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Original article

The cost effectiveness of rapid-acting insulin aspart compared with human insulin in type 2 diabetes patients: an analysis from the Japanese third-party payer perspective

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Abstract

Objectives:
The Nippon Ultra-Rapid Insulin and Diabetic Complication Evaluation Study (NICE Study) (NCT00575172) was a 5-year, open-label, randomised controlled trial which compared cardiovascular outcomes in Japanese type 2 diabetes patients intensively treated with regular human insulin or insulin aspart (NovoRapid; Novo Nordisk A/S, Bagsværd, Denmark), a rapid-acting insulin analogue. The aim of the present analysis was to evaluate the cost effectiveness of insulin aspart versus regular human insulin from the perspective of a Japanese third-party healthcare payer.

Research design and methods:
A discrete event-simulation model was developed in Microsoft Excel to assess the within-trial cost effectiveness and make longer-term clinical projections in patients treated with regular human insulin or insulin aspart. In addition to severe hypoglycaemia, the model captured myocardial and cerebral infarction events and percutaneous coronary intervention and coronary artery bypass graft procedures. Within-trial mortality, incidence of severe hypoglycaemia and cardiovascular event probabilities were derived from the annual rates observed during the trial period, while post-trial outcomes were calculated using the event rates from the trial, adjusted for increasing patient age. Event costs were accounted from the healthcare payer perspective and expressed in 2008 Japanese yen (JPY), while health-related quality of life (HRQoL) was captured using event and state utilities. Future costs and clinical benefits were discounted at 3% annually. Life expectancy, quality-adjusted life expectancy, cardiovascular event rates and costs were evaluated over 5- and 10-year time horizons and sensitivity analyses were performed to assess variability in model outcomes.

Results:
Over 5 years of treatment, insulin aspart dominated human insulin both in incremental life expectancy and in incremental quality-adjusted life-years (QALYS). Insulin aspart was associated with a small improvement in discounted life expectancy of 0.005 years (4.688 vs. 4.684 years) and an increase of 0.023 quality-adjusted life-years (QALYs) (3.800 vs. 3.776 QALYs) when compared with regular human insulin. Insulin aspart also incurred lower costs (JPY 481,586 vs. 594,717, difference −113,131) which resulted from the decreased incidence of cardiovascular events with insulin aspart (0.013 events per patient year vs. 0.030 on regular human insulin). Breakdown of costs indicated that pharmacy costs were higher with insulin aspart (JPY 346,608 vs. 278,468), but these costs were more than offset by the reduced costs associated with cardiovascular complications and hypoglycaemia over 5 years of treatment (JPY 134,978 vs. 316,249). Sensitivity analysis showed that insulin aspart was still cost-effective in the case where only 18% of the within-trial cardiovascular and mortality benefit over regular human insulin was captured in the model (assuming a willingness-to-pay threshold of JPY 5,000,000).

Limitations:
The NICE study cohort was relatively small ($n = 325$), meaning that caution should be exercised when calculating and interpreting the incremental cost-effectiveness ratio. Also, despite the differences in cardiovascular risk profile between the Japanese and UK populations, UKPDS-derived risk equations were used to project MI outcomes and PCI and CABG procedures and UKPDS HRQoL scores were applied to all health states. While these risk formulas and HRQoL utilities may not be directly applicable to the Japanese population, no equivalent Japanese-specific data are currently available.

Conclusions:
In a Japanese type 2 diabetes population, prescribing rapid-acting insulin aspart significantly reduced cardiovascular complications over 5- and 10-year time horizons, resulting in increased quality of life and decreased costs when compared with human insulin.

Introduction

Type 2 diabetes is a metabolic disorder that is associated with considerable clinical and economic burden. The condition is linked with a wide range of comorbidities, including stroke, myocardial infarction, sensory neuropathy, macrovascular mortality and all-cause mortality[1–10]. The majority of these complications are, in turn, associated with a considerable economic burden, both in terms of direct medical costs and indirect costs arising from premature mortality and lost productivity. In Japan, estimates placed the prevalence of type 2 diabetes at 6.9% in 2003, a figure that is expected to rise to 7.9% by 2025[11], while a recent study found the prevalence of undiagnosed diabetes to be 6.4% in males and 3.2% in females[12]. Given the relatively low prevalence of type 1 diabetes in Japan, the vast majority of these undiagnosed patients are also likely to have type 2 diabetes[13]. There is a relative paucity of data regarding the economic burden of diabetes in the Japanese setting, but a number of studies placed the total diabetes-related expenditure between 4% and 6% of the country's healthcare budget[14–16]. This compares with an estimated 12% of healthcare expenditure globally[17].The primary goal of diabetes management is to slow or prevent the onset or progression of these complications. Many recent studies, such as Steno-2, the Collaborative Atorvastatin Diabetes Study (CARDS), the Hypertension Optimal Treatment (HOT) study and the Heart Outcomes Prevention Evaluation (MICRO-HOPE), have indicated that a multifactorial approach to treatment including, for example, oral antidiabetics, antihypertensives and statins, is beneficial in terms of reducing complications and controlling the disease. However, diabetes is a chronic, progressive disease and even with this multi-faceted approach, patients ultimately require insulin to improve glycaemic control.

