Cost-effectiveness of Insulin Degludec Versus Insulin Glargine in Insulin-naive Chinese Patients With Type 2 Diabetes

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ABSTRACT

Purpose: The goal of this study was to investigate the long-term economic outcomes of insulin degludec versus insulin glargine use in Chinese patients with type 2 diabetes mellitus (T2DM) whose oral antidiabetic drugs did not provide sufficient glycemic control.

Methods: A published and validated Chinese diabetes health policy model, which reflects Chinese T2DM epidemiologic profiles, was used to assess the lifetime economic outcomes of microvascular and macrovascular complications and mortality. Efficacy and safety, medical expenditure, and utility data were derived from the literature, which were assigned to model variables for estimating the quality-adjusted life-years (QALYs) and costs, as well as incremental cost-effectiveness ratios. The analysis was conducted from the perspective of Chinese health care service providers. One-way and probabilistic sensitivity analyses were performed.

Findings: Compared with insulin glargine, insulin degludec was associated with 0.0053 QALY at an additional cost of $3278 in our simulated cohort. This outcome resulted in an incremental cost-effectiveness ratio of insulin degludec over insulin glargine of $613,443 per QALY gained. The one-way sensitivity analyses indicated that the results were sensitive to several model inputs.

Implications: Insulin degludec is unlikely to be cost-effective compared with insulin glargine for Chinese patients with T2DM whose disease is inadequately controlled with oral antidiabetic drugs. (*Clin Ther.* 2019;41:445–455)

Keywords: Chinese, Cost-effectiveness, Insulin degludec, Insulin glargine, Type 2 diabetes mellitus.

INTRODUCTION

The Global Burden of Disease Study showed that, due to population growth and aging, all-age disability-adjusted life-years (DALYs) for diabetes in 2016 were 57,233.7 (95% CI, 47,967.9–68,279.3) thousands, which increased by 24.4% (95% CI, 22.7–26.2) from 1990 to 2016.[1] A recent study also showed that China has a large diabetes burden: 1 in 4 people with diabetes worldwide lives in China, where 11.6% of adults have diabetes and 50.1% have prediabetes.[2,3] The entire Chinese economic burden from diabetes increased from 2.216 billion Chinese yuan in 1993 to 200 billion Chinese yuan in 2007.[4,5] Based on Chinese guidelines,[6] a patient-centered approach to controlling hyperglycemia is encouraged to decrease the risk of complications in people with T2DM. As a fundamental therapy for patients with diabetes, basal insulin may lead to better glycemic control.[7]

Basal insulin analogues, such as insulin glargine U100 (insulin glargine), have been widely used to improve glycemic control in patients with T2DM; this approach reduces the risk of hypoglycemia compared with use of neutral protamine Hagedorn insulin. However, the pharmacokinetic and pharmacodynamic properties of insulin glargine resulted in suboptimal glycemic control due to within-patient variability and periods of

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hyperglycemia and hypoglycemia.[8,9] Insulin degludec is a second-generation acylated insulin analogue with threonine deleted at position B30 and a 16-carbon fatty diacid attached to the lysine residue at position B29 via a gamma-glutamic acid spacer.[10] Compared with insulin glargine, insulin degludec is associated with equivalent glycemic control and a statistically significantly lower rate of nocturnal hypoglycemia in patients with diabetes.[8,9]

In China, insulin degludec has reached the market. With increasing constraints on health care budgets, it is important to determine the economic implications of introducing insulin glargine to the local health care system. By using our recently developed and validated Chinese Outcomes Model for T2DM (COMT),[11] the aim of the present analysis was to provide economic evidence regarding the use of insulin degludec and insulin glargine for treating insulin-naive Chinese patients with T2DM whose disease was inadequately controlled by oral antidiabetic drugs (OADs).

MATERIALS AND METHODS

Model Overview

This study provides an economic analysis of basal insulin treatment for patients with T2DM whose disease was inadequately controlled by OADs who were initially assigned to insulin degludec or insulin glargine use according to the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist (Appendix file). The analysis was conducted by using the COMT (Figure 1),[11] a validated Chinese diabetes policy analysis model that simulates a series of diabetic complications, including myocardial infarction, stroke, congestive heart failure, cardiovascular disease, blindness, end-stage renal disease, clinical neuropathy, foot ulcer and amputation, cardiovascular disease mortality, and all-cause mortality (Figure 1). Each complication has an independent model structure integrated with heath event and state, time-at-event, time-in-state, and clinical probabilities derived from published literature. In the simulation, interconnectivity and interaction among individual complication models were permitted to allow the complication risks to be updated by using tracker variables. Disease progression through the model is determined by using patient clinical and demographic characteristics, including age, sex, smoking status, systolic blood pressure, history of cardiovascular disease, use of antihypertensive and anticoagulant medications, glycosylated hemoglobin (HbA_{1c}) levels, total and HDL cholesterol levels, serum creatinine, urine albumin:creatinine ratio, and use of statin and oral diabetes medication. The disease progression was modeled by using annual time arguments. During the simulation, time-dependent risk variables were adjusted based on treatment changes, thereby leading to the likelihood of event incidence.

In line with most economic studies related to T2DM interventions,[12] lifetime health and economic outcomes, including costs, complication probabilities, life-year, and quality-adjusted life-year (QALY), were projected in the current analysis. Costs and QALY were discounted at 5% annually based on Chinese health economics recommendations.[13] When the incremental cost-effectiveness ratios (ICERs) were lower than the per capita gross domestic product of China in 2016 ($8382), cost-effectiveness was assumed. This economic study was based on a literature review and model techniques and did not require approval by the institutional research ethics board.

