Received: 23 August 2018 | Revised: 2 November 2019 | Accepted: 10 November 2019

DOI: 10.1111/bcp.14188

ORIGINAL ARTICLE

Cost-effectiveness of long-acting insulin analogues *vs* intermediate/long-acting human insulin for type 1 diabetes: A population-based cohort followed over 10 years

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Funding information
Ministry of Science and Technology, Taiwan, Grant/Award Number: MOST 104-2320-B-006-008-MY3; National Institute of Diabetes and Digestive and Kidney Diseases, Grant/Award Number: P30DK092926

Aims: This study assessed the cost-effectiveness of long-acting insulin analogues (LAIAs) *vs* intermediate/long-acting human insulin (ILAHI) for patients with type 1 diabetes (T1D) in real-world clinical practice.

Methods: Individual-level analyses were conducted within a longitudinal population-based cohort of 540 propensity score-matched T1D patients (LAIAs, n = 270; ILAHI, n = 270) with over 10 years of follow-up using Taiwan's National Health Insurance Research Database, 2004–2013, from third-party payer and healthcare sector perspectives. The study outcomes included the number needed to treat (NNT) to prevent one case of clinical events (eg, hypoglycaemia, diabetes-related complications), medical costs, and cost per case of events prevented. Cost estimates are presented in 2013 British pounds (GBP, £).

Results: The NNTs using LAIAs *vs* ILAHI to avoid one case of hypoglycaemia requiring medical assistance, outpatient hypoglycaemia and any diabetes-related complications were 12, 9 and 10 for mean follow-up periods of 5.84, 6.02 and 3.62 years, respectively. From third-party payer and healthcare sector perspectives, using LAIAs instead of ILAHI saved GBP6924-GBP7116 per case of hypoglycaemia requiring medical assistance prevented, GBP5346-GBP5508 per case of outpatient hypoglycaemia prevented, and GBP3570-GBP3680 per case of any diabetes-related complications prevented. Sensitivity analyses considering sampling uncertainty showed that using LAIAs over ILAHI yields at least a 76% probability of cost-saving for avoiding one case of hypoglycaemia requiring medical assistance, outpatient hypoglycaemia or any diabetes-related complications.

Conclusions: This real-world evidence reveals that compared with ILAHI, the greater pharmaceutical costs associated with LAIAs for patients with T1D could be substantially offset by savings from averted hypoglycaemia or diabetes-related complications.

KEYWORDS

cost-effectiveness analysis, intermediate/long-acting human insulin, long-acting insulin analogues, longitudinal cohort study, type 1 diabetes

Tsung-Ying Lee and Shihchen Kuo have equal first-authorship.

Principal investigator: The authors confirm that there is no principal investigator for this paper.

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1 | INTRODUCTION

Type 1 diabetes (T1D) is associated with an increased risk of vascular complications compared with the non-diabetic population.[1-3] The morbidity and mortality associated with diabetes have resulted in a substantial economic burden on national healthcare.[4] In 2009, the estimated number of patients with T1D in Taiwan was 8043, which accounts for less than 1% of the diabetic population; the age-standardized incidence rate was 31.3 per million persons.[5] Although T1D accounts for a small proportion of the diabetic population, it leads to a substantial economic burden in Taiwan. Our previous study showed that T1D was associated with lifetime healthcare expenditures of British Pounds (GBP, £) 65 158 per case in Taiwan.[6] Moreover, the annual healthcare costs per case for patients with T1D were estimated to be 1.5 to 3 times greater than those for patients with type 2 diabetes according to studies from the United States.[7,8]

Patients with T1D typically require multiple-dose insulin injections to mimic the natural secretory pattern of insulin in the body. Long-acting insulin analogues (LAIAs) have better pharmacokinetic and pharmacodynamic profiles,[9-12] resulting in a slight reduction in glycosylated hemoglobin ($HbA1_c$) (less than 0.5%) and a lower risk of hypoglycaemia compared with those for intermediate/long-acting human insulin (ILAHI) (eg, neutral protamine Hagedorn; NPH).[13] However, the price of LAIAs (ie, insulin glargine, insulin detemir) is four times higher than that of NPH according to Taiwan's National Health Insurance (NHI) price listings.[14] The economic value of LAIAs is debated[15,16] because of their high acquisition costs compared with that of ILAHI and the uncertainty of their effectiveness in improving solid clinical outcomes (eg, diabetes-related complications). Patients' age and treatment convenience could be important factors influencing clinicians' decisions in selecting LAIA *vs* ILAHI for patients with T1D in Taiwan. Specifically, for young children with T1D who are unable to use injectable insulin by themselves at school, it is more convenient for their parents to use a regimen of ILAHI and short-acting insulin twice daily (ie, before and after school). Older children, adolescents and adult patients with T1D are likely to be prescribed a four-times-daily regimen with LAIA once daily and rapid-acting insulin three times daily to reduce the risk of hypoglycaemia.