In 1985, a meeting held jointly by the World Health Organization (WHO) and the Juvenile Diabetes Foundation International concluded that there was a need to research new insulin formulations that would exhibit an improved pharmacokinetic profile to better match the insulin secretion profile that is observed post-prandially in non-diabetic individuals[18]. This recommendation led to the development and approval of insulin lispro and subsequently insulin glulisine and aspart, all of which belong to a class known as the rapid/short-acting insulin analogues (SAIAs). Insulin aspart is an analogue with a proline to aspartic acid substitution at position 28 of the B chain that causes the rapid dissociation of insulin hexamers into monomers and dimers upon administration[19]. As a result, insulin aspart is absorbed more quickly and reaches higher peak plasma concentrations within approximately half the time when compared with regular human insulin[20,21].

Since the pharmacokinetic properties of the SAIAs appear to be highly desirable, the clinical benefits over regular human insulin have been the focus of numerous studies. In 2006, a comprehensive meta-analysis of 49 studies (including 8,274 patients) was conducted by Siebenhofer *et al.* on behalf of the Cochrane Collaboration[22]. The study showed SAIAs to be equivalent with human insulins in terms of HbA_{1c} and overall hypoglycaemic events, and superior in terms of severe hypoglycaemic events (in type 2 diabetes patients). Although the study concluded that the SAIAs demonstrated only a minor overall clinical benefit, the authors noted that the vast majority of the included studies were of poor methodological quality and that further research, based on long-term efficacy and safety studies, was required. Furthermore, in the context of the present analysis, it should be noted that, of the studies included in the meta-analysis, only one was conducted in the Japanese setting.

The Nippon Ultra-Rapid Insulin and Diabetic Complication Evaluation-Study (NICE study; ClinicalTrials.gov number, NCT00575172) was a 5-year, open-label, randomised controlled trial which compared cardiovascular outcomes in Japanese type 2 diabetes patients intensively treated with short-acting regular human insulin ($n = 162$) or insulin aspart ($n = 163$)[23]. Where necessary, intermediate- or long-acting insulin was also used as part of a basal bolus regimen (at baseline, this was the case in 42% of patients randomised to the regular human insulin arm and 40% of patients in the insulin aspart arm). The primary endpoint of the trial was a composite cardiovascular endpoint comprising myocardial infarction (MI), angina pectoris, cerebral infarct/transient ischaemic attack (TIA), coronary artery bypass graft (CABG) or percutaneous coronary intervention (PCI). Secondary endpoints included HbA1c, postprandial glucose and fasting plasma glucose concentrations. The study showed a 43% reduction in incidence of the composite endpoint in patients on insulin aspart when compared with those on regular human insulin (6.4% or

12.8/1000/year vs. 11.3% or 22.2/1000/year, respectively, $p<0.02$). With regard to secondary endpoints, no statistically significant difference was observed in HbA_{1c} (7.5 ± 0.7 vs. $7.5\pm0.7\%$, respectively) or fasting plasma glucose (128 ± 42 vs. 133 ± 54 mg/dl, respectively). However, a significant decrease in 90-minute postprandial glucose was observed in patients on insulin aspart relative to those on regular human insulin (142 ± 58 vs. 226 ± 48 mg/dl, $p<0.02$).

The aim of the present study was to assess the cost effectiveness of insulin aspart versus regular human insulin from the perspective of a third-party healthcare payer in the Japanese setting based on the outcomes observed in the NICE study.

Table 1. Baseline cohort characteristics from the NICE study.

Characteristic	Mean value ($n=325$)
Age (years)	58
Proportion male	0.49
Fasting plasma glucose (mg/dl)	130
Postprandial plasma glucose (mg/dl)	200
HbA_{1c} (%)	7.5
Systolic blood pressure (mmHg)	117
Diastolic blood pressure (mmHg)	68
Body mass index (kg/m^2)	22.7
Low-density lipoprotein (mg/dl)	108
High-density lipoprotein (mg/dl)	62
Triglycerides (mg/dl)	128
Proportion current smokers	0.5

HbA_{1c}, glycated haemoglobin.

Methods

Model

A discrete-time cohort-level cost-effectiveness model with an annual cycle length was created in Microsoft Excel. The model comprised two temporally distinct sections, the first of which calculated within-trial outcomes based on complication incidence, mortality and cost data from the NICE trial. The second model section made post-trial projections using the trial outcomes as a baseline for progression formulas from the United Kingdom Prospective Diabetes Study (UKPDS) and a 2007 white paper on hypertension and stroke[24,25].

Within-trial outcomes were calculated by associating costs and utilities with the events observed in the NICE study (Table 2 and Table 3, respectively). The mean number of at-risk patients in each year of the NICE study was then combined with the event incidence, utility and cost data to calculate per-patient cost and effectiveness outcomes for each arm. Similarly, within-trial mortality was modelled based on mortality data from the NICE study. Half-cycle corrections were applied to eliminate any systematic over- or under-estimation of model outcomes.

