


# Developing a health economic model for Asians with type 2 diabetes based on the Japan Diabetes Complications Study and the Japanese Elderly Diabetes Intervention Trial

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## ABSTRACT

**Introduction** Cost-effectiveness analyses are becoming increasingly important in Japan following the introduction of a health technology assessment scheme. The study objective was to develop an economic model to evaluate the cost-effectiveness of two interventions for type 2 diabetes in a Japanese population.

**Research design and methods** The Japan Diabetes Complications Study/Japanese Elderly Diabetes Intervention Trial risk engine (JJRE) Cost-Effectiveness Model (JJCEM) was developed, incorporating validated risk equations in Japanese patients with type 2 diabetes from the JJRE. Weibull regression models were developed for progression of the model outcomes, and a targeted literature review was performed to inform default values for utilities and costs. To illustrate outcomes, two simulated analyses were performed in younger (aged 40 years) and older (aged 80 years) Japanese populations, comparing a hypothetical treatment with placebo.

**Results** The model considers a population based on user-defined values for 11 baseline characteristic parameters and simulates rates of diabetic complications over a defined time horizon. Costs, quality-adjusted life years, and an incremental cost-effectiveness ratio are estimated. The model provides disaggregated results for two competing interventions, allowing visualization of the key drivers of cost and utility. A scatterplot of simulations and cost-effectiveness acceptability curve are generated for each analysis.

**Conclusions** This is the first cost-effectiveness model for East Asian patients with type 2 diabetes, developed using Japan-specific risk equations. This population constitutes the largest share of the global population with diabetes, making this model highly relevant. The model can be used to evaluate the cost-effectiveness of anti-diabetic interventions in patients with type 2 diabetes in Japan and other East Asian populations.

## INTRODUCTION

Diabetes is now a global epidemic, and Asia is no exception. The prevalence of diabetes in Asia is increasing,<sup>1</sup> which can in part be attributable to an increasing rate of overweight

## Significance of this study

### What is already known about this subject?

► Diabetes is a global epidemic, and the East Asian population with type 2 diabetes constitutes the largest share of the global population with diabetes. The economic burden of diabetes in East Asia is disproportionately high, with the direct costs for diabetes accounting for 4.36% of the annual total healthcare costs. Several global diabetes economic models have been developed, but they may not be generalizable to patients in Japan as they are based on overseas risk equations.

### What are the new findings?

► A new long-term cost-effectiveness model has been developed for type 2 diabetes in Japan using Japanese-specific risk equations. To our knowledge, this is the first model to incorporate the Japan Diabetes Complications Study/Japanese Elderly Diabetes Intervention Trial risk engine (JJRE) into a health economic model for the purposes of estimating the risks and costs of microvascular and macrovascular complications, associated quality of life outcomes, and cost of treatment in Japanese patients with type 2 diabetes.

► The model considers a patient or population with type 2 diabetes based on user-defined values for 11 baseline characteristics parameters that were included as risk factors in the JJRE. The risk of retinopathy, overt nephropathy, coronary heart disease, stroke, and non-cardiovascular mortality is estimated over a defined time horizon of up to 40 years. Initial treatment effects in four risk factors (glycated hemoglobin, systolic blood pressure, body mass index, and non-high-density lipoprotein cholesterol) can be applied to compare the cost-effectiveness of two interventions.

and obesity due to recent economic development, nutrition transition, and increasingly sedentary lifestyles, as well as a predisposal to insulin resistance in Asian patients.<sup>2</sup> The economic burden of diabetes in East Asia

## Significance of this study

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

- ▶ Given the recent introduction of a health technology assessment program in Japan and the increasing economic burden of diabetes in Japan, this model allows for the cost-effectiveness of new or existing interventions for type 2 diabetes to be assessed, specifically in Japanese patients.

is also disproportionately higher compared with North America, and is estimated as \$318.89 billion for a total population of 85.68 million for East Asia vs \$499.40 billion for a total population of 178.86 million for North America.<sup>3</sup>