Patient Profile and Treatment Effects

The patient characteristic profile and efficacy and safety data of insulin degludec and insulin glargine were reported in a 26-week, randomized, open-label, parallel-group, treat-to-target trial that enrolled 560 Chinese subjects with T2DM whose disease was inadequately controlled by OADs.[14] This trial found that the mean absolute changes from baseline in HbA_{1c} levels were 1.3% for insulin degludec and 1.2% for insulin glargine, which were used in the first year of treatment. In the subsequent year, HbA_{1c} level was simulated to rise naturally (in a nonlinear fashion) due to the progressive nature of the disease, according to the HbA_{1c} trajectories analysis.[15] The annual incidences of nonsevere nocturnal, nonsevere diurnal, and severe hypoglycemic episodes were 3.07, 1.01, and 0.1, respectively, for insulin glargine therapy based on a real-world study with a UK population.[16] We assumed that the incidence of hypoglycemia was similar between Chinese and UK populations because insulin glargine effectively lowers HbA_{1c} levels in Asian patients with an incidence of hypoglycemia similar to that of non-Asian

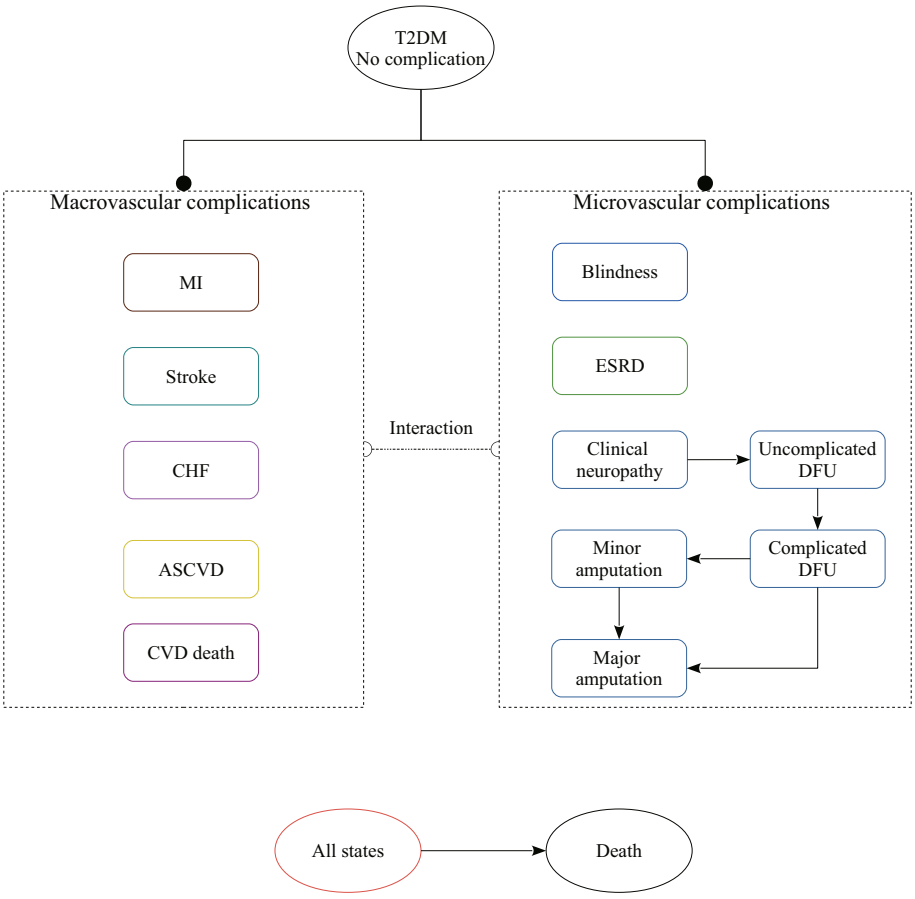

Figure 1. The structure of the Chinese type 2 diabetes mellitus (T2DM) health policy model. ASCVD = atherosclerotic cardiovascular disease; CHF = congestive heart failure; CVD = cardiovascular disease; DFU = diabetic foot ulcer; ESRD = end-stage renal disease; MI = myocardial infarction.

patients.[17] The rates of confirmed severe and nocturnal hypoglycemic episodes between insulin degludec and insulin glargine were derived from a recent meta-analysis that included 18 trials with 16,791 patients.[18]

Costs and Utilities

The current study was performed from the perspective of Chinese health care services providers, and only direct medical costs were considered in the model (Table I). All cost data are presented in 2017 US dollars ($). For insulin degludec and insulin glargine, the daily costs were calculated according to daily dosage. According to Chinese trials, the daily dosage of insulin degludec and insulin glargine was 31 U/day.[14] The prices of insulin degludec and insulin glargine were derived from local hospitals. The annual costs of medicine and glucose-testing strips were estimated from a large national population-based screening study[19] that interviewed 1482 adults with diabetes at 12 sites in China.

Other potential utilizations of direct health resource, such as the costs of hospitalization and outpatient visits due to complications (which were extracted directly from published literature or other local sources), were also reflected in the simulation.[4,20–24] The costs of severe hypoglycemic events were derived from a Chinese cost study, which included 275 patients who incurred hypoglycemic episodes.[25] The costs of nonsevere

Table I. Costs and health state utilities.