In the absence of cardiovascular risk data in a Japanese diabetes population, post-trial MI incidence was modelled using the UKPDS MI cumulative incidence formula[11,26], populated with the baseline physiological parameters of the NICE study cohort (Table 1). Baseline MI risk was calculated using the mean rate of MI over the duration of the entire NICE study. The UKPDS formula was used to calculate the cumulative incidence of MI in each year of the simulation. The quotient of the present year's cumulative incidence and the previous year's cumulative incidence was then applied as an annual multiplier to the baseline risk. The progression of incidence of MI was then used as a surrogate to model the annual increase in incidence of PCI and CABG procedures, using the incidence of within-trial procedures as the baseline in each case. Post-trial incidence of cerebral infarction was calculated using a straightforward model in which the probability of an event was assumed to double every 10 years (in patients aged 55 and over)[25]. The risk of cerebral infarction (relative to that observed in each arm of the NICE study) in year t after conclusion of the study was therefore represented by $(2^{0.1})^t$. Rates of severe hypoglycaemia were assumed to remain constant (at the end-of-study rate) for the duration of the extrapolation period. Post-trial mortality was modelled by calculating annual risk multipliers from age-indexed and gender-weighted Japanese life tables from the World Health Organization (using the same technique as that employed with the UKPDS risk formula)[27]. Mortality risk multipliers were then applied to the mean annual mortality observed during the NICE study. The data sources used to calculate event incidence rates in the within-trial and post-trial sections of the model are summarised in Figure 1.

Baseline cohort characteristics from the NICE study population were used in the post-trial simulation (Table 1). Mean values from all patients were used (although there were no statistically significant differences between patients in the regular human insulin and insulin aspart arms in terms of baseline demographics, physiology or concomitant therapies). It should be noted that, from a modelling perspective, the cohort characteristics only affect post-trial projections, as the within-trial portion of the model was based exclusively on the cardiovascular events and mortality reported from the NICE study.

Perspective, time horizon and discounting

The base-case analyses were performed over 5 and 10-year time horizons from the perspective of a third-party healthcare payer in Japan. The payer perspective was selected on the grounds that there is currently no apparent consensus in the Japanese health economic literature on whether a

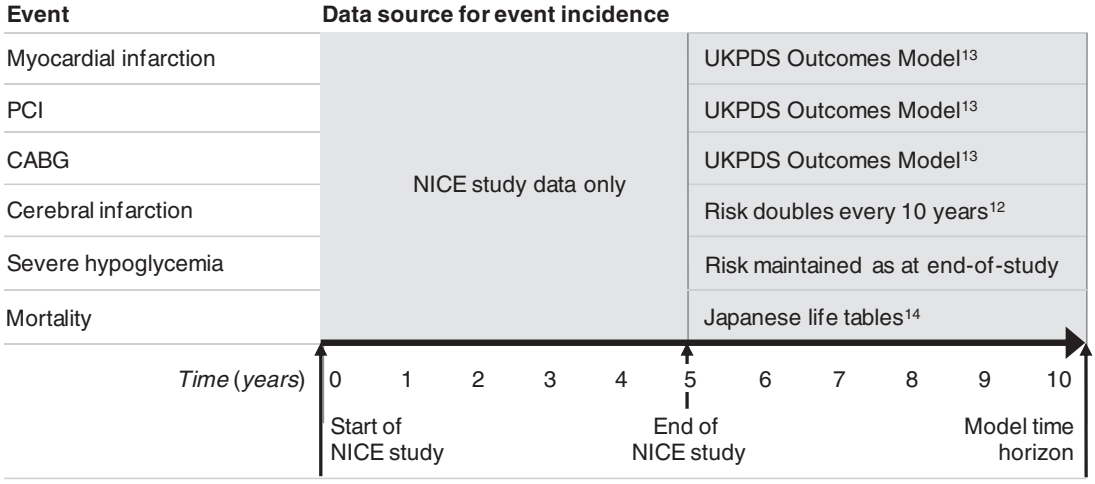


Figure 1. Data sources for event incidence over the model time horizon.

payer or societal perspective is most accepted[28–31]. A pragmatic literature search revealed that the majority of previous cost-effectiveness analyses in the Japanese setting had been performed from the payer perspective, indicating that the societal perspective is perhaps less well established. The 5-year outcomes are based exclusively on the outcomes observed in the NICE study, while the 10-year outcomes add 5 years of post-trial projection as described above. Given the relatively low event rates observed in the NICE study, modelling beyond a 10-year time horizon was considered unjustifiable. In line with previous health economic analyses in the Japanese setting, all future costs and clinical outcomes (those incurred or accrued in year 2 and onwards) were discounted at a rate of 3% annually[28–31]. To simplify the calculation of patient co-payment in the Japanese setting, it was assumed that all patients contributed 30% of costs[32].

Costs

With the exception of severe hypoglycaemia, adverse events costs were derived from hospital receipt data supplied by the Japanese Medical Data Centre in 2008 Japanese yen (JPY) and are presented in Table 2. In the absence of cost or resource-use estimates for severe hypoglycaemia in the Japanese setting, a value of €239 was used from a 2008 study into the cost of severe hypoglycaemia in Spain by Reviriego and colleagues[33]. This value was converted to JPY using the mid-2008 exchange rate of 167.6 yen to the euro (mid-market rate from Citibank, N.A.)[34].

