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Projected long-term outcomes in patients with type 1 diabetes treated with fast-acting insulin aspart versus conventional insulin aspart in the UK setting

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ABSTRACT

Aims

Many patients with type 1 diabetes mellitus (T1DM) fail to achieve optimal glycaemic control and mealtime insulins that more closely match physiological insulin secretion can help improve treatment. In the onset 1 trial, fast-acting insulin aspart (faster aspart) was shown to improve glycaemic control in patients with T1DM compared with conventional insulin aspart (insulin aspart). In the UK, faster aspart and insulin aspart are associated with the same acquisition cost, and therefore the present analysis assessed the impact of faster aspart versus insulin aspart on long-term clinical outcomes and costs for patients with T1DM in the UK setting.

Methods

The QuintilesIMS CORE Diabetes Model was used to project clinical outcomes and costs over patient lifetimes in a cohort with baseline characteristics from the onset 1 trial. Treatment effects were taken from the 26-week main phase of the onset 1 trial, with costs and utilities based on literature review. Future costs and clinical benefits were discounted at 3.5% annually.

Results

Projections indicated that faster aspart was associated with improved discounted quality-adjusted life expectancy (by 0.13 quality-adjusted life years) versus insulin aspart). Improved clinical outcomes resulted from fewer diabetes-related complications and a delayed time to their onset with faster aspart. Faster aspart was found to be associated with reduced costs versus insulin aspart (cost savings of GBP 1,715), resulting from diabetes-related complications avoided and reduced treatment costs.

Conclusions

Faster aspart was associated with improved clinical outcomes and cost savings versus insulin aspart for patients with T1DM in the UK setting.

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INTRODUCTION

It has been estimated that there are approximately 370,000 adults and 26,500 children living with type 1 diabetes mellitus (T1DM) in the United Kingdom (UK).^{1,2} Patients with T1DM are at a higher risk of chronic complications, and are at a higher risk of mortality than people without diabetes of the same age.³ In 2010/11, the direct costs attributable to T1DM in the UK were approximately GBP 1 billion.⁴ In addition, it is estimated that 830,000 sick days are taken per year as a result of T1DM, leading to indirect costs of around GBP 0.9 billion. Projections suggest that, if no changes are made to treatment patterns, direct and indirect costs will increase to GBP 1.8 billion and GBP 2.4 billion, respectively, by 2035/36.⁴

Long-term studies in patients with T1DM, such as the Diabetes Control and Complications Trial (DCCT) and the follow-up Epidemiology of Diabetes Interventions and Complications (EDIC) study, suggest that improving glycemic control can reduce the incidence of diabetes-related complications, lowering the clinical and economic burden of the disease.^{5,6} However, in the UK, in 2015, only 29.9% of patients with T1DM were achieving a glycemic control target of glycated hemoglobin (HbA1c) < 7.5%.⁷ This target has recently been lowered to 6.5% by the National Institute for Health and Care Excellence (NICE), and whilst no data have been published on the proportion of patients achieving the revised target, it is likely to be lower than for the previous guidance.¹

Fast-acting insulin aspart (faster aspart) is conventional insulin aspart (insulin aspart) in a new formulation for the treatment of diabetes requiring insulin. Faster aspart has been developed to have a faster onset of action which more closely matches physiological secretion of endogenous insulin.⁸ When compared with insulin aspart, faster aspart has a twice faster onset of appearance in the bloodstream, a twice higher insulin exposure within the first 30 minutes and a 74% greater glucose-lowering effect within the first 30 minutes following administration.⁹

Onset 1 was a 26-week multicenter, multinational, double-blind trial in patients with T1DM in which faster aspart was compared with insulin aspart, both in combination with insulin detemir in a basal-

bolus insulin regimen.¹⁰ The trial also included a 26-week open-label faster aspart post-meal dosing arm (also in combination with insulin detemir). The initial 26-week trial period was followed by an additional 26-week treatment period to assess long-term safety and efficacy. Compared with insulin aspart, mealtime faster-aspart was associated with a significantly greater reduction in the primary endpoint of the trial, HbA1c at 26 weeks. Faster aspart administered post-meal did not compromise glycemic control compared with insulin aspart administered at mealtime. Faster aspart compared with insulin aspart, both administered at mealtime, was also associated with statistically significant improvements in 1-hour and 2-hour post-prandial glucose (PPG) increments. No statistically significant differences in changes in body weight or rates of hypoglycemic events were observed, and the safety profiles of faster aspart and insulin aspart were similar.