Parameter	Expected Value	Range	Source
Costs, $			
Insulin glargine per day	3.28	1.64–3.28	Local charge
Insulin degludec per day	3.94	1.97–3.94	Local charge
Antidiabetic therapy per day (disease duration ≤3 y)	0.5	0.2–1.3	19
Antidiabetic therapy per day (3 < disease duration ≤6 y)	0.8	0.2–1.7	19
Antidiabetic therapy per day (6 ≤ disease duration <10 y)	1.2	0.3–2.5	19
MI hospitalization per event	7383.0	6505.2–8260.9	4, 20, 22, 23
Care after MI per year	455.4	288.6–622.2	4, 20, 22, 23
Stroke hospitalization per event	2875.2	2184.6–4738.3	4, 20, 22, 23
Care after stroke per year	506.9	445.9–828	4, 20, 22, 23
CHF per year	1507.7	1254.6–2632.3	4, 20, 22, 23
ESRD per year	13,803.2	13153.8–14569.2	4
Blindness per year	1642.0	1430.4–1853.5	4, 20, 22, 23
Clinical neuropathy per month	60.9	26.2–101.4	21
Uncomplicated DFU per event	76.2	0–226.2	21
Complicated DFU per event	2293.3	1228.5–2880.8	21
Minor amputation per event	3316.9	2165.2–5038.9	21
Major amputation per event	5019.2	2981.1–7738.2	21
Care after major amputation per month	338.1	0–600.7	21
Severe hypoglycemia per event	534.4	400.8–667.9	25
Cost proportions of nonsevere nocturnal vs severe hypoglycemia	0.015	0.019–0.012	26
Cost proportions of nonsevere diurnal vs severe hypoglycemia	0.010	0.012–0.007	26
Utility value			
T2DM without complications	0.876	0.736–1	27
Utility decrements			
MI hospitalization for 1 mo	1.000	0.236–1	27
MI after discharge	0.236	0.026–0.446	27
Stroke hospitalization for 1 mo	1.000	0.326–1	27
Stroke after discharge	0.326	0.036–0.616	27
CHF	0.236	0.026–0.446	27
ESRD	0.400	0.19–0.61	4, 20, 21–24
Blindness	0.157	0.007–0.307	4, 20, 21–24
Clinical neuropathy	0.185	0.015–0.355	28
Uncomplicated DFU	0.250	0.213–0.287	4, 20, 21–24
Complicated DFU	0.300	0.165–0.435	4, 20, 21–24
Minor amputation	0.320	0.204–0.436	4, 20, 21–24

Table I. (*Continued*)

Parameter	Expected Value	Range	Source
Major amputation	0.380	0.264—0.496	4, 20, 21—24
Nonsevere diurnal hypoglycemia	0.0041	0.0051—0.0031	26
Nonsevere nocturnal hypoglycemia	0.0067	0.0084—0.005	26
Severe hypoglycemia	0.0565	0.0706—0.0424	26

CHF = congestive heart failure; DFU = diabetic foot ulcer; ESRD = end-stage renal disease; MI = myocardial infarction; T2DM = type 2 diabetes mellitus.

nocturnal and nonsevere diurnal hypoglycemia were estimated by multiplying the Chinese cost of severe hypoglycemic episodes and the cost proportions of nonsevere nocturnal and nonsevere diurnal hypoglycemia by those of severe hypoglycemia in the United Kingdom.[26]

Health state utility values were retrieved from a recent study that enrolled 289 patients with T2DM in China and determined the health state utility values of diabetes, neuropathy, heart disease, and cerebrovascular disease using the EQ-5D-5L questionnaire.[27] Other utility values that were not included in this report, such as those of end-stage renal disease and amputation, were derived from previous studies.[4,20–24] The disutilities of nonsevere nocturnal, nonsevere diurnal, and severe hypoglycemia were 0.0054, 0.0077, and 0.0623, respectively.[26]

Sensitivity Analyses

To examine the potential drivers of economic outcomes, we conducted both a 1-way analysis and a probabilistic sensitivity analysis (PSA). The 1-way sensitivity analyses examined the gaps between the low and high values of the ICERs of an individual parameter, whose ranges were derived from the reported upper and lower intervals, as shown in Table I. If no relevant data were available, an assumed range of 75%—125% of the base-case values was used. For the PSA, probability distributions were attached to all parameters to run second-order Monte Carlo simulations (1000 iterations). The probability, proportions, utility value, and utility decrements were modeled by using beta distribution; cost, with a triangle distribution; and hazard ratio and patient characteristic profile, with a normal distribution. If no SE existed, then it was assumed to be 25% of the reported base-case value. Based on the results of the PSA, a cost-effectiveness acceptability curve was produced.

RESULTS

Base-case Analyses

Compared with insulin glargine, insulin degludec gained mean benefits in life expectancy and QALY of 0.0082 year and 0.0053 QALY, respectively, at additional total mean costs of $3278 over a patient's lifetime (Table II), leading to an ICER of $613,443 per QALY gained. These health detriments in the insulin degludec treatment arm were driven by the reduced cumulative incidence of myocardial infarction, stroke, and congestive heart failure.

Sensitivity Analyses

The 1-way sensitivity analyses revealed that the results of the model were more sensitive to the reduction of HbA_{1c} levels in the insulin glargine and insulin degludec strategy, the costs of insulin degludec and insulin glargine, and the probability of hypoglycemia because they were found to have a substantial impact on the ICER. The remainder of the sensitive variables, such as the disutility values and the costs of complications, had a moderate or small impact (Figure 2).

In the PSA (Figure 3), the cost per additional QALY gained for insulin degludec over insulin glargine was $1,029,804 (95% CI, 591,715—1,357,675). At an acceptable ICER of $27,351 (three times the gross domestic product per capita of China in 2017), insulin degludec produced a nearly 0% probability of cost-effectiveness, as shown in the cost-effectiveness acceptability curve (Figure 4).

Table II. Base-case results for insulin degludec versus insulin glargine.