Although several cost-effectiveness studies of LAIAs *vs* ILAHI among patients with T1D exist, the results remain inconclusive and no such study has been done in Taiwan. Studies have shown that some LAIAs (ie, glargine,[17,18] detemir[19-23] and degludec[23]) are more costly but also more effective than ILAHI, with a large variation in incremental cost-effectiveness ratio estimates, from GBP2562 to GBP99 683 per quality-adjusted life year, while others (ie, glargine[24] and detemir[25]) are cost-saving compared to ILAHI. Moreover, the results from previous studies[17-25] should be interpreted with caution. First, the model inputs in the model-based simulation studies were typically taken from a single clinical trial with limited sample size and follow-up time.[17-22,24,25] However, the efficacy data from clinical trials may not translate to clinical effectiveness/outcomes. The model inputs directly taken from clinical trials may not be generalizable to patients in a real-world setting because available treatments and recommended strategies may differ by country, and the risk equations, utilities, resource utilization and costs may be subject to change. For example, adherence to treatment in a real-world setting is often lower than that observed in clinical trials. Second, the projection of long-term outcomes (eg, incidence of diabetes-related complications) is usually done using short-term results based on clinical biomarkers (eg, $HbA1_c$) due to a lack of effectiveness data from real-world settings.[17-25] However, the extrapolation from clinical biomarkers to clinical events in cost-effectiveness analysis (CEA) should be done with caution. Third, the results of CEA depend on the willingness-to-pay (WTP) threshold made by health policy decision-makers, which varies by country and healthcare setting. These limitations highlight the importance of conducting CEA in a real-world setting from various perspectives to corroborate previous study findings.

Against this background, we estimated the real-world cost-effectiveness of LAIAs *vs* ILAHI among patients with T1D in Taiwan. Real-world evidence provides valuable information to complement the evidence from randomized controlled trials,[26] and it has increasingly appeared in recent studies of diabetes.[27-30] The effectiveness inputs in this CEA were based on our published comparative effectiveness study of basal insulins, in which reduced risks of hypoglycaemia and diabetes-related complications associated with LAIAs *vs* ILAHI were found.[29] The individual-level cost estimates were measured using Taiwan's National Health Insurance Research Database (NHIRD), which includes nationwide, population-based, longitudinal data.

What is already known about this subject

- Long-acting insulin analogues (LAIAs) yield better efficacy in glycaemic control and reduce the risk of hypoglycaemia relative to intermediate/long-acting human insulin (ILAHI) in clinical trials. In a real-world setting, however, few studies have demonstrated the effectiveness of LAIAs in preventing long-term diabetes-related complications and it remains unknown whether the high costs of LAIAs could be justified against their potential effectiveness compared with ILAHI.

What this study adds

- In a real-world setting, the high costs of LAIAs could be justified based on their effectiveness compared with ILAHI under a single-payer healthcare system.
- Based on the empiric data analysis from a nationwide claims database in Taiwan, LAIAs relative to ILAHI saved GBP852 and GBP876 per patient from third-party payer and healthcare sector perspectives, respectively, over a mean follow-up of 7.2 years.
- LAIAs should be considered as an economically reasonable first-line choice for the basal insulin regimen in the treatment of patients with type 1 diabetes.

2 | METHODS

2.1 | Data source

This study was approved by the Institutional Review Board of National Cheng Kung University Hospital (B-EX-103-015). This CEA utilized the claims data of a nationwide diabetes cohort to examine the long-term effectiveness and cost consequences of basal insulins. Specifically, individual-level data were obtained from the Longitudinal Cohort of Diabetes Patients (LHDB) 2004–2013 from the NHIRD, which contains emergency, outpatient, inpatient, and pharmacy claims. Taiwan's NHI is a single-payer, universal-access healthcare system that was introduced in 1995 and covers over 99% of Taiwan's population.[31,32] The application of the LHDB is described in detail elsewhere.[29,33]