Economic evaluation of new healthcare interventions plays a key role in ensuring efficient allocation of limited healthcare resources within the National Health Service (NHS), with the aim of maximizing healthcare gains across the population of the UK. In the UK, faster aspart and insulin aspart are associated with the same acquisition cost, and therefore the objective of the present analysis was to assess the impact of basal-bolus insulin therapy with mealtime faster aspart plus insulin detemir versus mealtime insulin aspart plus insulin detemir for patients with T1DM on long-term clinical outcomes and costs from a healthcare payer perspective in the UK setting.¹¹

MATERIALS AND METHODS

Model description

The analysis was performed using the QuintilesIMS CORE Diabetes Model.¹² The model is a validated, non-product specific diabetes policy analysis tool and is based on a series of inter-dependent sub-models that simulate the complications of diabetes. The model uses data from a range of published long-term clinical and epidemiological studies to make predictions of outcomes, including the Diabetes Control and Complications Trial (DCCT), the United Kingdom Prospective Diabetes Study (UKPDS), the

Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR), the United States Renal Disease Study (USRDS) and many others.¹² Long-term outcomes projected by the model have been validated against real life data in 2004 and more recently in 2014.^{13,14} Version 9.0 of the QuintilesIMS CORE Diabetes Model was used in the present analysis, as this model update includes risk equations specific to T1DM based on data from the Epidemiology of Diabetes Interventions and Complications (EDIC) study, and the Pittsburgh Epidemiology of Diabetes Complications Study, and includes the option to use a diminishing disutility for non-severe hypoglycemic events.¹⁵

Outcomes were projected over patient lifetimes (up to 70 years) to capture all relevant long-term complications and associated costs and assess their impact on life expectancy and quality-adjusted life expectancy, in line with good practice guidance for economic evaluation of interventions for diabetes.¹⁶ Future clinical benefits and costs were discounted at 3.5% annually, based on health economic guidance for the UK setting.¹⁷

Simulated cohort and treatment effects

The baseline cohort characteristics applied in the analysis were based on all patients included in the onset 1 study.¹⁰ Mean (standard deviation) age was 44.4 (13.9) years, with mean duration of diabetes of 19.9 (12.3) years, and mean HbA1c of 7.6 (0.7)%. The proportion of patients using tobacco products was based on the trial data, but the number of cigarettes smoked per day was assumed to be the same as the general UK population and was based on country-specific data, as was alcohol consumption.^{18,19}

Treatment effects applied in the faster aspart and insulin aspart arms (both in combination with insulin detemir) were taken from the 26-week main phase of the trial, in line with the primary endpoint, with data from mealtime insulin administration used (Table 1). Modeled data were used to account for any differences in the baseline cohort characteristics between the treatment arms.¹⁰

Following application of the treatment effects in the first year of the analysis, HbA1c was assumed to remain constant over time. There are currently no published progression equations for HbA1c in patients with T1DM, and data from long-term studies such as DCCT and EDIC suggest that HbA1c does not increase as patients age.⁶ Unlike type 2 diabetes mellitus (T2DM), T1DM is not a progressive disease and it is unlikely that substantial changes in HbA1c over time would be observed. Patients were assumed to receive faster aspart plus insulin detemir or insulin aspart plus insulin detemir for the duration of their lifetimes, with no treatment switching applied.

Costs and utilities

Costs were accounted from healthcare payer perspective (NHS) in 2015 pounds sterling (GBP). Diabetes medication resource use was based on the onset 1 trial, with modeled doses taken from the 26-week main phase of the trial. At the end of the trial, patients in the faster aspart arm received mean daily doses of 30.60 IU and 30.44 IU basal and bolus insulin, respectively, compared with 31.24 IU and 33.06 IU per day in the insulin aspart arm. Costs of medications and consumables (needles and self-monitoring of blood glucose test strips and lancets) were taken from the Monthly Index of Medical Specialities (MIMS).¹¹

Costs of treating diabetes-related complications were identified through literature review, with costs inflated to 2015 values using the Hospital and Community Health Services price index where necessary.^{20,21,22,23,24,25,26,27,28,29,30} Over time, patients develop complications that influence their overall health-related quality of life and therefore utilities, reflecting the patients quality of life, were applied in the year of the complication and in subsequent years based on published sources.^{12,31,32,33} Whilst utilities specific to T1DM have been published, no full set of utilities for all complications included in the QuintilesIMS CORE Diabetes Model have been published using a single method. There is significant evidence that utility estimates vary depending on the methods used, and, therefore, the majority of utilities were based on patients with T2DM or the general population, with consistency in

the methodology used to elicit the values. Application of utilities for patients with T2DM in patients with T1DM is a common approach in cost-effectiveness analyses of interventions for T1DM.^{34,35,36,37}

For disutilities applied following non-severe hypoglycemic events, a diminishing disutility approach as described by Lauridsen *et al.* was used.³⁸ This approach was chosen as there is evidence that the marginal impact of non-severe hypoglycemia on quality of life falls as the frequency of hypoglycemic events increases.