Outcome	Insulin Glargine	Insulin Degludec	Difference*
Events			
Myocardial infarction	8.68%	8.67%	−0.01%
Stroke	20.07%	20.03%	−0.04%
CHF	13.00%	12.98%	−0.02%
ESRD	3.638%	3.634%	0.00%
Blindness	3.96%	3.95%	0.00%
Clinical neuropathy	14.32%	14.32%	0.00%
Minor amputation	10.85%	10.85%	0.00%
Major amputation	7.97%	7.97%	0.00%
Total QALY	10.08	10.09	0.0053
Total life-years	20.76	20.77	0.0082
Total cost (US $)	21,344	24,623	3278
ICER (US $/QALY)	NA	613,443	—

CHF = congestive heart failure; ESRD = end-stage renal disease; ICER = incremental cost-effectiveness ratio; NA = not applicable; QALY = quality-adjusted life-year.
* Compared with the control strategy (insulin glargine).

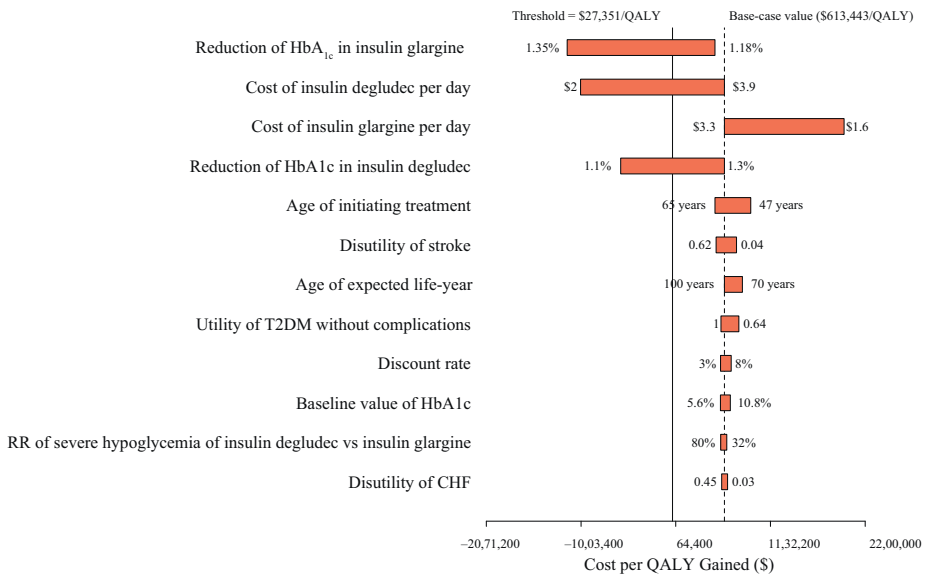

Figure 2. Tornado diagram representing the net health benefit in the 1-way sensitivity analysis of insulin degludec versus insulin glargine. The width of the bars represents the range of the results when the variables were changed. CHF = congestive heart failure; HbA_{1c} = glycosylated hemoglobin; RR = risk ratio; T2DM = type 2 diabetes mellitus; QALY = quality-adjusted life-year.

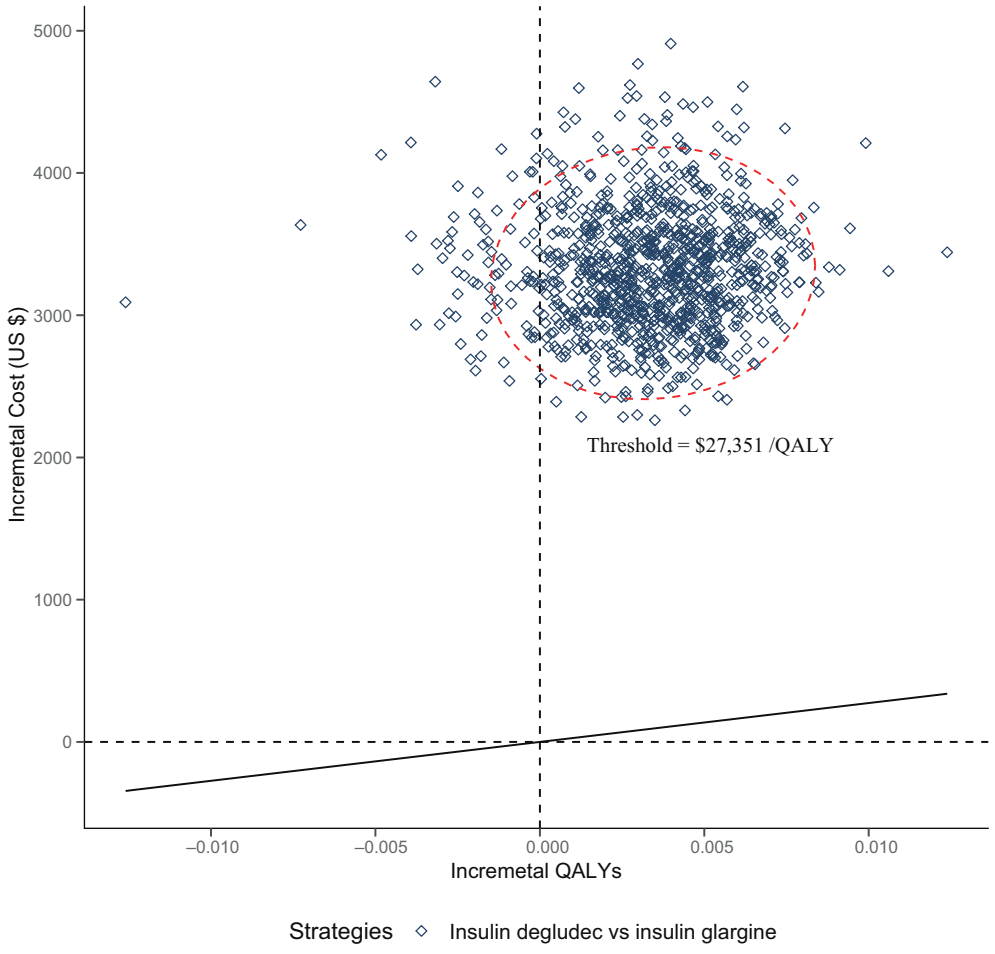

Figure 3. The probabilistic results of the incremental cost-effectiveness difference. The red ellipses surround 95% of the estimates. QALY = quality-adjusted life-year.