The Japanese government has maintained a universal health insurance for more than 50 years at a relatively low cost,<sup>4</sup> but social security spending is rising, estimated at 40 trillion yen in 2017 (8.3% of gross domestic product (GDP)) vs 32 trillion yen in 2007 (6.4% of GDP), due to a rapidly aging population and the use of new high-cost technologies.<sup>5</sup> The direct costs for diabetes (\$20.04 billion per year in 2015, equivalent to 2.43 trillion yen)<sup>6</sup> account for 4.36% of the annual total healthcare costs.<sup>3</sup> As a result of this, there is now an increased focus on economic evaluations for healthcare interventions in Japan;<sup>5 7 8</sup> however, until recently, there has been no formal structure in place to assess the cost-effectiveness of healthcare technologies.<sup>7</sup> The Japanese government therefore launched a pilot health technology assessment (HTA) program in April 2016.<sup>5</sup> The pilot scheme has now concluded and full implementation of HTA in Japan became effective from April 2019. It is anticipated that technologies involved in the treatment of diabetes could be in scope for HTA in the future, due to the substantial health and economic burden of this disease in Japan and the continued development of new innovative therapies.

Diabetic complications and costs of their management may take years to emerge; therefore, it is important that any economic evaluation of antidiabetic interventions considers long-term outcomes and their associated risks within a population. Several diabetes economic models have been developed;<sup>9</sup> however, these models may not be generalizable to patients in Japan as they are based on risk equations from the UK Prospective Diabetes Study (UKPDS), which was developed using a predominantly Caucasian population.<sup>10</sup> There are important differences between Japanese and Caucasian patients with diabetes; notably, there is a lower prevalence of obesity, and a lower incidence of diabetic retinopathy, overt nephropathy, and cardiovascular (CV) disease in Japanese patients.<sup>11–15</sup> Accordingly, Tanaka *et al*<sup>16</sup> generated a set of risk equations for type 2 diabetes using data from the Japan Diabetes Complications Study (JDCS) and the Japanese Elderly Diabetes Intervention Trial (J-EDIT), referred to as the JDCS/J-EDIT risk engine (JJRE), which was designed to meet the criteria in the guidelines of the Ministry of Health, Labour and Welfare in Japan. These equations accurately

estimated the risk for first occurrence of microvascular and macrovascular events in a Japanese cohort with type 2 diabetes, and found that the UKPDS risk engine overestimated the incidence of coronary heart disease (CHD) and stroke for Japanese patients.<sup>16</sup>

Given the recent developments in HTA and the increasing economic burden of diabetes in Japan, there is a need for a cost-effectiveness model specific to Japanese patients with diabetes. Therefore, the primary objective of this study was to develop the first cost-effectiveness model for type 2 diabetes using the JJRE.

## MATERIALS AND METHODS

### Study design

The JDCS/J-EDIT Cost-Effectiveness Model (JJCEM) is a health economic cohort Markov model, with an annual cycle, for analyzing the cost-effectiveness of competing interventions for the treatment of type 2 diabetes in Asia. The non-product-specific, transparent model can accurately estimate the risk of microvascular and macrovascular complications, cost of complications and treatments, quality-adjusted life years (QALYs), and the incremental cost-effectiveness ratio (ICER) between two competing interventions.

The primary sources informing the estimation of microvascular and macrovascular complications in the model are the Japanese risk equations developed by Tanaka *et al*.<sup>16</sup> In this study, pooled data from 1748 Japanese patients with type 2 diabetes were analyzed over a median follow-up of 7.2 years.

The process of model development consisted of two parts. The aim of the JJCEM was to calculate risks of microvascular and macrovascular complications using equations from the JJRE<sup>16</sup> with options for extrapolation beyond the end of follow-up in the JJRE and for selecting risk equations from epidemiological studies other than the JDCS and the J-EDIT. Therefore, first, to enable extrapolation, Weibull regression models were developed for CHD, stroke, non-CV mortality, overt nephropathy, and diabetes retinopathy using data from the JDCS and the J-EDIT (online supplemental figures S1–S5; and online supplemental table S1). The survival function at time  $t$  of the Weibull regression models is  $S(t) = \exp\{-\lambda \exp(X\beta) t^\rho\}$ , where  $\lambda$  represents the Weibull scale parameter,  $\rho$  the Weibull shape parameter and  $\beta$  the regression coefficients for the vector of risk factors  $X$ . Second, we conducted a targeted literature review to inform the default parameter values for utilities and costs of complications. Data sources included in the literature review were PubMed, EMBASE and Ichushi Web (Japanese language searches). Furthermore, gray literature searches were conducted using the Japanese Diabetes Society website, International Society for Pharmacoeconomics and Outcomes Research conference research database, Diabetes Network, and the Japan Diabetes Clinical Data Management Study Group patient registry website, to identify other potentially relevant