2.2 | Description of study cohort

Patients who had an ICD-9-CM diagnosis code of T1D (250.X1 or 250.X3) and were issued a Catastrophic Illness Card (CIC) for T1D were identified in the LHDB. We further excluded those who were prescribed with oral antidiabetic agents (except for metformin and thiazolidinediones) after the CIC for T1D was issued and those who had a history of chronic diabetes-related complications (ie, cardiovascular disease, nephropathy, neuropathy and retinopathy). Among patients identified as T1D, those who were newly prescribed with basal insulins (ie, LAIAs or ILAHI) and had persistent use of the basal insulin (ie, at least three refills with any gaps between two consecutive refills of fewer than 180 days) between 2004 and 2008 were included in the analyses. The propensity score (PS)-matching method was then applied to identify baseline comparable users of LAIAs (n = 270) with those on ILAHI (n = 270). The follow-up period for each study patient started from the first prescription of basal insulins until the occurrence of a diabetes-related complication, dropout from Taiwan's NHI program, death or the end of 2013, whichever came first, for the effectiveness estimates, and until dropout from Taiwan's NHI program, death or the end of 2013, whichever came first, for the cost estimates. After applying the PS-matching method, all baseline characteristics were comparable between the LAIA and ILAHI groups (mean age of each group was 18 years old). More details about the cohort extraction procedure, patient characteristics before and after PS matching and comparative effectiveness results of basal insulins can be found elsewhere.[29]

2.3 | Study method

As recommended by the Second Panel on Cost-Effectiveness in Health and Medicine,[34] the structure of the study methods is summarized in an Impact Inventory, consisting of potential effectiveness and cost consequences of basal insulins for the third-party payer (payer hereafter) and healthcare sector perspectives (Supplementary Table 1). For each perspective, we measured the effect of basal insulins on health outcomes in terms of the number needed to treat (NNT) for preventing diabetes-related complications and all direct medical costs, including future diabetes-related and -unrelated medical costs paid by a third-party payer and the copayment (for healthcare sector perspective). For each study patient, we measured their direct medical costs during the follow-up, which represented the expenditures for all medical services and products associated with medical management of their diseases paid by Taiwan's NHI program (eg, costs of emergency department visits, hospitalization, outpatient care, laboratory tests and medications) and the out-of-pocket expense paid by patients. The reporting of this study follows the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement (Table S2).

2.4 | Effect of basal insulins on health outcomes

The effectiveness of basal insulins was defined as the NNT for preventing one case of diabetes-related complications (ie, cardiovascular disease [CVD], nephropathy, retinopathy, neuropathy, hospitalized hyperglycaemia, any hypoglycaemia requiring medical assistance, outpatient hypoglycaemia and hospitalized hypoglycaemia) or all-cause death. NNT measures were estimated using Equations (1)–(3). First, we converted the incidence rates of diabetes-related complications obtained from our published study[29] into cumulative incidences using Equation (1)[35]:

$$CI = 1 - e^{-IR \times t} \quad (1)$$

where t denotes the average observational period for each outcome of interest among the study cohort, CI is the cumulative incidence of the outcome of interest during time t and IR is the incidence rate of the outcome of interest measured during time t. Second, absolute risk reduction (ARR) was measured as the difference in the cumulative incidences of the outcome of interest during time t between the LAIA group (CI_1) and the ILAHI group (CI_0) (Equation (2)). NNT was then estimated as 1 divided by the ARR (Equation (3)). For three outcomes in which a statistically significant difference in risks was found between the LAIA and ILAHI groups (ie, hypoglycaemia requiring medical assistance, outpatient hypoglycaemia and any diabetes-related complications), we calculated the 95% confidence intervals (CIs) using the Wald method.[36]

$$ARR = CI_0 - CI_1 \quad (2)$$

$$NNT = 1/ARR = 1/(CI_0 - CI_1) \quad (3)$$

2.5 | Medical costs

Each of the medical costs listed in the impact inventory was measured as a summary of cost components from the following claims files in Taiwan's NHIRD: emergency department, inpatient admission, outpatient visit and pharmacy. Cost components in these claims files include the costs of diagnosis, treatments (ie, examinations, procedures and special materials),

pharmaceutical services and medications. In Taiwan, copayments are typically required for patients but can be waived for patients with catastrophic diseases such as T1D.[37,38] In this study, copayments were considered as the out-of-pocket (OOP) expense paid by patients. In the analyses from the third-party payer perspective, we included all medical services and costs during the follow-up related to the emergency room, outpatient, inpatient and pharmacy components but excluded the OOP expense. In the analyses from the healthcare sector perspective, we also included the OOP expense.