Insulin usage was taken from the trial and per-unit insulin costs were supplied by Novo Nordisk Japan (Table 2). Total daily bolus doses of regular human insulin and insulin aspart were conservatively calculated based on insulin usage at the end of the NICE study, at which point insulin aspart dosage was significantly higher than regular human insulin (34.8 and 28.4 units per day, respectively). In the absence of basal insulin use data in every year of the NICE Study, daily doses (and the proportion of patients taking basal insulin) were assumed to increase linearly over the duration of the NICE study (from the baseline dose to the dose at the end of the study). In the insulin aspart arm, the mean daily dose increased from 12.2 units per day (in 40% of patients) at the start of the study to 14.6 units per day (in 56% of patients) at end of study. In the regular human insulin arm, the proportion of patients taking basal insulin remained constant, but the mean daily dose increased from 12.6 units to 14.2 units over the course of the study. Costs of concomitant medications such as oral antidiabetics, antihypertensives, antithrombotics and antihyperlipidaemics were not accounted as inter-arm differences in medication use were not statistically significant in the NICE study (and hence would have no direct impact on incremental outcomes).

Table 2. Event and pharmacy costs used in the modelling analysis.

Item	Cost in JPY (95% confidence interval)
Unit of insulin aspart	7.62
Unit of human insulin	7.45
Unit of basal insulin (Novolin)	3.73
Myocardial infarction event	2,011,380 (1,727,710–2,295,040)
Cerebral infarction event	1,393,160 (1,386,660–1,399,656)
Coronary artery bypass graft	2,466,200 (1,316,459–3,615,950)
Percutaneous coronary intervention	3,289,040 (2,725,142–3,852,947)
Severe hypoglycaemia	40,056

Insulin cost data supplied by Novo Nordisk A/S. Event cost data supplied by the Japanese Medical Data Centre. JPY, 2008 Japanese yen.

Table 3. Quality of life utilities.

State	Utility	Reference
Diabetes, no complications	0.814	16
MI, year of event	0.685	16
MI, years 2+ after event	0.736	16
Cerebral infarction, year of event	0.643	16
Cerebral infarction, years 2+ after event	0.545	16
CABG, year of event	0.814	Assumed
CABG, years 2+ after event	0.814	Assumed
PCI, year of event	0.814	Assumed
PCI, years 2+ after event	0.814	Assumed
Severe hypoglycaemia, year of event	0.802	16,20

MI, myocardial infarction; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention.

Estimation of quality-adjusted life expectancy

To account for the effect of cardiovascular events on health-related quality of life (HRQoL) (and in the absence of local HRQoL scores for diabetes patients), health utilities from the UKPDS were applied to all patients in the model. The baseline utility for patients with complication-free diabetes was taken to be 0.814, a value based on tobit regression analysis of 3,192 responses to the EuroQol EQ-5D quality of life instrument[35]. For patients experiencing MI or cerebral infarction, distinct utilities were applied in the year of the event and years subsequent to the event (Table 3). Patients who underwent CABG or PCI were assumed to have the same quality of life as diabetes patients with no complications (previous studies suggest that HRQoL may initially increase after CABG or PCI[36–38] although none of these studies have focused specifically on outcomes in diabetes patients). Severe hypoglycaemia was associated with a disutility of −0.0118 in the year of the event[39]. No subsequent state disutility was applied.

Sensitivity analyses

To assess the sensitivity of model outcomes to changes in input parameters, a series of one-, two- and multi-way sensitivity analyses were performed around the 5-year base case, including analyses around discounting, pharmacy and complication costs, HRQoL utilities and the efficacy of insulin aspart relative to regular human insulin. To address uncertainty in the NICE study outcomes, a series of the efficacy-based sensitivity analyses were used to form a break-even analysis, in which the cardiovascular and mortality event rates in the insulin aspart arm were increased in increments of 20% of the difference between the rates observed in the insulin aspart and regular human insulin arms of the NICE study. In turn, these outcomes were used to plot a net health benefit chart, assuming a willingness-to-pay (WTP) threshold of JPY 5,000,000/QALY[40]. Net health benefit is a means by which the outcomes of a cost-effectiveness analysis (i.e., incremental cost and effectiveness) are combined and expressed as a single measure (in this case incremental quality-adjusted life expectancy). In the present analysis, the incremental cost with insulin aspart (relative to human insulin) was converted to an equivalent quality-adjusted life expectancy value using the WTP threshold. This (negative) value was then subtracted from the projected incremental quality-adjusted life expectancy to give the total net health benefit in QALYs (ΔQALE – ΔCost/WTP).

Additional sensitivity analyses were performed around the cost of complications and procedures. Where 95% confidence intervals were available for costs (which was the case for MI, CI, CABG and PCI), analyses were performed with the costs set to the highest and lowest bounds of the confidence intervals. As confidence intervals were not available for the cost of severe hypoglycaemia, three additional analyses were performed in which the cost of all complications was set to JPY 0, 50% of the base case and 200% of the base case. The effect of discounting was explored in two analyses, which used values of 0% and 6% for cost and clinical discounting. Two sensitivity analyses were performed around HRQoL utilities, the first of which investigated the effect of setting all utilities to 0.814 (the base-case utility for complication-free type 2 diabetes) and the second of which explored the effect of increasing the utilities associated with CABG and PCI to 105% of that in the base case (0.855).