articles not indexed by the databases listed above. Initial population, intervention, comparator, outcome, study type criteria were defined and applied to identify available recently published model input values specifically for Japanese patients with type 2 diabetes. However, given the scarcity of the available research and literature within this emerging field, not all model values could be identified (eg, disutility related to non-severe hypoglycemic events). In this case, identified overseas values were applied as the default model input, in line with recently published guidance for economic evaluation in Japan.<sup>17</sup>

### Application of the model

To demonstrate the output of the JJCEM, a simulated cost-effectiveness analysis was performed for a hypothetical active treatment vs placebo in two different Japanese populations. The first (the younger population analysis) was a population of Japanese men aged 40 years with the following clinical characteristics: 8 years since diagnosis; glycated hemoglobin (HbA<sub>1c</sub>) 9.3% (78 mmol/mol); body mass index (BMI) 23 kg/m<sup>2</sup>; systolic blood pressure (SBP) 119 mm Hg; non-high-density lipoprotein cholesterol (non-HDL-c) 3.8 mmol/L; albumin-to-creatinine ratio (ACR) 0.8 mg/mmol.

Second (the older population analysis) was a population of Japanese men aged 80 years with the following clinical characteristics: 13 years since diagnosis; HbA<sub>1c</sub> 8.4% (68 mmol/mol); BMI 23 kg/m<sup>2</sup>; SBP 139 mm Hg; non-HDL-c 3.6 mmol/L; ACR 4.6 mg/mmol.

In both analyses, the populations were assumed to be a non-smoker, inactive (no exercise) and have no history of atrial fibrillation. Rates of hypoglycemia were assumed to be zero for both treatment arms for both analyses. Treatment effects for the hypothetical active treatment in both

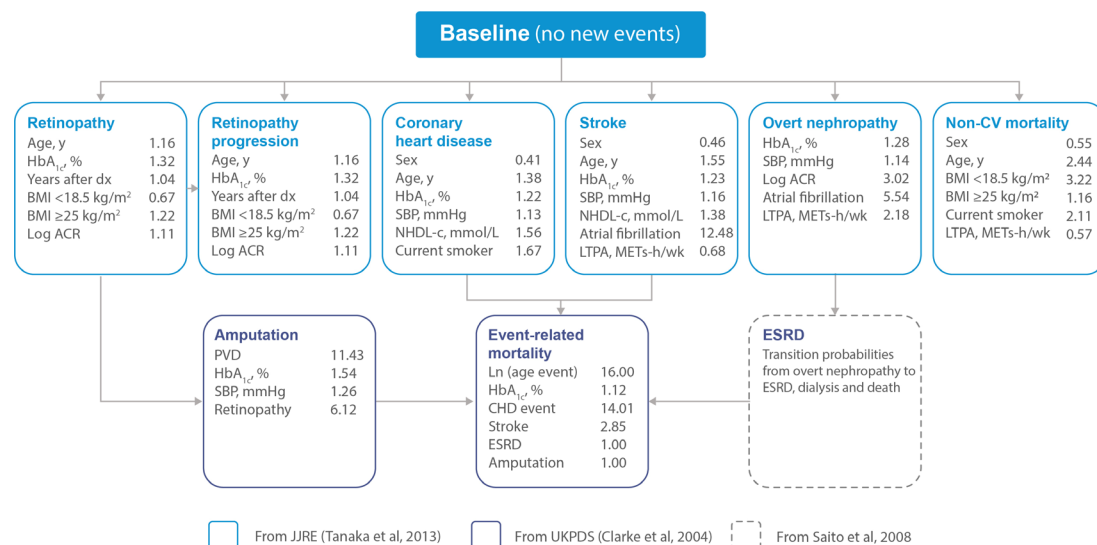
analyses were: HbA<sub>1c</sub> -1.50% (-17 mmol/mol); BMI -1.00 kg/m<sup>2</sup>; SBP -4.00 mm Hg; non-HDL-c -0.50 mmol/L; and the drug cost was set at 500 yen per day. Both analyses assumed that the treatment effects of all four risk factors (HbA<sub>1c</sub>, BMI, SBP and non-HDL-c) were applied during year 1, after which they were stable throughout the time horizon of the analysis for both treatment arms. Treatment effects and costs for the placebo arm were assumed to be zero.