To adjust for differences in baseline medical costs (ie, one year before the beginning of basal insulin therapy) for LAIA and ILAHI users, a regression-based adjustment was performed (Equation (4))[39]:

$$\text{cost}_j = \alpha + \beta_{\text{baseline}} \times \text{cost}_{\text{baseline}j} + \beta_{\text{treatment}} \times \text{treatment}_j \quad (4)$$

Total medical cost (cost_j) for a given patient j is an explanatory variable, and baseline cost ($\text{cost}_{\text{baseline}j}$) and basal insulin group (treatment_j = 1 for the LAIA group and treatment_j = 0 for the ILAHI group) are independent variables.

We used log-transformation to reduce the skewness of cost data and to improve the normality of our data. We then calculated the adjusted total medical costs for each perspective using Equation (5)[39]:

$$\ln\left(\text{cost}_{\text{adjusted}_j}\right) = \ln\left(\text{cost}_j\right) - \beta_{\text{baseline}} \times \left(\ln\left(\text{cost}_{\text{baseline}_j}\right) - \ln\left(\text{cost}_{\text{mean at baseline}}\right)\right) \quad (5)$$

where $\text{cost}_{\text{adjusted}_j}$ is the adjusted total medical cost for a given person j, β_{baseline} is the beta coefficient for baseline cost (ie, $\text{cost}_{\text{baseline}j}$) obtained from Equation (4), and $\text{cost}_{\text{mean at baseline}}$ is the mean baseline cost for all patients from the study cohort.

All cost estimates were standardized to the year 2013 using the Taiwan consumer price index (https://eng.stat.gov.tw/public/data/dgbas03/bs3/english/cpiidx.xls) and converted to 2013 GBP using an average exchange rate of GBP1:NT$46.4 from 2013.

2.6 | Cost-effectiveness analysis of basal insulins

NNT is a measure of treatment effectiveness and is interpreted as the average number of patients with T1D who would need to be treated with LAIA relative to ILAHI for a given follow-up period of time to prevent one case of diabetes-related complications or all-cause death. A lower absolute value of NNT indicates a more effective intervention. The incremental costs refer to the difference in the average per-patient medical costs during the given follow-up period between the LAIA and ILAHI groups. Thus, cost-effectiveness analyses were performed by multiplying the estimates of incremental costs between LAIAs and ILAHI by the NNT for a given study outcome from the payer and healthcare sector perspectives. The incremental cost-effectiveness ratio (ICER) was estimated as the incremental cost per one case of outcomes of interest prevented when LAIAs are used compared with ILAHI. Because NNT is intrinsically understandable and often used as a decision tool by clinicians, and can conveniently be combined with costs to calculate cost-effectiveness, it has become increasingly used as a tool in health economic evaluation studies, including those on chronic diseases such as diabetes, cancer, heart failure, atrial fibrillation, psoriasis and rheumatoid arthritis.[40-50] Moreover, the inclusion of NNT increases clinical relevance and the application of CEA results, and an increased understanding of the relationships between CEA and NNT may help clinicians apply CEA findings in practice.[40]

TABLE 1 Disaggregated results of effectiveness for cost-effectiveness analysis

	Incidence rates[a]		Mean follow-up time (years)			Estimated cumulative incidences			
Diabetes-related complications	ILAHI	LAIA	ILAHI	LAIA	Overall	ILAHI	LAIA	HR (95% CIs)	NNT
CVD	5.2	1.6	7.15	7.13	7.14	0.0363	0.0111	0.304 (0.084–1.106)	40
Nephropathy	23.7	24.3	6.72	6.55	6.64	0.1455	0.1490	1.027 (0.673–1.568)	−284
Retinopathy	64.1	58.5	5.66	5.64	5.65	0.3039	0.2813	0.918 (0.689–1.223)	44
Neuropathy	15.6	18.5	6.90	6.61	6.76	0.0999	0.1173	1.169 (0.710–1.925)	−57
Hospitalized hyperglycaemia	54.0	49.4	5.96	5.77	5.87	0.2717	0.2517	0.910 (0.670–1.237)	50
Hypoglycaemia that requires medical assistance	61.8	41.7	5.63	6.04	5.84	0.3029	0.2160	0.681 (0.498–0.930)	12
Outpatient hypoglycaemia	56.6	33.0	5.76	6.28	6.02	0.2886	0.1804	0.592 (0.424–0.828)	9
Hospitalized hypoglycaemia	7.4	12.0	7.05	6.76	6.91	0.0495	0.0798	1.622 (0.830–3.170)	−33
Any diabetes-related complications[b]	224.7	169.8	3.46	3.77	3.62	0.5564	0.4589	0.782 (0.639–0.956)	10
All-cause death	2.0	1.0	7.27	7.16	7.22	0.0146	0.0074	0.502 (0.092–2.739)	140

Abbreviations: CIs, confidence intervals; CVD, cardiovascular disease; HR, hazard ratio; ILAHI, intermediate/long-acting human insulin; LAIA, long-acting insulin analogue; NNT, number needed to treat.