Finally, sensitivity analyses were performed around MI and CI incidence rates, setting the rates in the regular human insulin arm to the same as those in the insulin aspart arm.

Results

Clinical outcomes

Over the 5-year duration of the NICE study, the incidence of all adverse cardiovascular events was lower in patients on insulin aspart than those on regular human insulin (0.013 vs. 0.030 events per patient year). Insulin aspart was also associated with a small improvement in discounted life expectancy of 0.005 years compared to human insulin (4.688 vs. 4.683 years) and an additional 0.023 quality-adjusted life-years (QALYs) (3.800 vs. 3.776 QALYs).

Over a 10-year period, insulin aspart was found to be associated with an improvement in discounted life expectancy of 0.043 years (8.546 vs. 8.503 years) and an improvement in quality-adjusted life expectancy of 0.062 QALYs (6.942 vs. 6.879 QALYs). A survival curve showing the proportion of patients alive over a 40-year time horizon is presented in Figure 2. The curve shows separation between the insulin aspart and regular human insulin arms after a mean age of 65 years.

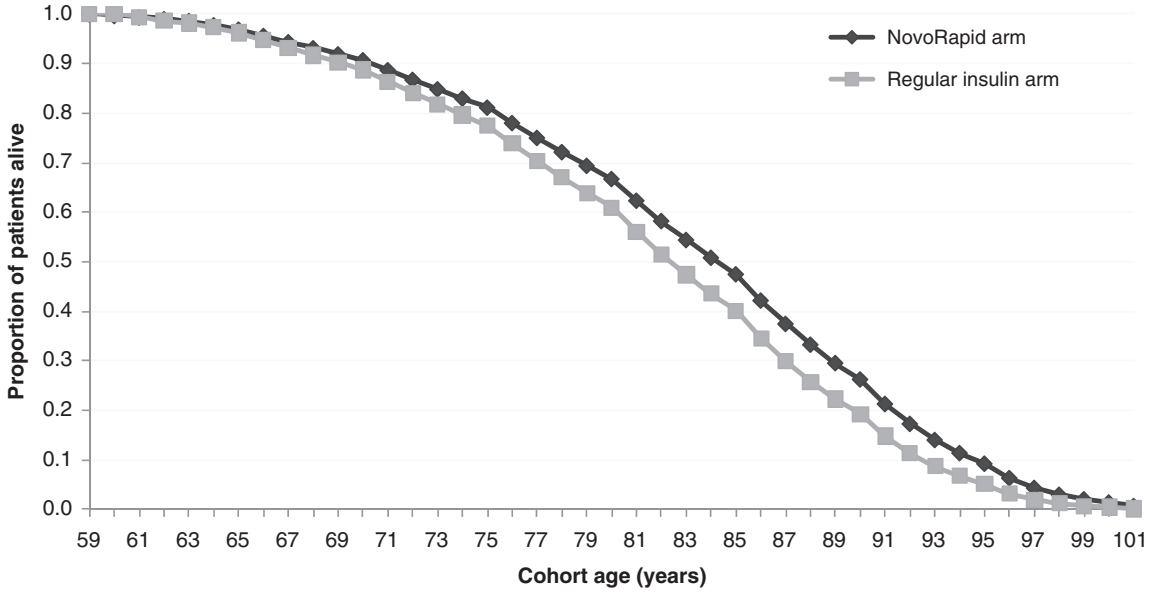


Figure 2. Survival curve showing proportion of patients alive in the insulin aspart and regular human insulin arms.

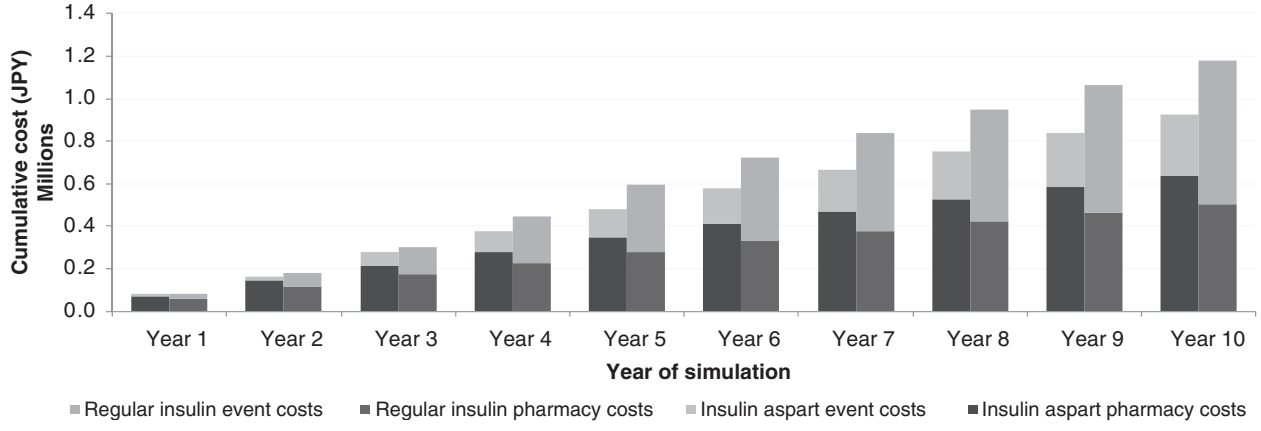


Figure 3. Pharmacy and event costs in the insulin aspart and regular human insulin arms over a 10-year time horizon.