A lifetime time horizon was chosen for both analyses to ensure that all patients had died (40 years for the younger population and 15 years for the older population). A discount rate of 2% for costs and utilities per annum was applied to both scenarios. Treatment was assumed to be constant for the simulation period.

## RESULTS

### Model structure

The structure of the model is shown in figure 1. The model considers a patient or population with type 2 diabetes based on user-defined values for 11 baseline characteristic parameters (age, percentage women, percentage smokers, duration of diabetes, HbA<sub>1c</sub>, SBP, non-HDL-c, BMI, percentage with atrial fibrillation, percentage with leisure-time physical activity of ≥3.8 metabolic equivalent hours per week, and log ACR), which were included as risk factors in the JJRE. Using the JJRE, the risk of retinopathy, overt nephropathy, CHD, stroke and non-CV mortality is then estimated over a defined time horizon (a time horizon of up to 40 years can be modeled). As previously described<sup>16</sup> and shown in figure 1, the risk of each complication is determined by a set of risk factors that are known to increase or decrease the risk of the



**Figure 1** Model schematic. The model schematic shows the baseline HRs (equal to the exp (coefficient)) for each risk factor per event. ACR, albumin-to-creatinine ratio; BMI, body mass index; CHD, coronary heart disease; CV, cardiovascular; dx, diagnosis; ESRD, end-stage renal disease; HbA<sub>1c</sub>, glycated hemoglobin; HR, hazard ratio; JDCS, Japan Diabetes Complications Study; J-EDIT, Japanese Elderly Diabetes Intervention Trial; JJRE, JDCS/J-EDIT risk engine; LTPA, leisure-time physical activity; METS, metabolic equivalents; NHDL-c, non-high-density lipoprotein cholesterol; PVD, peripheral vascular disease; SBP, systolic blood pressure; UKPDS, UK Prospective Diabetes Study.

associated event. The model also includes an option to estimate the risk of end-stage renal disease (ESRD)/dialysis and amputation; while these complications were not part of the JJRE, they represent a significant burden on the quality of life of patients and are costly to society. The default probabilities of progressing from overt nephropathy to ESRD, ESRD to dialysis, and dialysis to death are based on transition probabilities reported by Saito *et al*<sup>18</sup> for patients with type 2 diabetes in Japan. The risk factors and associated HRs for amputation are derived from the UKPDS Outcomes Model 1 (UKPDS OM1);<sup>19</sup> however, in order to reflect the lower rate of amputation in Japanese patients compared with Caucasian patients, an adjustment factor of 0.25 (based on the comparative values by Unwin<sup>20</sup>) is applied as part of the default setting. This adjustment factor is fully editable and can be changed by the user. A limitation of the JJRE is the absence of CV event-related mortality; only a small number of fatal CV events were observed in the JJRE population during the follow-up period, which may not be reflective of actual CV mortality rates in patients with type 2 diabetes in Japan. To address this, the model includes an option to estimate the risk of death within a year of first experiencing a CHD or stroke event; the risk factors and associated HRs for event-related mortality are derived from the UKPDS OM1. The UKPDS OM1 also links amputation and event-related mortality, as shown in figure 1, with an HR of 1.00. The perspective of the model is that of the healthcare system in Japan.

### Effects of intervention on risk factors

As the focus of the model is to compare the cost-effectiveness of two interventions, initial treatment effects (defined by the user) on four risk factors (HbA<sub>1c</sub>, SBP, BMI, and non-HDL-c) can be applied. The model then allows two options for simulating the progression of each of the four risk factors independently over time. The first option assumes that the treatment effects occur during year 1, after which they remain stable until the treatment is stopped (the timing of which is defined by the user), when treatment intensification is assumed to occur. The second option progresses the risk factors while on treatment, based on UKPDS OM1 risk factor progression equations.<sup>19</sup> With this option, treatment intensification occurs once the level of HbA<sub>1c</sub> reaches the user-defined threshold, and the risk factors are assumed to remain stable thereafter.