DISCUSSION

Reports of the clinical benefits of insulin degludec in clinical trials have caused great excitement among both endocrinologists and patients. Previous studies have found that ~30% of patients eventually require insulin therapy to keep HbA_{1c} values at optimum levels, and basal insulin is widely prescribed.[7,28] However, the widespread use of insulin degludec comes with a considerable increase in health care costs compared with insulin glargine; this increased cost is concerning to clinicians and payers. The need for precise economic evaluation of insulin degludec use in the Chinese context is becoming urgent. To our knowledge, this study is the first economic analysis estimated that in Chinese patients with T2DM inadequately controlled by OADs, the initiation of insulin degludec and insulin glargine were associated with improvements in length and quality of life. However, the similar glycemic durability associated with insulin degludec and insulin glargine translated to comparable health benefits. Due to the relatively lower cost of insulin glargine therapy, insulin degludec was not a cost-effective alternative. This finding is strengthened by using the COMT model, which has manifested good model validity for established effects of medicines on surrogate end points such as glucose, blood pressure, and lipid profiles in the Chinese population.

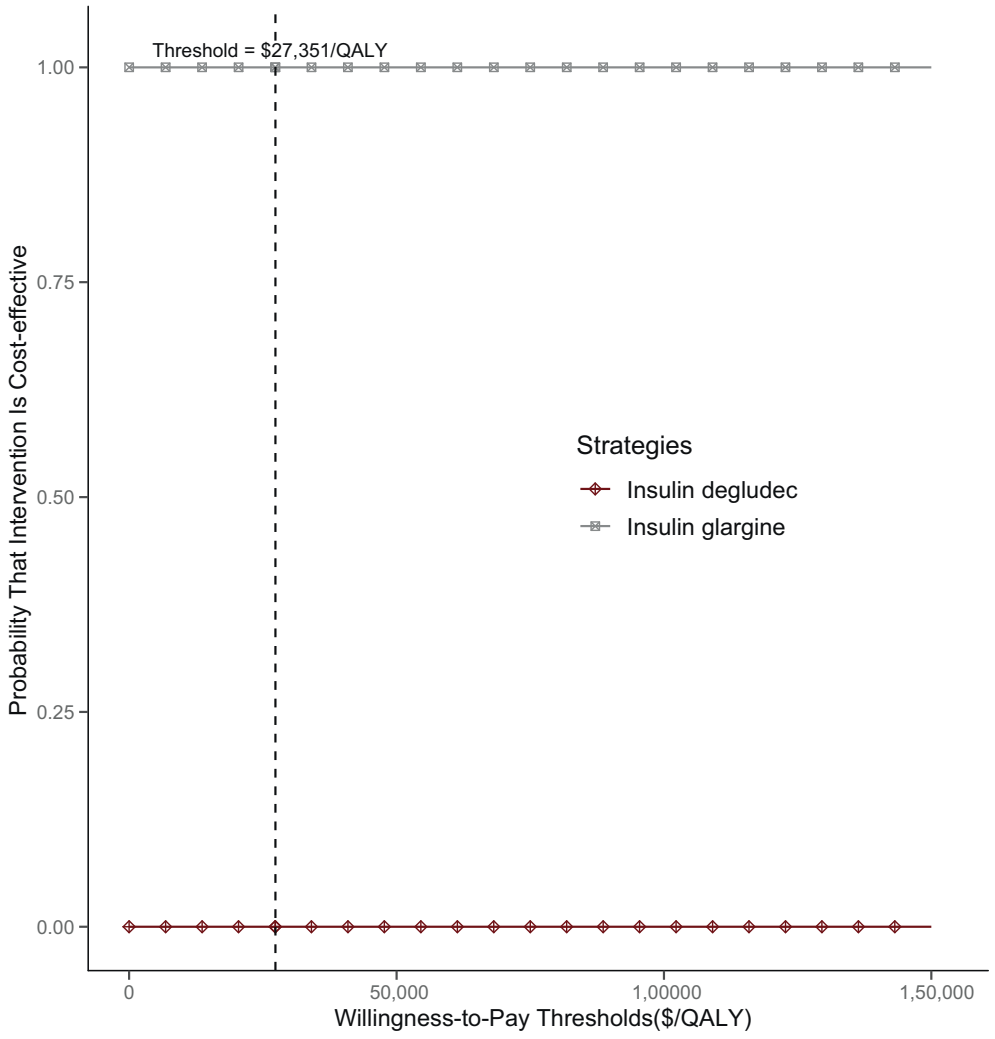

Figure 4. Cost-effectiveness acceptability curve for insulin degludec versus insulin glargine. QALY = quality-adjusted life-year.