Cost and cost effectiveness

Over the duration of the NICE study, insulin aspart was found to be cost saving (JPY 481,586 vs. 594,717, difference −113,131) when compared with human insulin (Table 4). Pharmacy costs in the insulin aspart arm were greater (JPY 346,608 vs. 278,468, an increase of JPY 68,140), but these were more than offset by a reduction in costs associated with cardiovascular complications over 5 years of treatment (JPY 134,978 vs. JPY 316,249, a reduction of JPY 181,271). Insulin aspart was therefore found to be the dominant option, reducing costs, CVD events and severe hypoglycaemia and thereby increasing quality-adjusted life expectancy.

Over a 10-year time horizon (including the trial period), insulin aspart was projected to save an average of JPY 252,923 (incurring costs of JPY 926,472 per patient vs. JPY 1,179,395 in the regular human insulin arm). As in the exclusively in-trial analysis, pharmacy costs were found to be higher (JPY 638,269 vs. JPY 506,817, difference JPY 131,453), but were again more than offset by cost savings resulting from a reduced incidence of cardiovascular complications (JPY 288,203 vs. JPY 672,578, difference JPY −384,376). Insulin aspart was therefore dominant compared with regular human insulin. A bar chart showing the cumulative costs in each year of the model is presented in Figure 3.

Sensitivity and break-even analyses

Outcomes of sensitivity analyses and the break-even analysis are presented in Table 5 and Figure 4. The break-even analysis showed that insulin aspart was dominant even in the case where only 29% of the cardiovascular and

Table 4. Within-trial and post-trial cost and effectiveness outcomes.

Outcome	Within-trial outcomes			Within-trial and post-trial outcomes		
	IAsp	HI	IAsp – HI	IAsp	HI	IAsp – HI
Life expectancy (years)	4.688	4.684	+0.005	8.546	8.503	+0.043
Quality-adjusted life expectancy (QALYs)	3.800	3.776	+0.023	6.942	6.879	+0.062
Mean per-patient pharmacy cost (JPY)	346,608	278,468	+68,140	638,269	506,817	+131,453
Mean per-patient adverse event cost (JPY)	134,978	316,249	−181,271	288,203	672,578	−384,376
Total cost (JPY)	481,586	594,717	−113,131	926,472	1,179,395	−252,923
ICER (JPY/QALY)	Insulin aspart dominant			Insulin aspart dominant		

HI, regular human insulin; IAsp, insulin aspart; ICER, incremental cost-effectiveness ratio; JPY, 2008 Japanese yen; QALY, quality-adjusted life-year.

mortality benefit from the NICE study were accounted in the model. Furthermore, the net health benefit chart (Figure 4B) showed insulin aspart to remain cost-effective down to only 18% of the benefit observed in the NICE study (given a willingness-to-pay threshold of JPY 5,000,000). Other sensitivity analyses showed that model outcomes were not sensitive to any one input parameter, with insulin aspart remaining dominant in all cases except for that in which all complication costs were set to JPY 0, where the ICER was found to be JPY 2,947,310/QALY gained.

Discussion

Based on the results of the NICE study, insulin aspart significantly reduced the incidence of cardiovascular complications and severe hypoglycaemia over 5- and 10-year time horizons, resulting in increased life expectancy and quality of life and decreased costs when compared with human insulin. The reduction in cardiovascular event rates in the insulin aspart arm of the NICE study was of particular interest, as statistically significant reductions in cardiovascular complications have not been widely observed in previous studies comparing SAIAs with regular human insulin. Also of note is that inter-arm differences in HbA_{1c} and fasting plasma glucose (FPG) were not statistically significant at end-of-study, corroborating prior evidence that HbA_{1c} and FPG may not be optimal indicators or predictors of cardiovascular risk in diabetes patients, as noted in previous SAIA versus regular human insulin studies[41].

The reduction in incidence of the composite cardiovascular endpoint (12.8/1000/year vs. 22.2/1000/year in the insulin aspart and regular human insulin arms, respectively; $p < 0.02$) should be interpreted in the context of the Japanese population, which has a markedly different cardiovascular risk profile from Western populations[42]. The fact that such reductions have not been widely observed previously may be due to the emphasis on Western populations in the vast majority of studies and meta-analyses investigating outcomes in SAIA-treated patients to-date. For example, of the 49 studies included in the Siebenhofer *et al.* meta-analysis, only one was based in the Japanese setting[43].