Sensitivity analyses

Sensitivity analyses were conducted to evaluate the key drivers of outcomes and to assess the effect of changes in modeling assumptions on the projected outcomes. The influence of time horizon on the outcomes projected by the model was investigated by running analyses over 10, 20 and 30 years. It should be noted that a time horizon of 70 years was required for all modeled patients to have died, and therefore shorter time horizons do not capture all complications and costs. To examine the effect of discounting on outcomes, simulations were performed with (symmetric) discount rates of 0% and 6%. A total of five simulations were run to assess the key drivers of clinical benefit associated with faster aspart. In the faster aspart arm, changes in HbA1c, blood pressure, serum lipids, body mass index and hypoglycemic events were set to the value in the insulin aspart arm in turn. A further analysis with only the statistically significant difference in HbA1c applied in the faster aspart arm, with all other parameters equal to the insulin aspart arm, was conducted.

To evaluate the impact of alternative assumptions around long-term parameter progression on projected outcomes, five sensitivity analyses were conducted. In the base case analysis, the difference in HbA1c between the treatment arms was assumed to persist for the entire simulation, with sensitivity analyses conducted with the difference abolished after 1, 5 and 10 years. A further analysis was conducted with the HbA1c difference abolished linearly over 10 years (i.e. the difference between the treatment arms disappeared gradually). A final analysis was conducted with HbA1c differences

between the treatment arms were maintained for the duration of patient lifetimes, but an increase of 0.045% per year was applied in both arms, based on data from the DCCT.⁵ This analysis reflects that patients with T1DM may develop some characteristics of T2DM due to weight gain and family history. In contrast to T1DM, T2DM is a progressive disease, with insulin resistance increasing and beta cell function declining over time.

The effect of over or underestimating the direct cost of treating diabetes-related complications was investigated in two scenarios by increasing and decreasing costs of complications by 20%. The base case analysis was conducted using a diminishing disutility approach for non-severe hypoglycemic events, and a sensitivity analysis was conducted using a static disutility approach with disutilities applied based on T1DM-specific data from Evans *et al.*^{32,38} The impact of hypoglycemia disutilities was further explored with no disutility applied following severe and non-severe events.

Version 9.0 of the QuintilesIMS Core Diabetes Model incorporates a number of risk equations to predict cardiovascular mortality and varying the risk equations used can be used to address structural uncertainty. The base case analysis used risk equations derived from the EDIC study, with risk equations based on data from Pittsburgh Epidemiology of Diabetes Complications Study applied in a sensitivity analysis.³⁹ In a further sensitivity analysis to examine structural uncertainty, a combined mortality risk equation was applied.⁴⁰

Reflecting the primary endpoint of onset 1, the 26-week data were applied in the base case analysis. The 52-week data, including the additional 26-week treatment period, were used in a sensitivity analysis with equivalent assumptions. An analysis was also conducted with the 26-week data applied in the first year of the analysis, and then treatment effects were applied to bring parameters to the values seen at 52 weeks in the second year of the analysis (the QuintilesIMS CORE Diabetes Model uses an annual cycle, and therefore it was not possible to apply changes at 6 months). Probabilistic sensitivity analysis (PSA) was performed using a second order Monte Carlo approach with sampling of baseline cohort characteristics, treatment effects, costs and utilities.

RESULTS

Base case analysis

In the base case analysis, long-term projections showed that faster aspart was associated with improved discounted life expectancy (by 0.11 years) and discounted quality-adjusted life expectancy (by 0.13 quality-adjusted life years [QALYs]) versus insulin aspart in patients with T1DM (Table 2).

Improved clinical outcomes resulted from a reduced incidence of diabetes-related complications over patient lifetimes (Figure 1a). In addition to a reduced incidence of complications, faster aspart was associated with a delayed time to onset of complications (Figure 1b), with mean time free of all complications increased by approximately 6 months and mean time to onset of myocardial infarction, stroke, end-stage renal disease, severe vision loss and amputation all delayed by 4 to 6 months.