Several studies have investigated the economic outcomes of using insulin degludec among patients with T2DM in European regions.[16,26,29–32] These reports showed that the ICERs for insulin degludec over insulin glargine ranged from approximately $7600/QALY in the United Kingdom to $34,300/QALY in Denmark, which indicates that insulin degludec was cost-effective in European regions. However, this finding was not consistent with the results of the current analysis. One potential reason might be the different clinical data inputs used. For example, the rate ratios of hypoglycemia for insulin degludec versus insulin glargine in the UK study reported by Evans et al[16] were extracted from the meta-analysis published before 2015; these ratios are considerably lower than the ones used in the current evaluation, which were derived from the latest meta-analysis that included 18 trials.[18] Previous studies and our analysis all suggest that hypoglycemia rates are a key driver of cost-effectiveness outcomes,[16,26,29–32] which could notably induce insulin degludec to be more favorable by reducing the rate ratios of hypoglycemia. To minimize the potential uncertainty around rates of hypoglycemia,

the latest reported data were used in the current analysis.

Notwithstanding the relevance of the treatment effect data to clinical practice, the local comparison was primarily conducted to facilitate cost-effectiveness analysis. The improvement in glycemic control observed with insulin glargine was a key driver of differentiation in terms of a favorable cost-effectiveness profile. The net health benefit of insulin degludec versus insulin glargine in the base-case analysis was partly contributed to by the antihyperglycemia efficacy (1.3% reduction in HbA_{1c} levels with insulin degludec and 1.2% with insulin glargine) in a Chinese study.[14] However, many clinical studies found that insulin glargine had relatively better efficacy of antihyperglycemia than insulin degludec in other populations.[9] For example, in a clinical trial performed in 6 Asian countries/regions (Hong Kong, Japan, Malaysia, South Korea, Taiwan, and Thailand), HbA_{1c} levels decreased by 1.24% and 1.35% in the insulin degludec and insulin glargine groups after 26 weeks, respectively.[33] Our one-way sensitivity analysis indicated that when the HbA_{1c} reduction of insulin glargine decreased to the upper limit (1.35%), insulin glargine became a dominant strategy due to its better health outcome with cheaper cost.

The current analysis still suffers from several limitations, and it should be considered with those in mind. First, a Chinese perspective was adopted as the cost and cost-effectiveness context (eg, threshold and discount rates), which may affect the transferability of these findings to other regions. However, due to the transparent input profiles and treatment effects, region-specific cost and utility data could be input to replicate this evaluation to inform local decision-makers. Second, although hypoglycemic events are a potential risk factor for subsequent cardiovascular outcomes, and all-cause mortality was reported previously,[34–36] the current analysis did not address this issue because a causal link has yet to be established beyond doubt. Third, as with other cost-effectiveness analyses using computer modeling techniques,[12] this analysis extrapolated the lifetime clinical and economic outcomes beyond the trial follow-up period by translating short-term surrogate end points (risk factor profiles) to the incidence of diabetes-related complications and mortality. Therefore, the long-term comparison of insulin degludec versus insulin glargine contains uncertainty, which should be addressed when explaining the findings. However, because our model was validated, the potential uncertainty of treatment should pertain to both the insulin degludec strategy and the insulin glargine strategy, which might not be considerably different. Finally, treatment effect data were extracted from clinical trials, which are substantially different from the real world[37] in terms of factors such as nonadherence to medications. However, because the findings of this study reflect the common clinical conditions for managing T2DM in China, we hope this study will provide relevant information for Chinese clinical and health policy decision-makers.

CONCLUSIONS

This economic analysis found that insulin degludec is likely to provide a paucity of health benefits at a relatively high cost compared with insulin glargine for patients in the Chinese health care system with T2DM inadequately controlled by OADs. These findings indicate that treatment with insulin glargine versus insulin degludec is a more efficient allocation of limited Chinese health resources for the management of T2DM and may be a factor for patients, physicians, and decision-makers in the selection of a reasonable basal insulin for the treatment of T2DM.

CONFLICTS OF INTEREST

The authors have indicated that they have no conflicts of interest regarding the content of this article.

The funding agency had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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Drs. Wu and Cheng contributed to the conception and design of the primary model, and they interpreted the results. Drs. Cheng and Wan developed the economic model, performed the

analyses, and drafted the manuscript. Drs. Cheng, Wan, and Ma collected the data. Drs. Cheng and Wan wrote the first draft of the manuscript, which was then critically revised by all authors. All authors approved the manuscript as submitted.

