Japan-specific risk equations for modeling diabetes in the Japanese setting: does it make a difference? EE286

Willis M[1], Nilsson K[1], Fridhammar A[1], Ota R[2], Tyagi A[3], Jensen M[3], Terauchi Y[4]

Aim

To inform Japanese decision-makers on the tradeoffs between local applicability and robustness of risk equations by comparing key cost-effectiveness outcomes when using JJRE and UKPDS-OM2 equations for type 2 diabetes (T2D).

Introduction

- T2D is characterized by chronic, progressive, debilitating, and life-threatening complications in multiple, inter-dependent organ systems[1].
- Given the long time horizons involved, economic modeling has been widely used to evaluate the cost-effectiveness of competing treatment alternatives.
- The IHE Diabetes Cohort Model of T2D (IHE-DCM-T2), one of these models, has been used to estimate the cost-effectiveness of interventions for T2D and to support HTA submissions in different parts of the world[2,3].
- Like other health-economic models, IHE-DCM-T2 relies on risk equations estimated using data from long-term trials to simulate outcomes over long time periods.
- For T2D, the most widely accepted risk equations since 2004 have been those derived from The United Kingdom Prospective Diabetes Study (UKPDS)[4,5], estimated using two decades of data encompassing 5,000+ patients and covering a broad set of the most important outcomes. Both the first and the second (improved) UKPDS Outcomes Models are supported in IHE-DCM-T2 (UKPDS-OM1 and UKPDS-OM2).
- Because event risks are local and may vary widely across countries and especially world regions, UKPDS risk equations may not accurately capture risks everywhere. For example, there are differences in etiology and epidemiology of T2D in the Asian population compared to the Caucasian population[6].
- In preparation for economic evaluations for the Japanese setting, we considered the possibility that UKPDS risk equations, in particular the improved UKPDS-OM2, and other Western risk equations would be inaccurate for patients in Japan.
- The Japan Diabetes Complications Study/Japanese Elderly Diabetes Intervention Trial risk engine (JJRE) risk equations from the JJRE Cost-Effectiveness Model (JJCEM)[7,8] were, thus, added to IHE-DCM-T2 model because JJRE was designed to meet the criteria in Japanese HTA guidelines and relies exclusively on Japanese data[7].
- While JJRE includes myocardial infarction (MI), angina, stroke, retinopathy, macroalbuminuria and non-cardiovascular mortality[7,8], it lacks important T2D-related complications such as heart failure (HF), end-stage renal disease (ESRD), severe visual loss (SVL), lower extremity amputation (LEA), and cardiovascular mortality and was estimated with fewer patient-years of data (1,748 patients with median follow-up of 7.2 years[8])
- It is unclear how much the use of JJRE equations will affect cost-effectiveness estimates and what the tradeoffs are in terms of internal versus external validity.

Methods

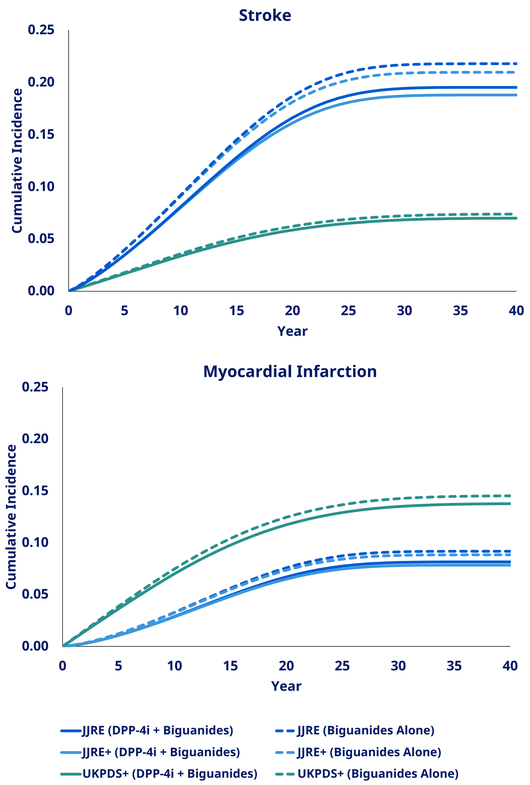
- We used IHE-DCM-T2 to simulate the health, economic, and cost-effectiveness implications of adding DPP-4 inhibitors to biguanide therapy vs. biguanides alone to treat Japanese T2D patients over 40 years, both in general and for subgroups based on sex and age.
- We performed this simulation using three different sets of risk equations:
  (1) the UKPDS-OM2 (augmented with risks for renal, neuropathic, retinopathic, and amputation risks from the NIH model[9] and hereafter called UKPDS+);
  (2) the JJRE risk equations (augmented with UKPDS-OM2 event mortality, similar to the implementation in JJCEM[7]),
  (3) the JJRE+ risk equations (augmented with risks for event mortality and HF from UKPDS-OM2, and ESRSD, neuropathy, amputation, blindness, and macular edema from the NIH model[9]).
- Other parameters were sourced as follows:
  - HbA1c lowering was sourced from a Japanese RCT[10].
  - Unit costs (¥151.38=1$ [11]) and QALY utility weights were sourced from published Japanese literature[7,12,13].
  - Baseline patient characteristics for the overall cohort and for the subgroups were sourced from a retrospective analysis of the J-DREAMS database[14].
  - The annual price of DPP-4 inhibitors was assumed to be ¥50,000 ($330).
- A public payer perspective was adopted. Cost and health outcomes were discounted 2% annually in line with guidelines for cost-effectiveness evaluation in Japan[15].