### Utilities and costs

The model applies published utility values at baseline (ie, no complications) and after the occurrence of an event (table 1), which were identified from the targeted literature review.<sup>19 21–25</sup> Utility values are provided for baseline health status and disutilities are subtracted from the baseline utility value to account for (a) the year that an event occurred, (b) each subsequent year after an event that the patient is alive, (c) hypoglycemic events (in the year of the event), and (d) if the BMI of a patient exceeds 25

kg/m<sup>2</sup>. Where no Japanese utility values were available, overseas values have been applied as default, in line with the recommended approach in the Japanese guideline on economic evaluation.<sup>22</sup>

Costs of events are also taken from published sources, and are provided for baseline health status (ie, the provision of routine care for a person with diabetes) and per event (table 1). Costs of treatment per day for both treatment arms are inputted by the user.

Incidence of complications follows the cohort Markov model with an annual cycle, as shown in figure 1. If a complication occurs, it can influence subsequent events (eg, a stroke increases the rate of mortality in future). Patients can have multiple complications, and the costs and utilities are calculated using parameters in table 1, assuming the effects of complications are additive. Both costs and utility values may remain constant in the years following the event (eg, for a chronic state such as dialysis) or change after the first year (eg, amputation, where the initial cost is likely to be greater than those for subsequent years). These different costs are provided in table 1; utilities are assumed to be equal in the year of the event and subsequent years by default, but values can be amended by the user.

All utility and cost inputs in the JJCEM are fully editable by the user.

### Sensitivity analysis

Probabilistic sensitivity analysis (PSA) is used to assess the uncertainty in the ICER due to parameter uncertainty. The model can be run through multiple simulations, the number of which is defined by the user; for each simulation, input parameters are varied simultaneously by randomly selecting input values from within their user-defined probability distribution. It is possible to vary all baseline characteristics, treatment effects for drug A and drug B, costs, and utilities. Each simulation generates a probabilistic ICER, which can be plotted on the cost-effectiveness plane to visualize the distribution of probabilistic ICERs. The cost-effectiveness acceptability curve illustrates the probability that each treatment is cost-effective at any given willingness-to-pay threshold, based on the probabilistic ICERs generated in the PSA simulations.

### Application of the model

The JJCEM provides the disaggregated results for two competing interventions, which allows for visualization of the key drivers of cost and utility, and the model is designed to facilitate rapid implementation of scenario analyses as the impact of any change to the inputs is immediately shown in the results. The deterministic results from the analysis per average person modeled are shown in table 2. In our example simulations, the model estimates that the treatment reduces the risk of all complications compared with placebo.

For this model application example purpose PSA was performed with 10000 simulations. The scatterplot of



**Table 1** Default utility values and costs\*

Parameter	Year of the event	Years 2+	Reference
<b>Default utility values</b>			
Baseline and if no events occur	0.862	0.862	Sakamaki <i>et al</i> <sup>21</sup>
Coronary heart disease	-0.064	-0.064	Shiroiwa <i>et al</i> <sup>22</sup>
Stroke	-0.129	-0.129	Takahara <i>et al</i> <sup>26</sup>
Amputation	-0.216	-0.216	Takahara <i>et al</i> <sup>26</sup>
Retinopathy	-0.054	-0.054	Shiroiwa <i>et al</i> <sup>22</sup>
Overt nephropathy	-0.026	-0.026	Takahara <i>et al</i> <sup>26</sup>
End-stage renal disease	-0.065	-0.065	Takahara <i>et al</i> <sup>26</sup>
Hemodialysis	-0.065	-0.065	Takahara <i>et al</i> <sup>26</sup>
Hypoglycemia—non-severe	-0.005	–	Evans <i>et al</i> <sup>24</sup>
Hypoglycemia—severe	-0.039	–	Takahara <i>et al</i> <sup>26</sup>
BMI (each unit over 25 kg/m <sup>2</sup> )	-0.0061	-0.0061	Bagust and Beale <sup>25</sup>
<b>Default costs (inflated to 2019 values†)</b>			
Baseline and if no events occur	¥76 363	¥76 363	Saito <i>et al</i> <sup>18</sup>
Coronary heart disease	¥2 232 727	¥254 618	Onishi <i>et al</i> <sup>27</sup>
Stroke	¥3 516 727	¥109 391	Fukuda <i>et al</i> <sup>28</sup>
Amputation	¥941 617	¥76 363	Davis <i>et al</i> <sup>29</sup> /Saito <i>et al</i> <sup>18</sup>
Retinopathy	¥379 887	¥76 363	Yanagi <i>et al</i> <sup>30</sup> /Saito <i>et al</i> <sup>18</sup>
Overt nephropathy	¥85 214	¥85 214	Saito <i>et al</i> <sup>18</sup>
End-stage renal disease	¥104 289	¥104 289	Saito <i>et al</i> <sup>18</sup>
Hemodialysis	¥5 954 466	¥5 954 466	Saito <i>et al</i> <sup>18</sup>
Severe hypoglycemic event	¥19 661	–	Mano <sup>31</sup>