[a]Incidence rates are presented as patient number per 1000 person-years.

[b]Any diabetes-related complications consisted of CVD, nephropathy, retinopathy, neuropathy, hospitalized hyperglycaemia or hypoglycaemia that requires medical assistance.

2.7 | Sensitivity analysis

To capture the sampling uncertainty in the ICER estimates, the non-parametric bootstrap method was applied to generate 1000 replicated estimates of incremental cost-effectiveness pairs[51] for the study subjects. The 95% CIs for ICER were defined as the 2.5th and 97.5th ranked ICER of the 1000 replicated estimates. A summary measure of the joint uncertainty of costs and effectiveness has been presented as cost-effectiveness acceptability curves (CEACs), which indicate the probability of cost-effectiveness at various WTP thresholds.[52] According to the World Health Organization,[53] an intervention strategy is considered cost-effective if the ICER is less than three times the gross domestic product (GDP) per capita (ie, GBP41 943 in Taiwan, 2013[54]), and it is considered highly cost-effective if the ICER is less than one GDP per capita (ie, GBP13 981 in Taiwan, 2013). Furthermore, we performed several sensitivity analyses to estimate the ICER based on the scenarios considered in our published effectiveness study[29]: (1) the effectiveness estimates were derived from the intention-to-treat (ITT) analysis (ie, the observation of individual patients was stopped/censored if patients died, withdrew from Taiwan's NHI or at the end of 2013, whichever came first) and the cost calculation was based on the ITT analysis with consideration of the occurrence of the event of interest as the censoring variable, (2) both the effectiveness and cost estimates were derived from the on-treatment (OT) analysis (ie, the observation of individual patients was stopped/censored if patients died, withdrew from Taiwan's NHI, at the end of 2013, or the treatment pattern changed [ie, switch or discontinuation], whichever came first) and (3) the effectiveness estimates were derived from the OT analysis and the cost calculation was based on the OT analysis with consideration of the occurrence of the event of interest as the censoring variable.

3 | RESULTS

3.1 | Effectiveness estimates

Our effectiveness study revealed that compared with ILAHI, LAIAs led to a significantly lower risk of hypoglycaemia and any diabetes-related complications.[29] Relative to ILAHI, 12, 9 and 10 patients (95% CIs 6 to 75, 6 to 27 and 6 to 74, respectively) would need to be treated with LAIAs for a mean of 5.84, 6.02 and 3.62 years to prevent a case of hypoglycaemia requiring medical assistance, outpatient hypoglycaemia and any diabetes-related complications, respectively (Table 1).

3.2 | Cost estimates

Table 2 outlines the disaggregated cost estimates per patient for LAIA and ILAHI users. The adjusted total cost per patient for LAIAs was lower than that for ILAHI, with a difference of −GBP852 per patient from the payer perspective and −GBP876 from the healthcare sector perspective, over a mean follow-up of 7.2 years. The cost differences were mainly due to differences in outpatient care and inpatient care. The cost estimates for medications are shown in Table S3. The cost of antidiabetic drugs per patient among the users of LAIAs was higher than that for ILAHI users, which was most likely due to the higher acquisition costs of LAIAs. However, the costs of other medications per patient were much lower in the LAIA group *vs* the ILAHI group. As a result, the overall medication cost per patient in the LAIA group was GBP552 less than that in the ILAHI group.

