
Subsequent years	-33.1	-23.1	-43.0
ESRD[a]			
1st year	-35.5	-24.9	-46.2
Subsequent years	-35.5	-24.9	-46.2
DRED[a]			
1st year	-9.8	-6.9	-12.8
Subsequent years	-9.8	-6.9	-12.8
Major hypoglycemia[a]			
Per event	-0.6	-0.4	-0.8

Sources: [a] Nguyen et al., 2017; [b] Palmer et al., 2004.
Abbreviations: DRED, diabetes-related eye disease; ESRD, end-stage renal disease.
Note: Lower and upper values are ±30% range limits.

CONCLUSION

In Thailand, gliclazide MR–based intensive glucose control was shown to be cost-effective compared with standard glucose control, as defined in the ADVANCE study.

RESULTS

Base case

- Over 5 years, IGC resulted in the avoidance of 6.5 additional ESRD events per 1,000 patients treated compared with SGC (3.5 events vs 10 events). Although the treatment costs were higher for IGC ($587) than SGC ($250), this was compensated by the savings from the reduced number of ESRD events with IGC ($133) vs SGC ($348), resulting in slightly higher cost for the IGC strategy (SGC, $962 vs IGC, $1,119).
- The resulting incremental cost-effectiveness ratios (ICER) were $24,166, $9,350, and $9,951 per ESRD event avoided, life years gained, and QALY gained, respectively (Table III).

Table III. Base case results

	Absolute		Incremental	
	SGC	Intensive GC	Δ	% change
ESRD event (per 1,000 patients)	10.0	3.5	-6.5	-65.0%
Life years	4.760	4.777	+0.017	+0.4%
QALYs	3.555	3.570	+0.016	+0.4%
Costs ($)	962	1,119	+157	+16.3%
Treatment	*250*	*587*	*+337*	*+95.2%*
Myocardial infarction	*127*	*130*	*+3*	*+2.6%*
Stroke	*122*	*119*	*-3*	*-2.4%*
ESRD	*348*	*133*	*-215*	*-61.7%*
DRED	*73*	*72*	*-1*	*-1.6%*
Hypoglycemic event	*42*	*77*	*+36*	*+85.0%*
ICER for ESRD avoided ($)			24,166	
ICER for life years gained ($)			9,350	
ICER for QALY gained ($)			9,951	

Abbreviations: DRED, diabetes-related eye disease; ESRD, end-stage renal disease; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life years.

Scenario and deterministic sensitivity analyses

- The ICER QALY was most sensitive to variations in the risk of death from any causes, the cost of treatment and the risk of experiencing ESRD events *(Figure 2)*.
- The ICER did not change substantially across the other parameters tested including health state utilities, discounting rates, and most health state costs (with the exception of the cost associated with ESRD events).
- The results from 9 possible scenario analyses suggested that IGC strategy is cost effective in 7 scenarios and cost saving in 1 scenario (Table IV).

Figure 2. Deterministic sensitivity analysis results on the ICER QALY

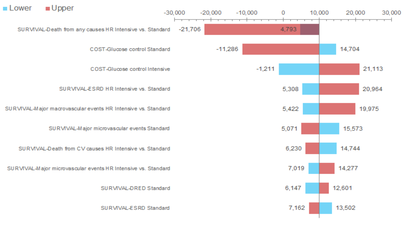


Table IV. Scenario analysis

No	Scenario	ICER USD/QALY	Result
5	Glimepiride at cornerstone SU VS Diamicron STD (Price 50% of Diamicron)	-7,128	Cost Saving
8	SU Median price (Other than Diamicron) VS Diamicron STD (Price 50% of Diamicron MR)	419	Cost Effectiveness
6	Glimepiride at cornerstone SU VS Diamicron Median Price (Price 80% of Diamicron MR)	2,403	Cost Effectiveness
2	Generic SU (Glipizide) as cornerstone SU VS Diamicron STD (Price 50% of Diamicron MR)	8,257	Cost Effectiveness at 2X GDP
1	SU Median price (Other than Diamicron) VS Diamicron Median Price (Price 80% of Diamicron MR)	9,951	Cost Effectiveness at 2X GDP
7	Glimepiride at cornerstone SU VS Diamicron MR	12,213	Cost Effectiveness at 2X GDP
3	Generic SU (Glipizide) as cornerstone SU VS Diamicron Median Price (Price 80% of Diamicron MR)	17,789	Cost Effectiveness at 3X GDP
9	SU Median price (Other than Diamicron) VS Diamicron MR	19,760	Cost Effectiveness at 3X GDP
4	Generic SU (Glipizide) as cornerstone SU VS Diamicron MR	27,598	Not Cost Effectiveness

Abbreviations: SU, sulfonylureas.

DISCUSSION

Key results

- The results indicate that gliclazide MR–based intensive glucose control is cost-effective in Thailand compared with standard glucose control.
- The ICERs for the base case analysis compare favorably with the World Health Organization (WHO) cost-effectiveness threshold for intervention, which, at 3 times GDP per capita (Marseille *et al.*, 2015) is approximately $24,510 in Thailand.

Implications

- There is an increasing demand for a more efficient allocation of scarce health care resources. This demand is particularly great in highly prevalent chronic diseases, such as T2DM, due to their potential impact on patient quality of life and health care expenditure.
- Thailand is in the early stages of adopting health technology assessments (HTAs) to guide decisions on allocation of health care resources (Vo *et al.*, 2018).
- Therefore, analyses, such as the current one, will be an important component of HTAs needed to support policymakers with decision-making.

Strengths

- Analysis based on clinical data from a large, randomized controlled trial.
- Sensitivity analyses showed that the model is highly sensitive to variations in treatment costs and clinical outcomes, demonstrating high internal validity.

Limitations

- No extrapolation beyond 5 years was done due to the high level of uncertainty involved.
- Less than half of the patients in ADVANCE were from the Asian region, and adaptation to the Thai population would have required the availability of more Thai data.
- The comparison used in the model omitted newer classes of drugs available for the management of T2DM. However, these new drugs remain very expensive. Therefore, SUs are probably more relevant to emerging countries, such as Thailand, given their affordability (Thrasher, 2017).

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