Results

Overall population

- Expected life-years were highest for both arms when using JJRE (13.62 and 13.51), followed by JJRE+ (13.28 and 13.17) and then UKPDS+ (13.19 and 13.07). However, estimated incremental life-years gained were nearly identical (See Table 1)
- Expected QALYs were highest with JJRE (10.97 and 10.84), followed by UKPDS+ (10.53 and 10.41) and JJRE+ (10.42 and 10.28). Incremental QALYs gained were similar (see Table 1).
- There were important differences in cumulative incidence of macrovascular events.
  - JJRE and JJRE+ produced cumulative stroke incidence estimates that were almost 3 times as large as those generated by UKPDS+, and with greater between-arm differences (see Figure 1).
  - Estimated cumulative MI incidence rates were, in contrast, almost twice as large when using UKPDS+ versus JJRE and JJRE+.
  - Consistent with results from recent Japanese registry-based studies[16,17], JJRE and JJRE+ generated estimates of stroke incidence that were greater than MI incidence.
  - The opposite relationship between stroke and MI was found for UKPDS+, which is consistent with previous findings that compared the relative incidence of stroke and MI between Japan and western countries[18].

Figure 1: Cumulative incidence of T2D-related complications



- There were also key differences in cumulative incidence of microvascular events.
  - The effect of HbA1c lowering on macroalbuminuria was smaller when using JJRE or JJRE+ compared with UKPDS+. With JJRE+, this affected ESRD as well since macroalbuminuria is a preceding stage of kidney disease in the model.
  - The incidence and progression of retinopathy, as well as the effect of HbA1c lowering on retinopathy, was greater when using JJRE or JJRE+ compared with UKPDS+.
- These differences in expected health outcomes translate into differences in total costs: $30,363 and $26,751 for JJRE, $42,551 and $39,249 for JJRE+, and $34,740 and $32,077 for UKPDS+ (see Table 1).
- The share of microvascular costs varied most, from about 30% for JJRE to about 50% for JJRE+ and UKPDS+.
- They also led to differences in incremental total costs: $3,612 for JJRE, $3,302 for JJRE+, and $2,662 for UKPDS+ (see Table 1).
- Macrovascular cost offsets were largest with JJRE and JJRE+ and smallest with UKPDS+. Microvascular cost offsets were non-existent with JJRE, small with JJRE+, and largest with UKPDS+.
- The ICERs were $28,706, $23,583 and $22,058 for JJRE, JJRE+ and UKPDS+, respectively.

Table 1: Cost-effectiveness of DPP-4i + Biguanides vs. Biguanides alone

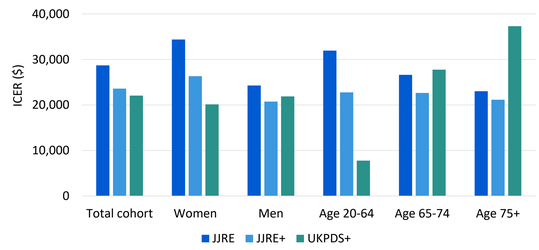
Risk Eq.	Outcome	DPP-4i + Biguanides	Biguanides Alone	Increment
JJRE	Life years	13.62	13.507	0.113
	QALYs	10.97	10.844	0.126
	Treatment Cost ($)	11,369	6,814	4,555
	Microvascular Cost ($)	8,808	8,801	7
	Macrovascular Cost ($)	10,186	11,136	-951
	Total Cost ($)	30,363	26,751	3,612
	ICER ($)	-	-	**28,706**
JJRE+	Life years	13.283	13.169	0.114
	QALYs	10.415	10.275	0.14
	Treatment Cost ($)	11,088	6,643	4,445
	Microvascular Cost ($)	21,152	21,387	-236
	Macrovascular Cost ($)	10,312	11,219	-907
	Total Cost ($)	42,551	39,249	3,302
	ICER ($)	-	-	**23,583**
UKPDS+	Life years	13.186	13.068	0.119
	QALYs	10.528	10.408	0.121
	Treatment Cost ($)	11,007	6,592	4,415
	Microvascular Cost ($)	13,911	15,516	-1,605
	Macrovascular Cost ($)	9,822	9,969	-148
	Total Cost ($)	34,740	32,077	2,662
	ICER ($)	-	-	**22,058**