3.3 | Costs per case of event prevented

The incremental costs of the average medical costs per patient per year between the LAIA and ILAHI users were calculated from the

TABLE 2 Disaggregated results of costs per patient over follow-up period (mean = 7.22 years) for cost-effectiveness analysis

(2013 GBP)	ILAHI group	LAIA group	ΔC
Third-party payer perspective			
Third-party payer costs	9427	8183	−1244
Third-party payer costs (adjusted[a])	8852	8000	−852
Healthcare sector perspective			
Emergency costs	231	226	−4
Diagnosis	54	50	−4
Treatment	156	154	−2
Pharmaceutical service	4	4	0
Medication	16	19	3
Outpatient costs	6908	5751	−1156
Diagnosis	795	692	−102
Treatment	2049	1550	−500
Pharmaceutical service	127	115	−12
Medication	3937	3395	−542
Inpatient costs	1511	1235	−276
Room	499	407	−92
Diagnosis	114	112	−1
Therapy and examination	506	469	−38
Pharmaceutical service	30	22	−7
Medication	309	181	−128
Special material	53	44	−9
Pharmacy costs	977	1147	171
Pharmaceutical service	34	31	−3
Medication	510	626	116
Special material	433	490	57
Out-of-pocket expense	199	177	−22
Healthcare sector costs	9626	8360	−1266
Healthcare sector costs (adjusted[a])	9061	8186	−876

Abbreviations: ΔC, difference in costs per case between LAIA and ILAHI users; ILAHI, intermediate/long-acting human insulin; LAIA, long-acting insulin analogue.

[a]Adjusted for baseline difference in medical costs between insulin groups.

payer (−GBP99) and healthcare sector (−GBP102) perspectives (Table S4). The base-case analysis demonstrates that using LAIAs *vs* ILAHI is cost-saving in terms of preventing one case of hypoglycaemia requiring medical assistance, outpatient hypoglycaemia and any diabetes-related complications (Table 3). For example, relative to ILAHI, 10 patients would need to be treated with LAIAs for 3.62 years to prevent one case of any diabetes-related complications, which would save GBP3570 and GBP3680 per case from the payer and healthcare sector perspectives, respectively.

Using the nonparametric bootstrapping method, the 95% CIs for estimated incremental costs were between −GBP2927 and −GBP1003 from the payer perspective and between −GBP3158 and −GBP809 from the healthcare sector perspective. The CEACs in Figure 1 indicate that the probabilities that LAIAs are cost-saving compared with ILAHI from the payer perspective (healthcare sector perspective) is 76.9% (77.3%), 76.8% (77.2%) and 76.5% (76.9%), respectively, for avoiding one case of hypoglycaemia requiring medical assistance, outpatient hypoglycaemia and any diabetes-related complications. Using one GDP per capita (ie, GBP13 981) as the WTP threshold, there was a 96.6–98.6% probability that LAIAs are highly cost-effective for preventing one case of these clinical events from the payer and healthcare sector perspectives. The results from several scenario sensitivity analyses shown in Tables S5–S11 demonstrate that LAIAs are either cost-saving or highly cost-effective compared with ILAHI, which is consistent with the findings from base-case analyses.

4 | DISCUSSION

This is the first real-world CEA of LAIAs *vs* ILAHI based on the comparative effectiveness results obtained from a large population-based cohort study of T1D in a real-world setting. Relative to ILAHI, LAIAs for patients with T1D are cost-saving for preventing one case of hypoglycaemia requiring medical assistance, outpatient hypoglycaemia and any diabetes-related complications, mainly owing to the reductions in outpatient and inpatient costs. LAIAs are highly cost-effective, with an almost 100% likelihood of falling below one GDP per capita for Taiwan (GBP13 981).

Although a direct comparison of our study with existing cost-effectiveness studies[17-25] may be a challenge due to the use of different analytic approaches, study perspectives and healthcare settings, this real-world, population-based cost-effectiveness research provides supporting data for favourable economic outcomes using LAIAs *vs* ILAHI in patients with T1D. In particular, our analyses were based on clinical data derived from a large population-based cohort study with long-term follow-up on a varied range of diabetes-related complications and all-cause death. Our study allows a sufficient time horizon to measure relevant health impacts and costs, which is rarely the case in trial-based cost-effectiveness studies. Moreover, we utilized Taiwan's NHIRD, which is a data source with a nationwide representative population, for a comprehensive estimation of all economic consequences of treatments reimbursed by Taiwan's NHI for

TABLE 3 Results of cost-effectiveness analysis of long-acting insulin analogues *vs* intermediate/long-acting human insulin