REFERENCES

1. GBD 2016 DALYs and HALE Collaborators. Global, regional, and national disability-adjusted life-years (DALYs) for 333 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet*. 2017;390:1260–1344. https://doi.org/10.1016/S0140-6736(17)32130-X.
2. Xu Y, Wang L, He J, et al. Prevalence and control of diabetes in Chinese adults. *JAMA*. 2013;310:948–959. https://doi.org/10.1001/jama.2013.168118.
3. Wang L, Gao P, Zhang M, et al. Prevalence and ethnic pattern of diabetes and prediabetes in China in 2013. *JAMA*. 2017;317:2515–2523. https://doi.org/10.1001/jama.2017.7596.
4. Wang H, Lin X, Zhang Z, et al. The economic burden of inpatients with type 2 diabetes: a case study in a Chinese hospital. *Asia Pac J Public Health*. 2015;27(2 Suppl): 49S–54S. https://doi.org/10.1177/1010539515572220.
5. Chan JCN, Zhang Y, Ning G. Diabetes in China: a societal solution for a personal challenge. *Lancet Diabetes Endocrinol*. 2014;2:969–979. https://doi.org/10.1016/S2213-8587(14)70144-5.
6. Chinese Diabetes Society. 2013 China guideline for prevention and treatment of type 2 diabetes. *Chin J Endocrinol Metabol*. 2014;30:893–942.
7. Pettus J, Santos Cavaiola T, Tamborlane WV, Edelman S. The past, present, and future of basal insulins. *Diabetes Metab Res Rev*. 2016;32:478–496. https://doi.org/10.1002/dmrr.2763.
8. Russell-Jones D, Gall MA, Niemeyer M, Diamant M, Del Prato S. Insulin degludec results in lower rates of nocturnal hypoglycaemia and fasting plasma glucose vs. insulin glargine: a meta-analysis of seven clinical trials. *Nutr Metab Cardiovasc Dis*. 2015;25:898–905. https://doi.org/10.1016/j.numecd.2015.06.005.
9. Liu W, Yang X, Huang J. Efficacy and safety of insulin degludec versus insulin glargine: a systematic review and meta-analysis of fifteen clinical trials. *Int J Endocrinol*. 2018;2018:8726046. https://doi.org/10.1155/2018/8726046.
10. Owens DR, Matfin G, Monnier L. Basal insulin analogues in the management of diabetes mellitus: what progress have we made? *Diabetes Metab Res Rev*. 2014;30:104–119. https://doi.org/10.1002/dmrr.2469.
11. Wu B, Ma J, Zhang S, Zhou L, Wu H. Development and validation of a health policy model of type 2 diabetes in Chinese setting. *J Comp Eff Res*. 2018 August 22. https://doi.org/10.2217/cer-2018-0001 [Epub ahead of print].
12. Charokopou M, Sabater FJ, Townsend R, Roudaut M, McEwan P, Verheggen BG. Methods applied in cost-effectiveness models for treatment strategies in type 2 diabetes mellitus and their use in health technology assessments: a systematic review of the literature from 2008 to 2013. *Curr Med Res Opin*. 2016;32:207–218. https://doi.org/10.1185/03007995.2015.1102722.
13. Wang X, Wang ZF, Xie YM, et al. Guideline for postmarketing Chinese medicine pharmacoeconomic evaluation. *Chin J Integr Med*. 2015;21:473–480. https://doi.org/10.1007/s11655-014-1749-y.
14. Mu YM, Guo LX, Li L, et al. The efficacy and safety of insulin degludec versus insulin glargine in insulin-naive subjects with type 2 diabetes: results of a Chinese cohort from a multinational randomized controlled trial. *Zhonghua Nei Ke Za Zhi*. 2017;56:660–666.
15. McEwan P, Bennett H, Qin L, Bergenheim K, Gordon J, Evans M. An alternative approach to modelling HbA1c trajectories in patients with type 2 diabetes mellitus. *Diabetes Obes Metab*. 2017;19:628–634. https://doi.org/10.1111/dom.12865.
16. Evans M, Chubb B, Gundgaard J. Cost-effectiveness of insulin degludec versus insulin glargine in adults with type 1 and type 2 diabetes mellitus. *Diabetes Ther*. 2017;8: 275–291. https://doi.org/10.1007/s13300-017-0236-9.
17. Chan JCN, Bunnag P, Chan SP, et al. Glycaemic responses in Asian and non-Asian people with type 2 diabetes initiating insulin glargine 100 units/mL: a patient-level pooled analysis of 16 randomised controlled trials. *Diabetes Res Clin Pract*. 2018;135:199–205. https://doi.org/10.1016/j.diabres.2017.11.025.
18. Zhang XW, Zhang XL, Xu B, Kang LN. Comparative safety and efficacy of insulin degludec with insulin glargine in type 2 and type 1 diabetes: a meta-analysis of randomized controlled trials. *Acta Diabetol*. 2018;55:429–441. https://doi.org/10.1007/s00592-018-1107-1.
19. Yang W, Zhao W, Xiao J, et al. Medical care and payment for diabetes in China: enormous threat and great opportunity. *PLoS One*. 2012;7, e39513. https://doi.org/10.1371/journal.pone.0039513.
20. Li T, Liu M, Ben H, Xu Z, Zhong H, Wu B. Clopidogrel versus aspirin in patients with recent ischemic stroke and established peripheral artery disease: an economic evaluation in a Chinese setting. *Clin Drug Investig*. 2015;35: 365–374. https://doi.org/10.1007/s40261-015-0290-x.
21. Wu B, Wan X, Ma J. Cost-effectiveness of prevention and management of diabetic foot ulcer and amputation in a health resource-limited setting. *J Diabetes*. 2018;10: 320–327. https://doi.org/10.1111/1753-0407.12612.