Risk Eq.: applied set of risk equations; QALY: quality-adjusted life year; ICER: incremental cost-effectiveness ratio

Subgroups

- Men vs. Women:
  - Expected QALYs followed the same pattern as for the overall population across the risk equations. However, men had fewer expected QALYs than women, and this difference was larger when using JJRE and JJRE+ compared with UKPDS+.
  - Total costs followed a similar pattern as for the overall population across the risk equations. However, women had larger incremental cost than men when using JJRE and JJRE+, while there was little difference when using UKPDS+.
  - JJRE and JJRE+ produced higher ICERs for women compared to men, while the opposite was the case for UKPDS+ (see Figure 2).
  - The ICER for women was more sensitive to the choice of risk equation ($20,121-$34,376) than for men ($20,749-$24,282) . See Figure 2.
- 20-64 years vs. 65-74 years vs. ≥75 years
  - Expected QALYs and QALYs gained followed the same pattern as for the overall population across the risk equations but were decreasing with age. The differences between age groups were smaller when using JJRE or JJRE+ compared with UKPDS+.
  - Costs and incremental costs were decreasing with age except when using UKPDS+ where incremental costs were largest in the 65-74 year subgroup. The differences in incremental costs were larger with JJRE or JJRE+ compared with UKPDS+.
  - In the 20-64 age subgroup JJRE and JJRE+ produced a substantially higher ICER than UKPDS+, while in the 75+ age group the relationship was reversed (see Figure 2).
  - UKPDS+ was more sensitive to changes in age ($7,774-$37,308), than JJRE ($23,014-$31,940) and JJRE+ ($21,145-$22,769). See Figure 2.

Figure 2: Variability in ICERs across subgroups



Discussion

- The choice of risk equation affected both absolute costs and incremental costs, leading to different ICERs. Despite meaningful differences in absolute life-years and QALYs, incremental gains in life-years and QALYs were less changed by choice of risk equation, except in the age subgroups.
- Even though Japanese HTA bodies may prefer the JJRE risk equations, they will have to consider complementing them with non-Japanese risk equations for important T2D-related complications omitted in the JJRE. The effect of this is illustrated in the current study by the difference between JJRE and the more comprehensive JJRE+.
- Strengths: The model used, IHE-DCM-T2, is comprehensive, validated, and thus suitable for this type of analysis. The comparison included two different implementations of JJRE, with and without adding complications from other risk equations. Patient characteristics were sourced from a large contemporary cohort of Japanese T2D patients, which even included subgroups based on sex and age.
- Limitations: Only HbA1c treatment effects were considered, and no drifts in biomarkers were applied. Future work to investigate the importance of other biomarkers could modify the risk equation differences. The results are, of course, limited to the comparison considered and are not general to all potential applications.

Conclusion

The results indicate that the choice between JJRE and UKPDS-OM2, as well as adding risk equations for omitted T2D-related complications in JJRE, can substantially influence the cost-effectiveness in a Japanese clinical setting.

Affiliations: [1]The Swedish Institute for Health Economics, Lund, Sweden, [2]Novo Nordisk Pharma Ltd., [3]Novo Nordisk A/S, [4]Yokohama City University
This study was sponsored by Novo Nordisk. The authors acknowledge the medical writing assistance of Karin Wahlberg at the Swedish Institute for Health Economics, Lund, Sweden.

Presented at ISPOR 2024, 5-8 May, Atlanta, GA, USA.

References:
1. ADA Consensus Panel. Diabetes Care. 2004;27(9):2262-5.
2. Lundqvist A et al. PLoS One. 2014;9(10):e110235.
3. Willis M et al. Pharmacoeconomics. 2020;38(9):953-69.
4. Clarke PM et al. Diabetologia. 2004;47:1747–1759.
5. Hayes AJ et al. Diabetologia. 2013;56(9):1925-33.
6. Gujral, U.P.et al. Ann. N.Y. Acad. Sci. 2013;1281:51-63
7. Tanaka S et al. BMJ Open Diab Res Care. 2021;9(1):e002177.
8. Tanaka S et al. Diabetes Care. 2013;36(5):1193-9.
9. Eastman, R.C., et al. Diabetes Care, 1997;20(5):725-34.
10. Nishio S et al. Diabetes Metab Syndr Obes. 2015;8:163-71.
11. IMF Representative Exchange Rates (April 2024)
12. Ishii H et al. J Med Econ. 2018; (5):488-496.
13. Takahara M et al. Acta Diabetol. 2019;56(3):309-19.
14. Ohsugi M et al. Diabetes Res Clin Pract. 2021;178:108845.
15. Available from: https://c2h.niph.go.jp/en/tools/index.html
16. Iwase, M., et al. Diabetes Res Clin Pract, 2023;201:110732.
17. Iwase, M., et al. Diabetes Res Clin Pract, 2021;172:108518.
18. Ishikawa, S., et al. J Epidemiol, 2008;18(4):144-50.