			ΔC over mean follow-up time[c]		Costs per case with event of interest prevented over mean follow-up time	
Event of interest	NNT	Mean follow-up time (years)[b]	Third-party payer perspective	Healthcare sector perspective	Third-party payer perspective	Healthcare sector perspective
Individual complications						
CVD	40	7.14	−705	−725	−28 200	−29 000
Nephropathy	−284	6.64	−656	−675	186 304	191 700
Retinopathy	44	5.65	−558	−574	−24 552	−25 256
Neuropathy	−57	6.76	−667	−687	38 019	39 159
Hospitalized hyperglycaemia	50	5.87	−580	−596	−29 000	−29 800
Hypoglycaemia that requires medical assistance[a]	12	5.84	−577	−593	−6924	−7116
Outpatient hypoglycaemia[a]	9	6.02	−594	−612	−5346	−5508
Hospitalized hypoglycaemia	−33	6.91	−682	−702	22 506	23 166
Any diabetes-related complication[a,d]	10	3.62	−357	−368	−3570	−3680
All-cause death	140	7.22	−713	−734	−99 820	−102 760

Abbreviations: Δ*C*, difference in costs per case between LAIA and ILAHI users; CVD, cardiovascular disease; NNT, number needed to treat.

[a]Compared with ILAHI use, LAIA use was associated with a significantly lower risk of these events.

[b]The follow-up period of time per person for each event of interest started from the first prescription of basal insulins until occurrence of an event, withdrawal from Taiwan's NHI program, death or the end of 2013, whichever came first.

[c]Average difference in the cost per patient per year between LAIA and ILAHI users is estimated in detail in Table S4.

[d]Any diabetes-related complications consisted of CVD, nephropathy, retinopathy, neuropathy, hospitalized hyperglycaemia or hypoglycaemia that requires medical assistance.

Note: All cost estimates are in 2013 GBP.

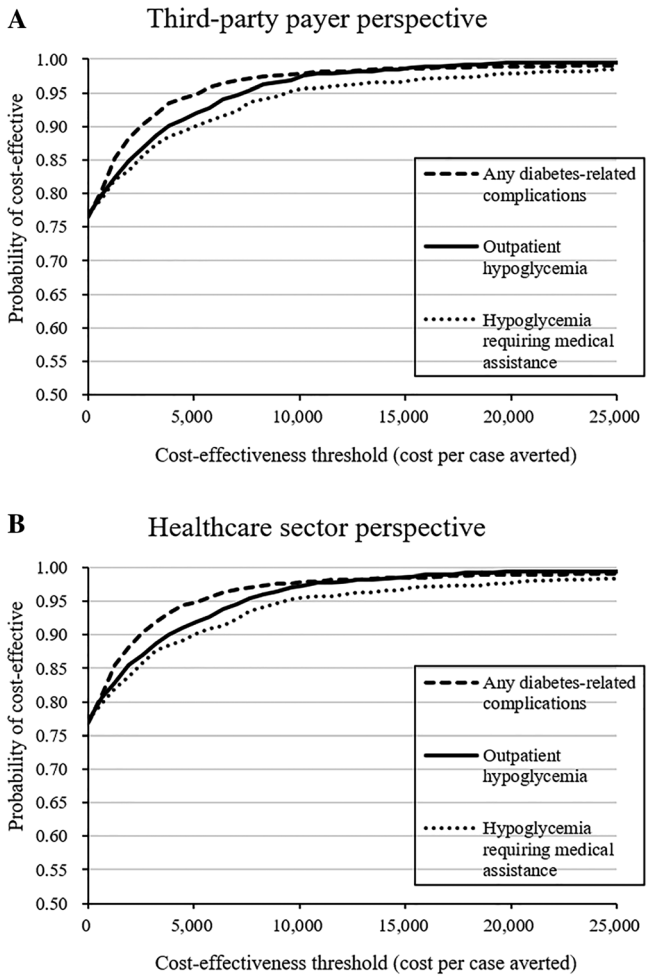

FIGURE 1 Cost-effectiveness acceptability curves using 1000 bootstraps (cost estimates are in 2013 GBP) (A) from the third-party payer perspective and (B) from the healthcare sector perspective

individuals with T1D. A cost analysis study of basal insulins for T1D in a real-world setting was previously conducted using Germany's claims database,[55] but a CEA was not performed and the cost estimates were based on only a 1-year period. The study demonstrated a trend of lower annual costs for insulin glargine users owing to the lower costs of bolus insulin, blood glucose test strips, lancets, needles and antihypoglycaemic treatments *vs* NPH users. The results of this short-term cost analysis are consistent with our findings that LAIAs have higher acquisition costs, but other relevant medical costs for LAIA users (Tables 2 and S3) are lower than those for ILAHI users, therefore the lower economic burden associated with the use of LAIAs *vs* ILAHI may be partly due to lower medical resource consumption (eg, examinations, other treatments) in the short term and lower risks of diabetes-related complications in the long term.