\*All utility and cost inputs in the JJCEM are fully editable by the user.

†Costs were inflated using the Japanese medical care consumer price index from 2019 and the corresponding year of the data source. BMI, body mass index; JJCEM, Japan Diabetes Complications Study/Japanese Elderly Diabetes Intervention Trial risk engine Cost-Effectiveness Model.

simulations and cost-effectiveness acceptability curve for each scenario are shown for the younger and older population analyses in [figure 2](#). For this example, the treatment was more cost-effective vs placebo when considering an older patient population compared with a younger population, as shown by the cost-effectiveness acceptability curves, which reach 100% at a lower willingness-to-pay threshold in the older population compared with the younger population. The QALY gains were higher in the younger population, as shown in the cost-effectiveness planes, but the costs were also higher due to a longer treatment duration. The points on the scatterplot for the older population are more condensed than for the younger population, resulting in a steeper cost-effectiveness acceptability curve. However, in both populations, the treatment has a greater than 95% probability of being cost-effective at a threshold of 3 000 000 yen per QALY gained.

## DISCUSSION

Due to differences between Caucasian and Japanese patients with diabetes,<sup>11–13</sup> long-term cost-effectiveness models developed using predominantly Caucasian populations (such as the UKPDS OM) may not be generalizable to patients in Japan. Therefore, and in anticipation

of the further development of the HTA system in Japan, a long-term cost-effectiveness model for type 2 diabetes has been developed (the JJCEM), using the risk equations from the JJRE. To our knowledge, this is the first model to incorporate the JJRE into a health economic model for the purposes of estimating the risks and costs of microvascular and macrovascular complications, associated quality of life outcomes, and cost of treatment in Japanese patients with type 2 diabetes. As demonstrated in our example simulations, the model is able to estimate the cumulative number of complication events and overall survival associated with two competing interventions within a defined time horizon. The model also uses the estimated costs and QALYs associated with each intervention to calculate an ICER and generate a cost-effectiveness acceptability curve for use in decision-making.

Due to differences in the outcomes included in the risk engines, it is not possible or relevant to directly compare the output of the JJCEM with other global diabetes models like the UKPDS OM. However, we believe that the incorporation of a risk engine that was informed and validated in a large Japanese cohort makes this model highly suitable for economic assessments and decision-making in Japan. As previously described by Tanaka *et al*,<sup>16</sup> the JJRE