22. Shao H, Zhai S, Zou D, et al. Cost-effectiveness analysis of dapagliflozin versus glimepiride as monotherapy in a Chinese population with type 2 diabetes mellitus. *Curr Med Res Opin*. 2017;33:359–369. https://doi.org/10.1080/03007995.2016.1257978.
23. Gu S, Mu Y, Zhai S, Zeng Y, Zhen X, Dong H. Cost-effectiveness of dapagliflozin versus acarbose as a monotherapy in type 2 diabetes in China. *PLoS One*. 2016;11:e0165629. https://doi.org/10.1371/journal.pone.0165629.
24. Wu B, Zhang S, Lin H, Mou S. Prevention of renal failure in Chinese patients with newly diagnosed type 2 diabetes: a cost-effectiveness analysis. *J Diabetes Investig*. 2018;9:152–161. https://doi.org/10.1111/jdi.12653.
25. Ya-ming Z, Wu J, Xie K. Incidence and cost of hypoglycemia episode in patients with type 2 diabetes mellitus (T2DM). *Chin Rural Health Serv Adm*. 2012;32:1195–1198.
26. Evans M, Mehta R, Gundgaard J, Chubb B. Cost-effectiveness of insulin degludec vs. insulin glargine u100 in type 1 and type 2 diabetes mellitus in a UK setting. *Diabetes Ther*. 2018;9:1919–1930. https://doi.org/10.1007/s13300-018-0478-1.
27. Pan CW, Sun HP, Zhou HJ, et al. Valuing health-related quality of life in type 2 diabetes patients in China. *Med Decis Making*. 2016;36:234–241. https://doi.org/10.1177/0272989X15606903.
28. Heymann AD, Kritz V, Hemo B, Kertes J, Becker M. A changed pattern of insulin use following the introduction of basal analog insulin treatment in primary care. *Prim Care Diabetes*. 2013;7:57–61. https://doi.org/10.1016/j.pcd.2012.12.005.
29. Lalić N, Russel-Szymczyk M, Culic M, Tikkanen CK, Chubb B. Cost-effectiveness of insulin degludec versus insulin glargine u100 in patients with type 1 and type 2 diabetes mellitus in Serbia. *Diabetes Ther*. 2018;9:1201–1216. https://doi.org/10.1007/s13300-018-0426-0.
30. Mezquita-Raya P, Darbà J, Ascanio M, Ramírez de Arellano A. Cost-effectiveness analysis of insulin degludec compared with insulin glargine u100 for the management of type 1 and type 2 diabetes mellitus—from the Spanish National Health System perspective. *Expert Rev Pharmacoecon Outcomes Res*. 2017;17:587–595. https://doi.org/10.1080/14737167.2017.1345628.
31. Pollock RF, Tikkanen CK. A short-term cost-utility analysis of insulin degludec versus insulin glargine U100 in patients with type 1 or type 2 diabetes in Denmark. *J Med Econ*. 2017;20:213–220. https://doi.org/10.1080/13696998.2016.1245663.
32. Ericsson Å, Pollock RF, Hunt B, Valentine WJ. Evaluation of the cost-utility of insulin degludec vs insulin glargine in Sweden. *J Med Econ*. 2013;16:1442–1452. https://doi.org/10.3111/13696998.2013.852099.
33. Onishi Y, Iwamoto Y, Yoo SJ, Clauson P, Tamer SC, Park S. Insulin degludec compared with insulin glargine in insulin-naïve patients with type 2 diabetes: a 26-week, randomized, controlled, Pan-Asian, treat-to-target trial. *J Diabetes Investig*. 2013;4:605–612. https://doi.org/10.1111/jdi.12102.
34. Goto A, Goto M, Terauchi Y, Yamaguchi N, Noda M. Association between severe hypoglycemia and cardiovascular disease risk in Japanese patients with type 2 diabetes. *J Am Heart Assoc*. 2016;5:e002875. https://doi.org/10.1161/JAHA.115.002875.
35. Lu CL, Shen HN, Hu SC, Wang JD, Li CY. A population-based study of all-cause mortality and cardiovascular disease in association with prior history of hypoglycemia among patients with type 1 diabetes. *Diabetes Care*. 2016;39:1571–1578. https://doi.org/10.2337/dc15-2418.
36. Luk AOY, Ho TST, Lau ESH, et al. Association of self-reported recurrent mild hypoglycemia with incident cardiovascular disease and all-cause mortality in patients with type 2 diabetes: prospective analysis of the Joint Asia Diabetes Evaluation Registry. *Medicine (Baltimore)*. 2016;95:e5183. https://doi.org/10.1097/MD.0000000000005183.
37. Chatterjee S, Davies MJ, Khunti K. What have we learnt from "real world" data, observational studies and meta-analyses. *Diabetes Obes Metab*. 2018;20(1 Suppl):47–58. https://doi.org/10.1111/dom.13178.

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APPENDIX A. SUPPLEMENTARY DATA

CHEERS Checklist

Items to include when reporting economic evaluations of health interventions

The **ISPOR CHEERS Task Force Report,** *Consolidated Health Economic Evaluation Reporting Standards (CHEERS)—Explanation and Elaboration: A Report of the ISPOR Health Economic Evaluations Publication Guidelines Good Reporting Practices Task Force*, provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp.

Section	Item No	Recommendation	Reported on page No/line No
Title and Abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	1/1—2
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	1/9—28
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.	2/1—11
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	3/12—26
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	2/24—26
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	3/29—30
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	1/30—32
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	3/2—3
Discount rate	9		3/4

(*Continued*)

Section	Item No	Recommendation	Reported on page No/line No
		Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	3/2—4
Measurement of effectiveness	11a	*Single study-based estimates*: Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	NA
	11b	*Synthesis-based estimates*: Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	3/13—26
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	4/1—5
Estimating resources and costs	13a	*Single study-based economic evaluation*: Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	NA
	13b	*Model-based economic evaluation*: Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	3/29—43
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	3/30—31
Choice of model	15		2/30—44

(*continued on next page*)

(*Continued*)

Section	Item No	Recommendation	Reported on page No/line No
		Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	3/13—26; 4/12—19
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	4/8—19
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	Table 1
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	Table 2
Characterizing uncertainty	20a	*Single study-based economic evaluation*: Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	NA
	20b	*Model-based economic evaluation*: Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	4/35—38

(*Continued*)

Section	Item No	Recommendation	Reported on page No/line No
Characterizing heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	4/28–33
Discussion			
Study findings, limitations, generalizability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	4/41–44; 5/1–44; 6/1–11
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	Title page
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	Title page

For consistency, the CHEERS Statement checklist format is based on the format of the CONSORT statement checklist.

The **ISPOR CHEERS Task Force Report** provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* link or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp.

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