Evaluation of direct costs suggested that the mean cost per patient receiving faster aspart was GBP 1,715 lower than in the insulin aspart arm over a patient lifetime (Figure 2a). Faster aspart was associated with cost savings as a result of avoided diabetes-related complications, most notably as a result of avoided ulcer and neuropathy complications, and avoided ophthalmic complications, where mean per patient savings of GBP 516 and GBP 225, respectively, were identified. Faster aspart was associated with cost savings after 1 year for the majority of complications, but cost savings as a result of avoided renal complications were only apparent after 15 years (Figure 2b). Cost savings as a result of all complications avoided increased over patient lifetimes, before plateauing 40 years into the analysis. Faster aspart was also associated with reduced treatment costs, driven by the lower doses of basal and bolus insulins, with mean cost savings of GBP 478 per patient. Estimation of long-term clinical outcomes indicated that both life expectancy and quality-adjusted life expectancy were improved with faster aspart treatment compared with insulin aspart, at a cost saving from a healthcare payer perspective.

Sensitivity analyses

Faster aspart was associated with improved clinical outcomes and reduced costs from a healthcare payer perspective versus insulin aspart in all sensitivity analyses conducted (Table 3). Variation in the time horizon had the greatest impact on the results. Over shorter time horizons, faster aspart was associated with smaller clinical benefits and smaller cost savings than in the base case analysis. This was due to the improvements in physiological parameters (predominantly HbA1c) associated with faster aspart resulting in a reduced risk of diabetes-related complications over the long-term. Changing the discount rates also highlighted the long-term benefits of improved glycemetic control with faster aspart, with clinical benefits and cost savings increased when discount rates of 0% were applied.

Abolishing each of the changes in physiological parameters associated with faster aspart identified that the improvement in HbA1c compared with insulin aspart was the key driver of improved clinical outcomes and cost savings. When this difference between the treatment arms was abolished the clinical benefit with faster aspart fell to 0.05 QALYs. The analyses with alternative HbA1c progression approaches reflect the uncertainty around long-term changes in HbA1c and that patients with T1DM may develop some characteristics of T2DM, with faster aspart remaining associated with improved outcomes and reduced costs compared with insulin aspart in all analyses conducted.

Using the static approach to disutilities applied following non-severe hypoglycemic events resulted in reduced quality-adjusted life expectancy in both arms relative to the base case, with the benefit with faster aspart falling to 0.12 QALYs. Similarly, when no hypoglycemia disutilities were applied, the quality-adjusted life expectancy benefit with faster aspart was 0.12 QALYs. PSA showed similar mean results to the base case, but increased measures of variance around the mean outcomes. Assuming a willingness-to-pay threshold of GBP 20,000 per QALY gained, the analysis indicated that there was an 87.0% probability that faster aspart would be cost-effective versus insulin aspart.

DISCUSSION

Based on clinical effectiveness data from the onset 1 trial, the present analysis projected that basal-bolus insulin therapy with faster aspart plus insulin detemir was likely to improve clinical outcomes versus basal-bolus insulin therapy with insulin aspart plus insulin detemir for patients with T1DM in the UK setting. The key driver of improved clinical outcomes was a greater improvement in HbA1c, resulting in a reduced incidence and increased time to onset of diabetes-related complications. This led to improvements in both duration and quality of life in the faster aspart arm. The improvements in glycemic control associated with faster aspart in onset 1 were achieved with a similar risk of hypoglycemic events as with insulin aspart treatment, as opposed to previous observations where improvements in glycemic control have been compromised by an association with an increase in hypoglycemic events.^{5,6} Projected over patient lifetimes, faster aspart was associated with cost savings as a result of diabetes-related complications avoided, which were apparent from the first year of the analysis and increased over time. Faster aspart was also associated with cost savings associated with lower doses of both basal and bolus insulins, as the two formulations are associated with the same acquisition cost. Faster aspart was considered cost and life-saving versus insulin aspart as part of a basal-bolus insulin regimen for treatment of T1DM in the UK setting.

While the improvement in HbA1c with faster aspart over insulin aspart may be relatively modest (0.15%), maintaining this difference over the long-term may substantially reduce the risk of developing diabetes-related complications. This reduces both mortality and morbidity associated with T1DM. For healthcare payers, this improved patient management may also result in significant cost savings due to avoidance of costly treatment of complications.

The present modeling analysis does not take into account changes in PPG control, as this parameter cannot be captured in the QuintilesIMS CORE Diabetes Model. In the onset 1 study, faster aspart was associated with statistically significant improvements in PPG increments compared with insulin aspart.¹⁰ It has been suggested that lower PPG may be associated with a reduced risk of diabetes-

related complications, with guidance from the International Diabetes Federation stating that post-meal hyperglycemia is independently associated with macrovascular disease, ophthalmic disease and cancer.⁴¹ A 2012 review found that higher PPG was associated with increased all-cause and cardiovascular mortality, increased incidence of major cardiovascular events, and progression of diabetic retinopathy.⁴² However, the impact of reduced PPG may to some extent be indirectly included in the present analysis, as HbA1c was used as the measure of glycemic control. Some studies have suggested that PPG makes a significant contribution to HbA1c in patients who are relatively well controlled, although other studies have been more cautious and have suggested that fasting plasma glucose is a better indicator of HbA1c, particularly in patients with a very high HbA1c.^{43,44}