**Table 2** Deterministic results from the application of the model per average person modeled

Parameter	Treatment	Placebo	Incremental
<b>Younger population results</b>			
<b>Outcomes</b>			
Overall survival, years	25.86	23.30	2.56
Percent alive at time horizon	0.0	0.0	0.0
Discounted QALYs	16.11	14.56	1.55
Cumulative events within time horizon			
Coronary heart disease	47.1%	61.1%	-14.0%
Stroke	56.0%	68.4%	-12.5%
Retinopathy	55.0%	59.2%	-4.2%
Overt nephropathy	9.6%	12.8%	-3.2%
ESRD	8.0%	11.3%	-3.4%
Hemodialysis	6.1%	9.0%	-2.8%
Amputation	3.2%	6.8%	-3.5%
<b>Discounted costs, ¥</b>			
Diabetes drug costs			
Treatment	3 571 265	0	3 571 265
Diabetes management (no complications)	1 494 315	1 374 302	120 013
Complications			
Coronary heart disease	883 112	1 213 304	-330 191
Stroke	1 059 957	1 397 376	-337 419
Retinopathy	411 363	445 265	-33 902
Overt nephropathy	19 254	25 221	-5 966
ESRD	15 360	19 483	-4 123
Hemodialysis	651 037	786 699	-135 661
Amputation	18 194	39 060	-20 866
<b>Total costs, ¥</b>	<b>8 123 857</b>	<b>5 300 708</b>	<b>2 823 149</b>
<b>ICER</b>	<b>¥1 825 163 per QALY</b>		
<b>Older population results</b>			
<b>Outcomes</b>			
Overall survival, years	7.49	6.75	0.74
Percent alive at time horizon	0.0	0.0	0.0
Discounted QALYs	5.50	4.88	0.62
Cumulative events within time horizon			
Coronary heart disease	28.0%	40.3%	-12.2%
Stroke	53.1%	68.0%	-14.8%
Retinopathy	19.1%	21.8%	-2.7%
Overt nephropathy	89.8%	95.6%	-5.8%
ESRD	64.7%	73.7%	-9.0%
Hemodialysis	34.9%	42.2%	-7.3%
Amputation	0.9%	2.0%	-1.2%
<b>Discounted costs, ¥</b>			
Diabetes drug costs			
Treatment	1 240 987	0	1 240 987
Diabetes management (no complications)	519 263	471 673	47 590
Complications			
Coronary heart disease	355 302	511 481	-156 179

Continued

**Table 2** Continued

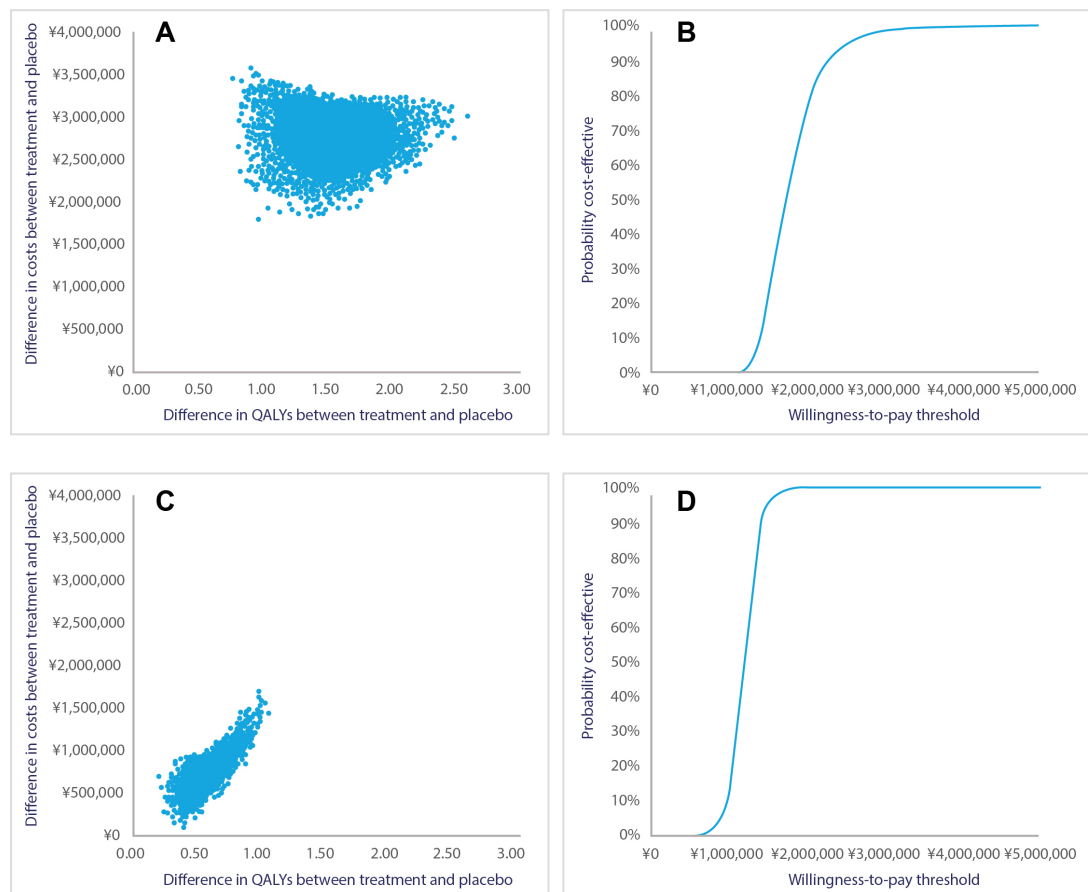
Parameter	Treatment	Placebo	Incremental
Stroke	981 055	1 321 155	-340 100
Retinopathy	85 798	96 838	-11 040
Overt nephropathy	169 670	189 681	-20 012
ESRD	72 510	77 280	-4 771
Hemodialysis	1 214 615	1 194 563	20 053
Amputation	3 771	8 473	-4 703
<b>Total costs, ¥</b>	<b>4 642 971</b>	<b>3 871 145</b>	<b>771 826</b>
<b>ICER</b>	<b>¥1 247 591 per QALY</b>		