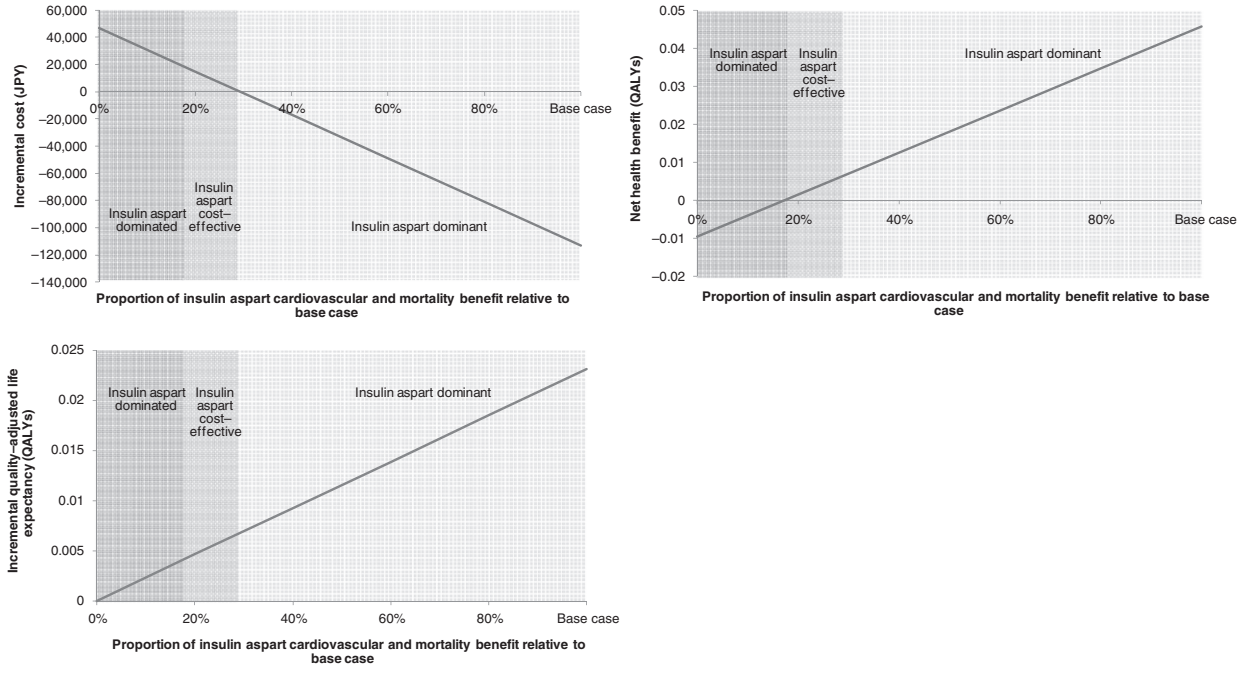
The only physiological endpoint recorded in the NICE study that showed a significant inter-arm difference at end-of-study was mean 90-minute post-prandial glucose (PPG) concentration, which was significantly lower with insulin aspart than regular human insulin (142 ± 58 vs. 226 ± 48 mg/dl, respectively, $p < 0.02$). A link between decreased PPG and lower cardiovascular risk has been reported in previous studies[44,45]. Indeed, a number of such studies have noted that progression of cardiovascular risk is more closely correlated with PPG excursions than either FPG or HbA_{1c}[46,47]. The increase in cardiovascular risk associated with acute hyperglycaemic episodes may result from vascular inflammation caused by hyperglycaemia-induced production of proinflammatory cytokines such as tumour necrosis factor-alpha, interleukin (IL)-6, IL-1 beta, and IL-8[48]. The increase in cytokine production has been found to be mitigated by infusion of insulin and subsequent return to normoglycaemia, providing a potential physiological explanation for the risk reduction observed in the NICE study, in which insulin aspart patients experience fewer and less severe glycaemic spikes[28]. From an economic perspective, the costs and HRQoL utilities associated with cardiovascular complications are such that even a relatively small reduction in risk has a dramatic effect on incremental cost and effectiveness outcomes.

The present study has a number of limitations that should be acknowledged. Firstly, the size of the cohort in the NICE study was relatively small ($n = 325$). As previous studies have noted, caution should be exercised when calculating and interpreting incremental cost-effectiveness ratios in such small populations, especially when statistical uncertainty data are unavailable[49]. However, the break-even analysis and net health benefit chart presented in Figure 4 attempt to address these concerns by modelling a range of reduced cardiovascular and mortality benefits for insulin aspart versus regular human insulin. The analysis showed that, even with a 71% reduction in the adverse event and mortality rate benefits observed in the trial, insulin aspart would remain dominant over regular human insulin and would still be cost effective after an

Table 5. Sensitivity analyses (5-year base case).