In addition to improving glycemic control, the rapid onset of action of faster aspart and the faster appearance in the bloodstream may provide patients with T1DM with increased flexibility around timing of doses.^{8,9} Currently, mealtime insulins must be injected pre-prandial, and this may result in hypoglycemia if the meal is delayed or not consumed. Faster aspart represents a mealtime insulin with the option of post-meal dosing when needed, without compromising glycemic control compared with insulin aspart.¹⁰ This opportunity for post-meal dosing, when required, may improve convenience, and furthermore, flexibility of timing of insulin dosing has been shown to be associated with improved quality of life in patients with diabetes, beyond the impact on hypoglycemic events.^{45,46} The present analysis did not capture the utility of flexible insulin dosing, as data were used from the arms of the trial in which mealtime dosing was specified, but this impact on quality of life may be seen in real-world clinical practice, and remains an area of interest for future research.

A limitation of the analysis, common to a number of health economic analyses and particularly of those for diabetes interventions, was the reliance on relatively short-term clinical trial data to make long-term projections. However, in the absence of long-term trial data, modeled projections represent a valuable source of information for healthcare decision makers aiming to allocate resources efficiently to maximize healthcare across the population. Furthermore, projecting outcomes over patient lifetimes is recommended in guidelines for economic evaluation of interventions for patients

with diabetes. The present analysis aimed to minimize the impact of this by using a model of diabetes based on published long-term epidemiological studies that has been extensively published and validated.^{13,14}

A further limitation may be the clinical data used to inform the analysis. The study was based on a randomized controlled trial (onset 1), and therefore there is an assumption that the effects observed in the trial would be transferable to clinical practice in the UK setting. Registry data provides evidence of the impact of interventions in the real-world, but it was not possible to use registry data in the present analysis, as, at the time the analysis was conducted, faster aspart was not available in the UK. As faster aspart becomes more widely used, data from registries such as the Clinical Practice Research Datalink (CPRD) could be used to conduct equivalent long-term analyses. Additionally, data from registries would allow the clinical effects to be assessed in a larger patient number and over a longer duration than was possible in the onset 1 trial. However, the onset 1 trial represents the best data source currently available to inform the present analysis.

Faster aspart has been shown to have a greater glucose-lowering effect within the first 30 minutes following injection compared to insulin aspart due to the faster appearance within the bloodstream, and the onset 1 trial found that this resulted in improved glycemic control in patients with T1DM.

Long-term projections, as part of the present analysis, suggested that treatment with faster aspart plus insulin detemir was likely to improve long-term clinical outcomes for patients with T1DM at a reduced cost from a UK healthcare payer perspective versus insulin aspart plus insulin detemir.

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Conflict of interests: BH and WV are employees of Ossian Health Economics and Communications. Ossian received funding from Novo Nordisk A/S to perform the present analysis. SB was an employee of Novo Nordisk when this research was conducted. AS is an employee of Novo Nordisk A/S. DR-J has received research funding, advisory panel fees and lecture panel honoraria from Astra Zenica, Boehringer Ingelheim, Cellnovo, Lilly, Novartis, Novo Nordisk, and Sanofi. SRH has received personal fees from Sanofi Aventis, Eli Lilly, Takeda, Novo Nordisk and Astra Zeneca for serving on Speaker panels, and is an employee of the University of Sheffield, which has received remuneration from Eli Lilly, Boehringer Ingelheim, Novo Nordisk Eli Lilly and Takeda for consultancy.

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TABLES AND FIGURES

Table 1 Treatment effects applied in the first year of the analysis

	Faster aspart (mean (SD))	Insulin aspart (mean (SD))
HbA1c (%)	-0.32 (0.56)*	-0.17 (0.56)
Systolic blood pressure (mmHg)	-1.47 (11.70)	-1.15 (11.70)
Diastolic blood pressure (mmHg)	-0.40 (9.40)	+0.40 (8.90)
Total cholesterol (mg/dL)	+0.25 (24.99)	+0.88 (24.99)
HDL cholesterol (mg/dL)	+0.34 (9.75)	-0.39 (9.75)
LDL cholesterol (mg/dL)	-0.50 (20.59)	-0.03 (20.59)
Triglycerides (mg/dL)	+0.52 (55.22)	+6.12 (55.22)
Body mass index (kg/m ²)	+0.23 (0.99)	+0.19 (0.99)
Severe hypoglycemia event rate (events per 100 patient years)	25	27
Non-severe hypoglycemia event rate (events per 100 patient years)	5,849	5,811
Percentage of severe hypoglycemic events that were nocturnal (%)	24.0	37.0
Percentage of non-severe hypoglycemic events that were nocturnal (%)	12.0	13.0

HbA1c, glycated hemoglobin; HDL, high density lipoprotein; LDL, low density lipoprotein; SD, standard deviation.