ESRD, end-stage renal disease; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

overcomes the limitations associated with extrapolating risk equations developed in a Caucasian population to a Japanese population, and accurately estimates the risk of long-term diabetic complications. Accordingly, the costs and utilities estimated in the JJCEM should more accurately reflect the costs and utilities associated with these complications in the real world.

The model is highly flexible, allowing for the estimation of cost-effectiveness across a range of baseline characteristics under a number of assumptions, and switches for elements

of the model that retrieve data from sources other than the JJRE can all be independently turned on or off. Notably, the JJCEM expands on the JJRE through the inclusion of outcomes that were not incorporated in the JJRE due to a lack of data within the cohort. These include amputation, transition to ESRD/hemodialysis, and CV event-related mortality, which were derived from the UKPDS OM1 or Japanese data,<sup>18 19</sup> and are outcomes which are likely to affect the long-term quality of life and life expectancy of patients in Japan.



**Figure 2** Cost-effectiveness acceptability curves and scatterplots of simulations. (A) Scatterplot of simulations for the younger population analysis. (B) Cost-effectiveness acceptability curve for the younger population analysis. (C) Scatterplot of simulations for the older population analysis. (D) Cost-effectiveness acceptability curve for the older population analysis. QALYs, quality-adjusted life years.

The outputs from the JJCEM must be interpreted in the context of study limitations. First, there is a lack of availability of long-term data (in particular mortality, utility and cost data) in Asia,<sup>10</sup> leading to greater uncertainty in estimates using a time horizon longer than 20 years. Indeed, the initial guidance for economic evaluations in Japan acknowledges the paucity of domestic quality of life surveys.<sup>22</sup> Therefore, the validity of the JJCEM could be improved by the collection and incorporation of more long-term data as these become available. Second, although the JJRE was developed based on data from 59 hospitals nationwide, and cross-validated using standard criteria for prediction models,<sup>16</sup> the external validity of the JJCEM to other populations is unknown. Further validation studies are still important. Third, overt nephropathy was included as an outcome in the JJRE, but the JJCEM attempted to link overt nephropathy to ESRD, dialysis and death using transition probabilities published by Saito *et al.*<sup>18</sup> This was an assumption above the results from the JJRE and therefore may be uncertain; however, in the model settings these transition probabilities can be switched off, and ESRD, dialysis and death from ESRD can be excluded from the results or alternative transition probabilities can be inputted by the user. Finally, although individual complications can influence subsequent events, the model does not consider interactions of multiple complications in the same person due to lack of evidence for interaction parameters. That is, the effects of complications on the utility and total cost are assumed to be additive.

## CONCLUSION

To our knowledge, the JJCEM is the first cost-effectiveness model for East Asian patients with type 2 diabetes to be developed using Japan-specific risk equations. The East Asian population with type 2 diabetes constitutes the largest share of the global population with diabetes,<sup>1</sup> thereby making this model highly relevant. The model provides a means for evaluating the cost-effectiveness of anti-diabetic interventions in patients with type 2 diabetes in Japan and other East Asian populations. Future work should focus on the collection of more Japanese-specific data to inform the model and the external validation of the model to the wider Asian population.

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