Several limitations in our study need to be addressed. First, our analysis did not include direct nonmedical costs (eg, transportation costs) and indirect costs (eg, lost productivity for individuals) due to data unavailability, and thus the results of this study may not be extrapolated to a societal or individual patient's perspective. Second, the costs of lancets and blood glucose meters were not estimated because such materials are not reimbursed by Taiwan's NHI. However, we estimated the costs of needles and test strips, which accounted for most of the costs related to self-monitoring of blood glucose. Third, degludec, an ultra-long-acting insulin analogue, was not included in our analyses because it was unavailable in Taiwan in the study period. Fourth, some diabetes-related complications could greatly reduce a person's quality of life and thus should be considered in a cost-utility analysis. However, due to a lack of representative utility data for Taiwanese patients with T1D, a cost-utility analysis was not conducted. Fifth, including NNT in CEA studies may increase the understanding and relevance of CEA findings to clinical decision-makers, but we acknowledge its limitations.[56] For instance, our study used NNT to quantify the treatment effectiveness as a function of the difference in the probability of developing an outcome event between two treatment groups, which can only measure one type of benefit (eg, any diabetes-related complications in the present study) at one time. In future studies, a survival analysis that estimates the area under survival curves between two treatment groups could be used to measure the aggregated benefit (eg, quality-adjusted life years gained), which would provide a more comprehensive measure to account for treatment benefits. Sixth, this study was based on a PS-matched cohort that consisted of two comparable drug groups (ie, LAIA and ILAHI), while some unmatched subjects who were treated with LAIA or ILAHI may not be included in the analyses.[57,58] Our study results therefore may limit the generalizability to those matched patients treated with LAIA or ILAHI. Seventh, although we found a comparable prescription refill pattern of insulins between the two study groups, we did not account for patients' adherence behaviour for insulin therapy in this economic analysis study. This is because the claims-based data did not reveal the detailed information of insulin dosages that patients actually consumed. Moreover, our published comparative-effectiveness cohort study that was used to generate the effectiveness input parameters for this economic analysis study had implemented two procedures to minimize the potential impact from medication non-adherence.[29] First, our study only included the stable users for insulin therapy, defined as at least three consecutive refills from the same insulin group among the first five prescriptions after initiation of LAIA or ILAHI and any gaps between two consecutive refills less than 180 days. Second, our sensitivity analysis also examined the result of economic analysis that was based on the effectiveness parameters which were generated from the "as-treated" scenario, where study patients who discontinued insulin therapy were censored in the analyses. Finally, the results of this study may only reflect T1D patients under a single-payer system and universal healthcare insurance coverage.

We provided real-world evidence that the use of LAIAs *vs* ILAHI has a high likelihood of being cost-saving for patients with T1D to avoid hypoglycaemia and diabetes-related complications from the third-party payer and healthcare sector perspectives in Taiwan. LAIAs should be considered as an economically reasonable first-line choice for a basal insulin regimen for the treatment of patients with T1D. We expect that the results of this study will inform clinical professionals and health policymakers when prioritizing treatment strategies for patients with T1D given limited healthcare resources.

ACKNOWLEDGEMENTS

We gratefully thank National Cheng Kung University and its affiliated hospital for all support. The project was supported by Grant Number P30DK092926 (MCDTR and MCDTR Methods and Measurement Core) from the National Institute of Diabetes and Digestive and Kidney Diseases, which had no role in the design and conduct of the study, collection, management, analysis and interpretation of the data, preparation, review or approval of the manuscript, and decision to submit the manuscript for publication.

This project was funded by the Taiwan Ministry of Science and Technology (MOST 104-2320-B-006-008-MY3). The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

COMPETING INTERESTS

There are no competing interests to declare.

CONTRIBUTORS

S.K. and H.T.O. conceived the concept of this study. T.Y.L. was responsible for data collection and performed the statistical analysis. C.Y.Y. contributed to statistical analyses and provided statistical consultation. T.Y.L. drafted the manuscript. T.Y.L., S.K. and H.T.O. made substantial contributions to the interpretation of data and revised the manuscript. T.Y.L. and H.T.O. are the guarantors of this work and had full access to all the data in the study.

DATA AVAILABILITY STATEMENT

Research data are not shared.

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Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Lee T-Y, Kuo S, Yang C-Y, Ou H-T. Cost-effectiveness of long-acting insulin analogues *vs* intermediate/long-acting human insulin for type 1 diabetes: A population-based cohort followed over 10 years. *Br J Clin Pharmacol*. 2020;86:852–860. https://doi.org/10.1111/bcp.14188