* $p < 0.05$.

Table 2 Results of the base case analysis

	Faster aspart (Mean (SD))	Insulin aspart (Mean (SD))	Difference
Discounted life expectancy (years)	17.38 (0.16)	17.27 (0.19)	+0.11
Discounted quality-adjusted life expectancy (QALYs)	11.54 (0.12)	11.40 (0.14)	+0.13
Discounted direct costs (GBP)	50,004 (1,363)	51,719 (1,261)	-1,715
ICER (life expectancy)		Faster aspart dominant	
ICER (quality-adjusted life expectancy)		Faster aspart dominant	

GBP, 2015 pounds sterling; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; SD, standard deviation.

Table 3 Results of the sensitivity analyses

Analysis	Discounted quality-adjusted life expectancy (QALYs)			Discounted direct costs (GBP)			ICER (GBP per QALY gained)
	Faster aspart	Insulin aspart	Difference	Faster aspart	Insulin aspart	Difference	
Base case	11.54	11.40	+0.13	50,004	51,719	-1,715	Faster aspart dominant
30 year time horizon	10.60	10.50	+0.10	41,423	42,974	-1,551	Faster aspart dominant
20 year time horizon	8.85	8.79	+0.06	30,468	31,606	-1,138	Faster aspart dominant
10 year time horizon	5.55	5.53	+0.02	15,506	15,971	-464	Faster aspart dominant
0% discount rates	19.72	19.40	+0.32	101,998	105,422	-3,424	Faster aspart dominant
6% discount rates	8.59	8.51	+0.08	33,511	34,645	-1,134	Faster aspart dominant
HbA1c difference abolished	11.45	11.40	+0.05	51,150	51,719	-570	Faster aspart dominant
Blood pressure difference abolished	11.54	11.40	+0.13	50,027	51,719	-1,693	Faster aspart dominant
Lipid difference abolished	11.51	11.40	+0.11	49,967	51,719	-1,753	Faster aspart dominant

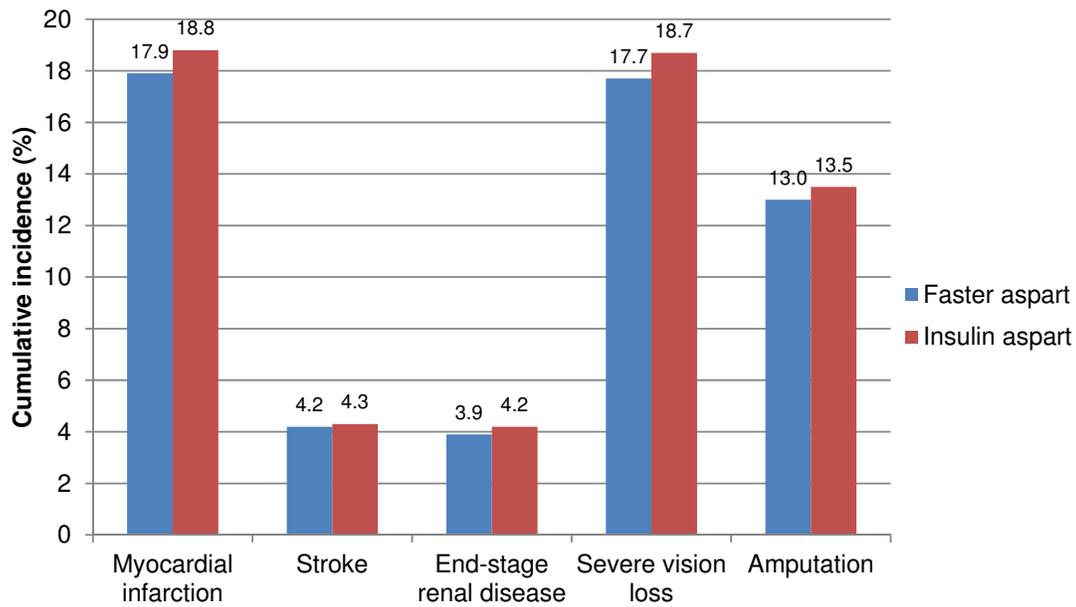
Analysis	Discounted quality-adjusted life expectancy (QALYs)			Discounted direct costs (GBP)			ICER
	Faster aspart	Insulin aspart	Difference	Faster aspart	Insulin aspart	Difference	(GBP per QALY gained)
Body mass index difference abolished	11.53	11.40	+0.13	50,023	51,719	-1,696	Faster aspart dominant
Hypoglycemia difference abolished	11.49	11.40	+0.09	50,015	51,719	-1,704	Faster aspart dominant
Statistically significant differences only	11.50	11.40	+0.10	50,165	51,719	-1,554	Faster aspart dominant
HbA1c benefit abolished after 1 year	11.45	11.40	+0.05	51,061	51,719	-658	Faster aspart dominant
HbA1c benefit abolished after 5 years	11.46	11.40	+0.06	50,564	51,719	-1,155	Faster aspart dominant
HbA1c benefit abolished after 10 years	11.49	11.40	+0.09	50,453	51,719	-1,267	Faster aspart dominant
HbA1c benefit abolished linearly over 10 years	11.48	11.40	+0.07	50,973	51,719	-746	Faster aspart dominant
HbA1c increasing over time in both arms	11.22	11.07	+0.14	54,121	56,003	-1,882	Faster aspart dominant
Cost of complications +20%	11.54	11.40	+0.13	56,847	58,813	-1,966	Faster aspart dominant
Cost of complications -20%	11.54	11.40	+0.13	42,713	44,183	-1,470	Faster aspart dominant