Parameter	Value	Quality-adjusted life expectancy (QALYs)			Total cost (JPY)			ICER (JPY/QALY)
		IAsp	HI	IAsp – HI	IAsp	HI	IAsp – HI	
Base case	N/A	3.800	3.776	0.023	481,586	594,717	−113,131	Insulin aspart dominant
Cost and clinical discount rate	0%	4.034	4.008	0.025	514,126	638,566	−124,440	Insulin aspart dominant
Cost and clinical discount rate	6%	3.579	3.558	0.021	451,023	553,646	−102,623	Insulin aspart dominant
Pharmacy costs	JPY 0	3.800	3.776	0.023	134,978	316,249	−181,271	Insulin aspart dominant
Pharmacy costs	50% of base case	3.800	3.776	0.023	308,282	455,483	−147,201	Insulin aspart dominant
Pharmacy costs	200% of base case	3.800	3.776	0.023	828,194	873,185	−44,991	Insulin aspart dominant
All complication costs	JPY 0	3.800	3.776	0.023	346,608	278,468	68,140	2,947,310
All complication costs	50% of base case	3.800	3.776	0.023	414,097	436,592	−22,496	Insulin aspart dominant
All complication costs	200% of base case	3.800	3.776	0.023	616,564	910,965	−294,401	Insulin aspart dominant
Cost of MI, CI, CABG and PCI	Lower 95% confidence interval bound	3.800	3.776	0.023	459,275	542,581	−83,306	Insulin aspart dominant
Cost of MI, CI, CABG and PCI	Upper 95% confidence interval bound	3.800	3.776	0.023	503,896	646,852	−142.956	Insulin aspart dominant
All HRQoL utilities	0.814	3.816	3.812	0.004	481,586	594,717	−113,131	Insulin aspart dominant
CABG and PCI utilities	105% of base case	3.802	3.780	0.021	481,586	594,717	−113,131	Insulin aspart dominant
MI incidence	Same in both arms	3.794	3.776	0.017	532,529	594,717	−62,187	Insulin aspart dominant
CI incidence	Same in both arms	3.788	3.776	0.012	508,769	594,717	−85,948	Insulin aspart dominant
Incidence of mortality and all cardiovascular complications and procedures	0% of benefit*	3.777	3.776	0.001	641,695	594,717	46,978	47,253,567
	20% of benefit*	3.782	3.776	0.005	609,673	594,717	14,956	2,762,557
	40% of benefit*	3.786	3.776	0.010	577,651	594,717	−17,066	Insulin aspart dominant
	60% of benefit*	3.791	3.776	0.014	545,629	594,717	−49,088	Insulin aspart dominant
	80% of benefit*	3.795	3.776	0.019	513,607	594,717	−81,109	Insulin aspart dominant

CABG, coronary artery bypass graft; CI, cerebral infarction; HI, regular human insulin; HRQoL, health-related quality of life; IAsp, insulin aspart; ICER, incremental cost-effectiveness ratio; JPY, 2008 Japanese yen; MI, myocardial infarction; PCI, percutaneous coronary intervention; QALYs, quality-adjusted life-years. *These sensitivity analyses are also presented in Figure 4 and represent a scenario in which the cardiovascular and mortality event rates observed in the insulin aspart arm of the NICE study were increased step-wise toward those observed in the regular human insulin arm, hence reducing the modelled benefit of insulin aspart versus regular human insulin.



Incremental cost = cost of insulin aspart arm – cost of regular human insulin arm; Incremental quality–adjusted life expectancy (QALE) = QALE in insulin aspart arm – QALE in regular human insulin arm

Figure 4. Break-even analysis showing (A) incremental costs, (B) net health benefit and (C) incremental QALE over a range of the observed cardiovascular and mortality benefits of insulin aspart when compared with regular human insulin (over a 5-year time horizon).

82% reduction. Secondly, in the absence of local data, UKPDS HRQoL scores were applied to all health states. To evaluate the influence of utility scores associated with complications, a sensitivity analysis was performed where no changes in utility were applied when complications occurred (i.e., all patients had a utility score of 0.814 regardless of complication status). As a result of the increased mortality in the regular human insulin arm, insulin aspart remained dominant in this analysis, although the inter-arm difference in quality-adjusted life expectancy fell to 0.0037 (from 0.0231 in the base case). Finally, despite the differences in cardiovascular risk profile between the Japanese and UK populations, UKPDS-derived risk formulas were used to project MI outcomes and PCI and CABG procedures. While these risk formulas may not be directly applicable to the Japanese population, no equivalent Japanese-specific data are currently available. It should also be noted that these formulas only affect the post-trial projection section of the model, not the within-trial section (in which all cardiovascular event, hypoglycaemia and mortality data were taken directly from the NICE study).

Conclusion

The NICE study was the first study to focus specifically on cardiovascular risk in Japanese patients taking SAIAs. The findings showed a 43% reduction in incidence of the composite endpoint (MI, angina pectoris, CI/TIA, CABG or PCI) in patients on insulin aspart when compared with those on regular human insulin. However, given the unique cardiovascular profile of the Japanese population, future large-scale, long-term randomised controlled trials investigating cardiovascular outcomes in Japanese diabetes patients would be a welcome addition to the current evidence base. While the health economic outcomes of this analysis should be interpreted in the appropriate context, the evidence suggests that insulin aspart was both cost- and life-saving even when only 29% of the observed cardiovascular benefit was captured in the modelling analysis. Therefore, marginally higher daily pharmacy costs with insulin aspart should not be a barrier to reimbursement and widespread uptake amongst type 2 diabetes patients requiring insulin in the Japanese setting.

Transparency

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Declaration of financial/other relationships

R.P. and W.V. are currently employed by Ossian Health Economics and Communications GmbH, Basel, Switzerland,

which has received consulting fees from Novo Nordisk A/S. T.P. is currently employed by Novo Nordisk A/S. H.N. is currently employed by Osaka Saiseikai Nakatsu Hospital, Osaka, Japan.

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