Analysis	Discounted quality-adjusted life expectancy (QALYs)			Discounted direct costs (GBP)			ICER
	Faster aspart	Insulin aspart	Difference	Faster aspart	Insulin aspart	Difference	(GBP per QALY gained)
Static hypoglycemia disutility	7.95	7.83	+0.12	50,004	51,719	-1,715	Faster aspart dominant
No hypoglycemia disutility	12.80	12.68	+0.12	50,004	51,719	-1,715	Faster aspart dominant
Pittsburgh cardiovascular risk equations	10.79	10.69	+0.10	48,130	49,755	-1,625	Faster aspart dominant
Combined mortality based on Western Australia data	12.12	12.00	+0.11	60,104	62,511	-2,406	Faster aspart dominant
52-week data	11.47	11.35	+0.12	51,760	53,676	-1,916	Faster aspart dominant
25 and 52-week data	11.51	11.37	+0.14	51,483	53,256	-1,773	Faster aspart dominant
PSA	11.12	11.00	+0.13	49,692	51,448	-1,756	Faster aspart dominant

GBP, 2015 pounds sterling; HbA1c, glycated hemoglobin; ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis.

Figure 1 Cumulative incidence and mean time to onset of diabetes-related complications over patient lifetimes

a)



b)

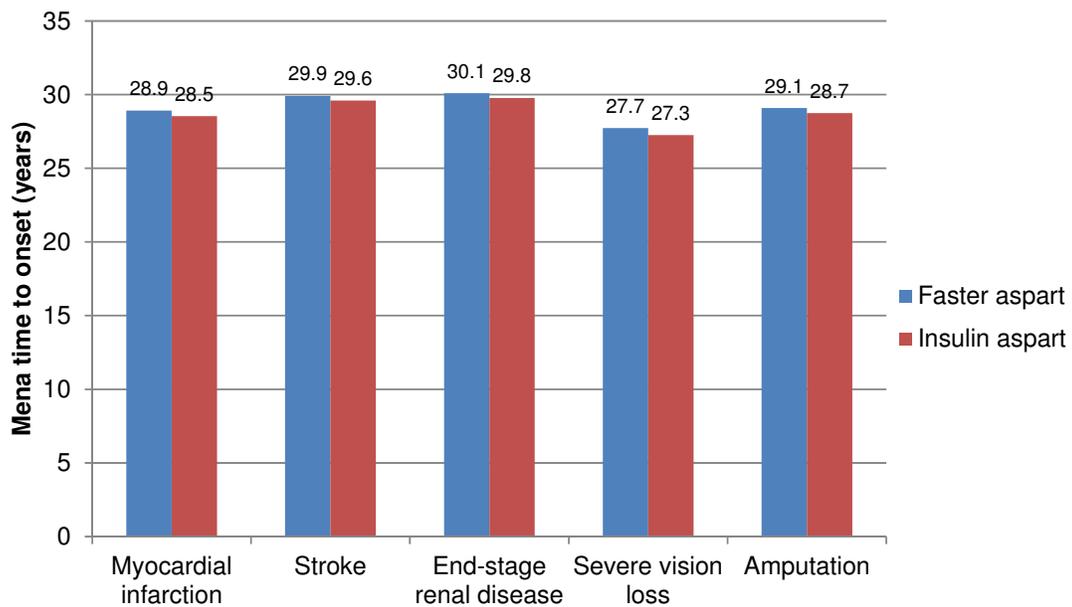
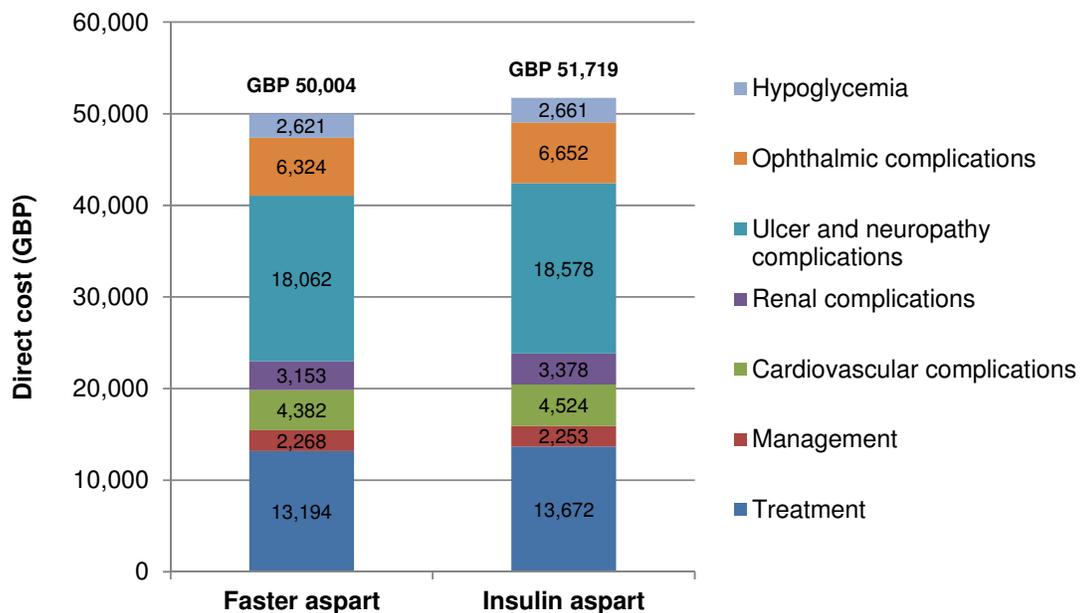
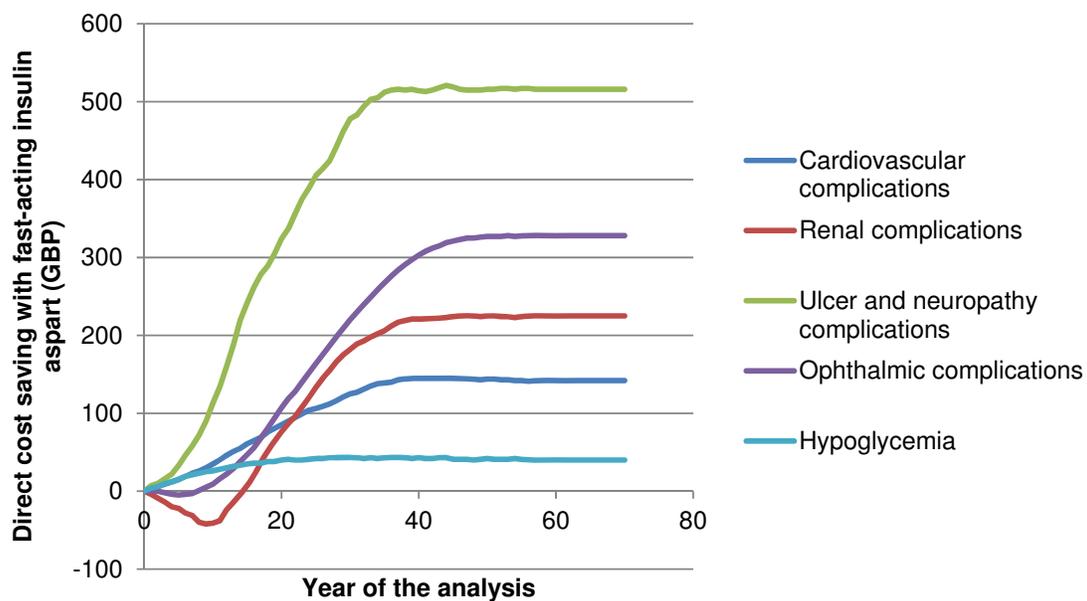


Figure 2 Direct costs over patient lifetimes with faster aspart and insulin aspart and cost savings with faster aspart as a result of avoided diabetes-related

a)



b)



GBP; 2015 pounds sterling